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Treatment for oral squamous cell carcinoma: Impact of surgeon volume on survival

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ABSTRACT

Background: The volume-outcome relationship is a well-known phenomenon in surgical oncology. The aim of this study was to quantify the impact of surgeon volume on the treatment outcome of oral squamous cell carcinoma (OSCC) patients.

Methods: All new OSCC cases treated with curative intent between 2008 and 2013 were included. A heterogeneous set of predictor variables was collected, including patient, tumour and treatment factors. The outcomes of interest were recurrence-free survival (RFS), overall survival (OS) and disease-specific survival (DSS). To investigate the cut-off in surgeon volume, the number of OSCC resections was analysed in multiplies of 5 cases per annum according to DSS, using univariable regression analysis.

Results: 534 cases were recruited. Independently, the negative predictors for patient survival were age, perineural invasion, worsening tumour staging, and extracapsular spread. High-volume surgeon was determined to be most significant at 20 cases per annum and significantly associated with improved RFS (HR: 0.67), OS (HR: 0.44), and DSS (HR: 0.39).

Conclusions: Results from this study support the rationalisation of OSCC management at high-volume centres and in the hands of experienced surgeons for better patient survival. Head and neck surgeons should perform a minimum of 20 OSCC cases per year to maintain competency in OSCC ablation.

Introduction

Surgery remains the fundamental treatment for oral squamous cell carcinoma (OSCC) with adjuvant therapy reserved for high-risk disease [1]. The surgeon's role can be pivotal in achieving complete tumour ablation with adequate surgical margins, where high-volume surgeons were shown to deliver better surgical margins [2]. While this suggests the potential benefits for OSCC patients to be treated at high-volume centres by high-volume surgeons, the evidence to support volume-outcome relationships in OSCC management is limited in the current literature.

The impact of surgeon volume on patient outcome can occur on multiple levels, and surgical margin is unlikely to be the sole contributing factor. Other factors include the quality of both operative and multidisciplinary care. Indeed, such associations have been well-documented in other oncological specialities, where high-volume surgeons and high-volume hospitals were associated with improved lymph node harvesting [3,4], higher flap reconstruction rate [5], reduced post-operative mortality and complication rate [4–6], and better access to adjuvant therapy [6], allied health services and patient follow-up [7].

In a systematic review by Eskander and his colleagues [8], low volume surgeons treating OSCC had a 25% higher mortality rate. However, these studies were population based, and did not include important confounders such as surgical techniques, adjuvant therapies, and tumour or patient specific factors in their analysis. It is important to investigate and control for these parameters when examining the impact of surgeon volume.

The aim of this study is to identify a statistically significant cut-off for surgeon volume in optimising treatment outcome after adjusting the effect of clinically relevant covariates. We hypothesised that there is a

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significant association between patient survival and surgeon experience in the management of OSCC.

Materials and methods

Study design

This research was approved by the human research ethics committees at Royal Brisbane and Women's Hospital and the Sydney Local Health District. In a retrospective approach, patient cases were recruited from all new OSCC treated at the two institutions between 1st of January 2008 and 31st of December 2013. The inclusion criteria were histologically established squamous cell carcinoma within the oral cavity that had primary surgical treatment with curative intent. OSCC treated prior to 2008, recurrent tumours and those with distant metastasis at the time of diagnosis were excluded. The two hospitals were selected on their similar protocols in managing OSCC patients following multidisciplinary team approach with the decision for adjuvant therapy based on histopathology post-surgery and associated patient background, using 3D-conformal or intensity-modulated radiotherapy.

Study variables

A list of clinically relevant variables that may impact on prognosis was grouped into patient, tumour and treatment factors. Among patient factors, age (years) and gender were recorded. Tumour factors included perineural invasion (PNI), lymphovascular invasion (LVI), margin status (involved, < 5 mm, ≥ 5 mm), tumour (T) classification, nodal (N) classification, presence of extracapsular spread (ECS), and tumour subsite. T and N classification were recorded as per 7th edition of cancer staging manual by American Joint Committee on Cancer [9].

Treatment factors included ablative surgeon volume, surgical access, neck dissection, type of reconstruction and whether the patient received post-operative radiotherapy (PORT). Ablative surgeon volume was grouped into two groups of low-volume and high-volume based on the average number of OSCC resections per year. Reconstructive type was coded as nil (primary closure or no closure), locoregional flap, skin graft, and free flap. For cases with reconstruction, their approach was further coded as same or different, depending on whether the reconstructive surgeon was the same surgeon who performed the ablative surgery or not. Surgical access was coded as access procedure when mandibulotomy, drop-down, midface degloving, lip-split and Weber-Ferguson approach was used. The number of lymph nodes retrieved was recorded for patients who received neck dissection. Specific threshold of 18 lymph nodes dissected is adopted as a quality indicator for neck dissection performed by surgeons [10].

Statistical analysis

The primary outcomes of interest were disease recurrence and mortality. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of last follow-up or recurrence at any site, with patients dying from other causes being censored at the time of death. Disease-specific survival (DSS) was calculated from the date of surgery to the date of last follow-up or death from OSCC, with patients dying from other causes being censored at the time of death. Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up.

To investigate the cut-off in surgeon volume, the number of OSCC resections was analysed in multiplies of 5 cases per annum according to DSS, using univariable regression analysis. High-volume surgeon was defined at the level of most statistical significance. Serial univariable analyses were performed at 5, 10, 15 and 20 OSCC patients treated per annum in surgeon volume, and the p-values in DSS improvement were 0.27, 0.14, 0.08, and < 0.01 respectively. The cut-off was determined to be 20 OSCC patients treated per annum.

Table 1
Characteristics of Included Cases (N = 534).

Characteristics	N	Percentage
Gender		
Female	209	39%
Male	325	61%
T Classification		
T1	206	39%
T2	175	33%
T3	28	5%
T4	125	23%
N Classification		
N0	364	68%
N1	56	11%
N2	114	21%
Extracapsular Spread		
Yes	75	14%
No	459	86%
Perineural Invasion		
Yes	146	27%
No	388	73%
Lymphovascular Invasion		
Yes	64	12%
No	470	88%
Site		
Buccal	35	7%
Floor of Mouth	109	20%
Hard Palate	13	2%
Mandible	68	13%
Maxilla	23	4%
Retromolar Trigone	35	7%
Tongue	251	47%
Post-Operative Radiotherapy		
Yes	214	40%
No	320	60%
Ablative Surgeon Volume		
Low-Volume	250	47%
High-Volume	284	53%
Surgical Margin		
Clear ≥ 5 mm	138	26%
Close > 0 mm	338	63%
Involved ≤ 0 mm	58	11%
Neck Dissection		
Yes	390	73%
No	144	27%
Lymph Node Count		
< 18 Lymph Nodes	53	14%
≥ 18 Lymph Nodes	337	86%
Surgical Access		
Access Procedures	74	14%
Non-Access Procedures	460	86%
Reconstructive Type		
Nil	182	34%
Locoregional Flap	70	13%
Skin Graft	49	9%
Free Flap	233	44%
Free Flap Reconstructive Approach (N = 233)		
Same Surgeon	118	51%
Different Surgeon	115	49%

Remaining associations between each treatment outcome and predictor variables were explored under univariable regression analysis with backward elimination process. Variables with statistical association of p-value (p) less than 0.10 were retained and refitted in a non-interaction multivariable model. The statistical associations were estimated by Cox Proportional Hazards regression and presented in Hazard Ratio (HR). Analyses were performed using STATA 15.0 (StataCorp, College Station, TX).

Results

A total of 534 OSCC cases were recruited. The median age was 62 years, ranging from 18 to 105 years. The proportion of male cases was 61%. The median follow-up was 3.6 years post primary surgical

Table 2
Univariable Regression Analysis.

	Recurrence-Free Survival			Disease-Specific Survival			Overall Survival		
Predictor Variables	HR	*p*-value	95% CI	HR	*p*-value	95% CI	HR	*p*-value	95% CI
Increasing Age	1.00	0.45	0.99–1.02	1.01	0.30	0.99–1.03	1.02	< 0.01	1.01–1.04
Gender - Male	0.84	0.29	0.60–1.17	1.18	0.52	0.71–1.97	1.08	0.73	0.74–1.58
T2	0.75	0.18	0.50–1.14	1.14	0.69	0.59–2.20	1.16	0.51	0.75–1.81
T3	1.00	0.99	0.41–2.41	1.82	0.28	0.62–5.32	1.67	0.27	0.67–4.14
T4	1.35	0.13	0.91–2.01	3.40	0.15	0.98–6.12	2.28	< 0.01	1.49–3.48
N1	1.33	0.32	0.76–2.32	1.85	0.17	0.87–3.95	1.26	0.43	0.71–2.42
N2	2.66	< 0.01	1.86–3.81	3.59	0.11	0.95–6.17	2.68	< 0.01	1.80–3.98
Extracapsular Spread	2.00	0.28	0.90–2.98	3.78	< 0.01	2.13–6.70	2.50	0.10	0.93–3.81
Perineural Invasion	1.87	0.31	0.71–2.63	2.92	< 0.01	1.80–4.75	2.28	< 0.01	1.60–3.26
Lymphovascular Invasion	1.90	0.22	0.83–2.89	2.19	0.10	0.85–4.15	1.84	0.21	0.96–2.92
Cancer Sites (in reference to Buccal)									
Floor of mouth	1.12	0.78	0.50–2.52	1.23	0.73	0.38–4.05	0.96	0.93	0.44–2.11
Hard Palate	1.50	0.44	0.54–4.22	1.50	0.67	0.23–9.63	1.39	0.60	0.41–4.69
Mandible	0.95	0.91	0.41–2.23	1.21	0.77	0.34–4.22	0.64	0.33	0.26–1.58
Maxilla	1.79	0.24	0.68–4.71	2.70	0.17	0.66–10.97	1.33	0.55	0.52–3.43
Retromolar Trigone	1.20	0.70	0.47–3.06	2.84	0.13	0.75–10.83	1.78	0.17	0.79–4.04
Tongue	1.00	1.00	0.47–2.15	1.17	0.78	0.39–3.55	0.78	0.52	0.37–1.64
Post-Operative Radiotherapy	1.31	0.10	0.95–1.82	1.68	0.19	0.78–2.72	1.31	0.14	0.91–1.89
High-Volume Surgeon	0.71	0.04	0.51–0.99	0.53	0.01	0.32–0.87	0.53	< 0.01	0.36–0.76
Close Surgical Margin	1.16	0.48	0.78–1.72	1.22	0.52	0.67–2.22	1.37	0.17	0.88–2.15
Involved Surgical Margin	1.75	0.15	0.95–3.05	2.85	0.13	0.76–6.28	3.12	0.11	0.91–5.53
Neck Dissection	1.06	0.74	0.75–1.51	1.29	0.37	0.73–2.28	1.17	0.44	0.78–1.76
< 18 Lymph Node Count	1.03	0.56	0.62–1.62	1.10	0.45	0.58–2.10	1.05	0.86	0.63–1.74
Access Procedures	1.67	0.19	0.89–2.57	2.04	0.17	0.95–3.75	1.58	0.15	0.98–2.56
Reconstructive Type									
Locoregional Flap	0.95	0.85	0.57–1.59	0.97	0.94	0.48–1.98	1.00	0.99	0.59–1.67
Skin Graft	1.11	0.73	0.62–1.96	1.62	0.21	0.77–3.42	1.34	0.35	0.73–2.44
Free Flap	1.15	0.46	0.79–1.69	1.75	0.19	0.62–3.23	1.19	0.92	0.78–1.79
Different Surgeon	1.25	0.28	0.84–1.87	0.90	0.73	0.51–1.61	1.53	0.11	0.99–2.36

treatment. Table 1 describes the characteristics of the 534 included OSCC cases.

During follow-up, 142 patients developed recurrent disease and 124 patients died, of which 80 patients died of OSCC. The 5-year RFS, OS and DSS rates were 73%, 77% and 85%, respectively. 233 patients received free flap reconstruction, where 118 patients were reconstructed by the same surgeon (51%) and 115 patients were treated by a second surgical team (49%). On univariable analysis of this sub-group, the RFS, OS and DSS were 86%, 90%, 98% in the same surgeon reconstructive approach, respectively, comparing to 84% ($p = 0.86$), 88% ($p = 0.91$), 96% ($p = 0.14$) in the different surgeon reconstructive approach, respectively.

Table 2 presents the results of univariable regression analysis, while Table 3 presents the results of multivariable Cox Proportional Hazards regression models. Age was shown to be a significant predictor of OS (HR 1.03 per year; $p = < 0.01$). Higher T classification was associated with reduced OS (T4 category HR 1.75; $p = 0.02$) and PNI was associated with both worse OS (HR 1.60; $p = 0.03$) and DSS (HR 2.23; $p = < 0.01$).

Of the 390 patients who had neck dissection, 53 patients had neck dissection with less than 18 lymph nodes harvested (14%) with no significant correlation to patient survival. Advanced nodal disease was associated with reduced survival with N2 disease having 2.4 times increased risk of death ($p = < 0.01$) and 2.8 times increased risk of recurrence ($p = < 0.01$), and ECS was associated with 3.2 times increased risk of death due to OSCC ($p = < 0.01$).

Twenty surgeons participated in the study. Only two high-volume surgeons were treating more than 20 OSCC per year with total number of 123 and 161 patients treated, respectively, in the 6-year study period. The remaining eighteen low-volume surgeons ranged 1–95 OSCC patients treated in total. The high-volume surgeon group was found to have significantly improved RFS (Fig. 1), DSS (Fig. 2) and OS (Fig. 3) with HR of 0.67 ($p = 0.02$), 0.39 ($p = < 0.01$) and 0.44 ($p = < 0.01$), respectively.

Sub-analysis demonstrated higher proportion of early tumours in patients treated by low-volume surgeons: T1 = 43% and T4 = 20%; comparing to high-volume surgeons: T1 = 34% ($p = 0.03$) and T4 = 27% ($p = 0.03$). Involved surgical margin was significantly higher in the low-volume surgeon group (14%) than the high-volume surgeon group (7%; $p = < 0.01$), while the lymph node count from neck dissection was significantly lower when performed by low-volume surgeons with an average of 6 lymph nodes less per neck side than high-volume surgeons ($p = < 0.01$). Among 18 surgeons in the low-volume group, two surgeons performed neck dissection with median lymph node dissected < 18 per unilateral neck. The two high-volume surgeons performed median lymph nodes dissected ≥18 per unilateral neck. The use of access procedure was also more frequent in the high-volume

Table 3
Multivariable Cox Proportional Hazards Regression Model.

Treatment Outcomes	Predictors	Hazard Ratio	*p*-value	95% CI
Recurrence-Free Survival	High-Volume Surgeons	0.67	0.02	0.48–0.93
	N1 Classification	1.30	0.37	0.74–2.28
	N2 Classification	2.76	< 0.01	1.93–3.96
Disease-Specific Survival	High-Volume Surgeons	0.39	< 0.01	0.22–0.69
	Extracapsular Spread	3.24	< 0.01	1.71–6.15
	Perineural Invasion	2.23	< 0.01	1.31–3.81
Overall Survival	Increasing Age	1.03	< 0.01	1.01–1.04
	High-Volume Surgeons	0.44	< 0.01	0.29–0.64
	Perineural Invasion	1.60	0.03	1.04–2.47
	N1 Classification	1.01	0.97	0.53–1.94
	N2 Classification	2.41	< 0.01	1.50–3.88
	T2 Classification	0.97	0.89	0.60–1.56
	T3 Classification	1.12	0.81	0.44–2.86
	T4 Classification	1.75	0.02	1.10–2.77

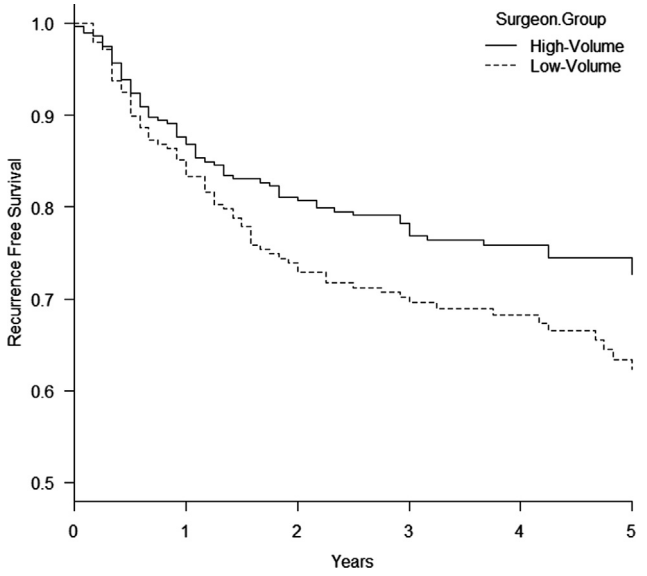

Fig. 1. Kaplan Meier Curve for Recurrence Free Survival for High- and Low-Volume Surgeon Groups (p = 0.037).

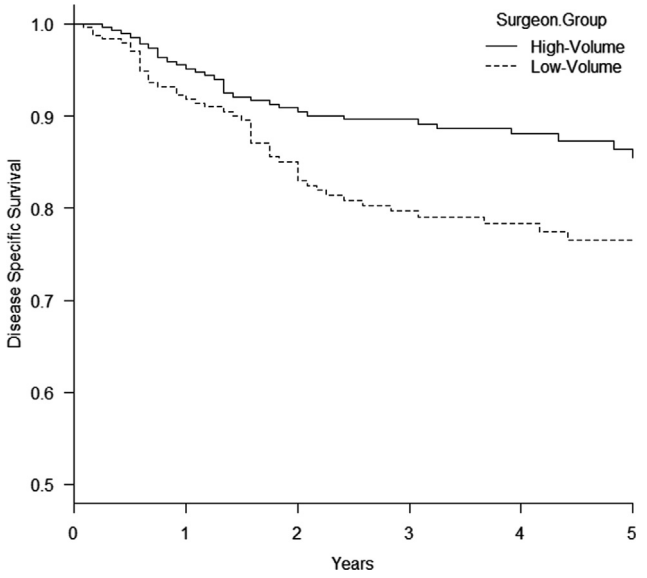

Fig. 2. Kaplan Meier Curve for Disease Specific Survival for High- and Low-Volume Surgeon Groups (p = 0.01).

surgeon group (18%) than the low-volume surgeon group (9%; $p = < 0.01$). Table 4 summarises the differences in tumour characteristics and treatment factors between low-volume and high-volume surgeon groups.

Discussion

The volume-outcome relationship has been commonly described in the healthcare system, with its significance in delivering better clinical outcomes, if the health services are performed by physicians and surgeons at hospitals that usually provide a high volume of similar services [11]. Our results demonstrated the significance of surgeon's exposure in managing OSCC, where, in comparison to other surgical variables, surgeon volume was the single most important surgical factor in improving patient survival. Patients treated by high-volume surgeons had approximated a 60% reduction in mortality compared to patients in the low-volume group.

This study's finding is consistent with the results of two population-based studies conducted by Lee et al. [12] and Lin and Lin [13] during the year 2005 and 1997–1999, respectively. With a large sample of 7922 OSCC patients from their National Health Insurance research database, the two studies showed the potential benefits in cancer survival when OSCC patients were managed by high-volume surgeons with reported HR of 0.66–0.81 [12,13]. While the lack of consideration on tumour factors, adjuvant therapies, and surgical techniques limit the interpretation of these studies, our study supports the authors' hypothesis on surgeon volume as a significant prognostic factor for the treatment outcome of OSCC patients.

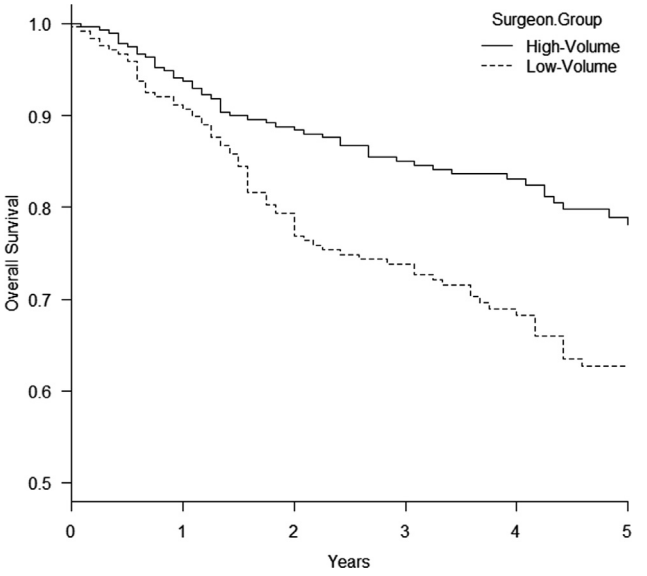

Fig. 3. Kaplan Meier Curve for Overall Survival between High- and Low-Volume Surgeon Groups (p = 0.01).

Table 4
Characteristics between Patients treated by Low-Volume and High-Volume Surgeons.

	Low-Volume (N = 250)		High-Volume (N = 284)		*p*-value
Tumour Characteristics					
T Classification					
T1	108	43%	98	34%	0.03
T2	78	31%	97	34%	0.46
T3	15	6%	13	5%	0.61
T4	49	20%	76	27%	0.03
N Classification					
N0	176	70%	188	66%	0.32
N1	28	11%	28	10%	0.71
N2	46	19%	68	24%	0.06
Histologic Adverse Features					
Perineural Invasion	75	30%	71	25%	0.19
Lymphovascular Invasion	29	12%	37	13%	0.73
Extracapsular Spread	32	13%	43	15%	0.51
Treatment Factors					
Surgical Access					
Access Procedure	22	9%	52	18%	< 0.01
Surgical Margin					
Clear ≥ 5 mm	57	23%	81	29%	0.07
Close > 0 mm	157	63%	181	64%	0.81
Involved ≤ 0 mm	36	14%	22	7%	< 0.01
Neck Dissection					
Yes	178	71%	212	75%	0.18
Lymph Node Count (Mean) per neck side	25	Range 7–102	31	Range 15–124	< 0.01
Post-Operative Radiotherapy					
Yes	99	40%	115	40%	0.83

On the analysis of remaining surgical factors, poor surgical margin, neck dissection, surgical access and reconstructive approach were not found to be significant predictors for treatment outcome. Sub-analysis between low-volume and high-volume surgeon groups demonstrated the quality of surgery delivered is higher when performed by high-volume surgeons. The rate of involved surgical margin was significantly lower and the lymph node count in neck dissection was significantly higher in the high-volume surgeon group. Overall, the quality of neck dissection performed in our study has met this standard with only two low-volume surgeons had less than 18 lymph nodes dissected in their neck dissection.

However, the exact underlying mechanism of the volume-outcome association remains subject to debate and is likely to be multifactorial in nature. While compromised surgical margins can lead to poor outcome for OSCC patients [14], the impact of surgeon volume demonstrated on prognosis may not be explained by its effect on margins and/or quality of neck dissection alone [2].

In surgical oncology, there is evidence supporting the value of surgeons' technical skill sets and the benefits in procedure-specific experience, rather than general experience [15,16]. In head and neck oncology, this experience significantly increased the number of elective neck dissections performed [17] and the number of lymph nodes harvested [3]. Furthermore, high case volume generates funding for hospital resources. Studies have shown that patients treated by high-volume surgeons at high-volume centres received better coordination in cancer treatment with timely provision of adjuvant therapy and increased opportunities for primary health prevention, multidisciplinary consultations, patient education, and improved adherence to treatment follow-up [5–7].

The findings of volume-outcome studies essentially raise concern in the ongoing demand for healthcare systems to adopt policies on decentralisation of cancer care services. Decentralisation and regionalisation of medical care have been favoured across many healthcare systems due to unmet needs in our growing diverse population [18]. However, these policies are often complex, as they rely on geography, resources, culture, societal preferences, and local governance of communities involved [18]. Indeed, despite the estimates on the number of avoidable deaths and lives saved in regionalisation studies [19–21], it remains a challenge to determine the cut-off for optimal surgeon and hospital volumes.

For thyroidectomy, Adam et al. [22] recently demonstrated the importance for surgeons to perform a minimum of 25 cases per year in maintaining their competency, but no published guidelines have been found for other head and neck subsites. The cut-off was drawn at 20 cases per year in this study, which was found to have significant impact on patient survival after adjusting for other covariates. This provides insights to the surgeon volume required to optimise surgical care for OSCC patients.

The majority of OSCC were ablated via per oral approach in this study with access procedure performed in 14% of patients treated. The use of access procedure was twice as frequent in the high-volume surgeon group, but this had no independent impact on survival outcomes. As well as the surgeon's experience and preference, approaches to oral cavity resection are guided by the size and site of the tumour. Per oral approach is traditionally reserved for early-stage OSCC with the advantage of minimal functional and aesthetic disorder [23]. Access procedure is preferred for tumours that are bulky or located at posterior parts of oral cavity for satisfactory ablation with clear margins. While the increased use of access procedure in the high-volume surgeon group is likely due to the higher proportion of T4 OSCC patients treated in this group, their specific experience in access procedure may also contribute to this observation.

At the trade-off for oncological safety, access procedure can lead to increased post-operative morbidity. Støre and Boysen [24] found a high rate of 27% in wound healing complication in 18 OSCC patients with mandibulotomy. However, Cilento et al. [25] demonstrated much lower complication rates with malunion (0%), oral incompetence (14.6%), and fistula (6.8%) in 41 patients with lip-split mandibulotomy. Despite the low rate of access procedure observed in this study, the incidence of involved margin was 11%, which is consistent with recently published data [26–28]. Battoo and his colleagues [26] supported the practicality of per oral approach, achieving clear margin in 81% of 79 patients with T2 and T3 OSCC.

Microvascular free flap was the most common type of reconstructive approach observed in this study (44%). Advances in techniques for free-tissue transfer have significantly improved functional and oncological outcomes in head and neck reconstruction in the last two decades [29]. In addition, it is common practice for reconstruction to be performed by a second surgical team to prevent surgeon fatigue and the potential in compromising resection margins due to consternation for difficult reconstruction. Neither reconstructive type nor approach had significant impact on treatment outcome in our analysis.

There are two major limitations in this study. Firstly, the study is of retrospective approach and the sampling process is subjected to potential bias and confounding variables not included in the analysis. The potential confounders may include patient co-morbidities and other tumour factors such as depth of invasion. However, this limitation can be difficult to overcome, since it will be ethically challenging to conduct a trial, randomising patients to high- and low-volume treatment groups. Therefore the inferences made in this study need to be applied with the awareness that the two treatment groups can be inherently different due to selection and residual biases.

Secondly, this study is based on institutions in Australia and its healthcare system. This may limit the application of our findings to other countries and their healthcare systems. It is important to recognise the differences in how health services are delivered across the world. The diversity in medical training, practice pattern, and resource allocation could also have an influence on the identified volume-outcome association in OSCC surgery.

Conclusion

This study demonstrated the impact of volume-outcome association in the management of OSCC patients and emphasises the value in centralising their curative surgeries. After adjusting for other treatment factors, surgeon's specific experience was found to be the only significant treatment in improving patient survival. We propose that head and neck surgeons need to perform a minimum of 20 cases per year to maintain competency in OSCC ablation.

Declaration of Competing Interest

None Declared.

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