



Oral cavity cancer treatment outcomes in Western Australia

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Background: Oral cavity cancers (OCC) account for a significant proportion of head and neck malignancies and pose a significant disease burden given the poor quality of life outcomes and high mortality rates. We evaluated the treatment outcomes of OCC treated at Sir Charles Gairdner Hospital (SCGH), Western Australia (WA).

Methods: A retrospective cohort study was conducted at one of the largest tertiary hospitals in the state. The hospital-based cancer registry was used as a primary source of data, including cases presented between January 2012 and December 2016. Review of medical records was performed for those patients with missing data. The study was approved by the Institutional Safety Board (ISB) in accordance with the hospital regulations (SCGH).

Results: One hundred and one patients with primary diagnosed OCC received treatment during the period. The majority of patients were male, and most were treated primarily with surgery. Twenty-six patients (25.7%) developed recurrence during follow-up, with a median time to recurrence of 10.5 months. Of the patient with recurrence, 73% (19/26) died because of their recurrence. A total of 38 patients died during follow-up (37.6%), with a 3-year overall survival of 66.3% (95% CI, 55.2–75.2%), and a 3-year disease-specific survival (DSS) of 83.2% (95% CI, 72.2–90.1%).

Conclusions: OCC continues to be a therapeutic challenge for the head and neck surgeon. Given the relatively asymptomatic nature of early disease, OCC diagnosed at a late stage is not uncommon, therefore positive lymph-nodes are important when evaluating survival. This study examines up-to-date treatment outcomes for OCC in WA and highlights the variation in mortality rates observed globally.

Keywords: Oral cavity; cancer; malignancy; carcinoma; survival; treatment outcome

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Introduction

Oral cavity cancers (OCC) account for a significant proportion of head and neck malignancies. There has been a gradual decline in incidence globally over the past three decades, however, OCC pose a significant disease burden given the high mortality rates and poor quality of life outcomes. Consequently, appropriate prevention and management is paramount for patients with OCC. The aim of this study is to evaluate the treatment outcomes

of OCC treated at a tertiary hospital in Perth, Western Australia (WA).

The oral cavity anatomically extends from the skin-vermilion junction of the lips to the hard and soft palate junction, and frequent sites of malignancy include the tongue (40%) and floor of mouth (30%) (1-3). Squamous cell carcinomas (SCC) represent the majority of the malignant lesions identified in those with OCC (4). Demographic risk factors for the development of OCC include age greater than 50 years old and gender (higher risk in males) and both these

factors are associated with poorer prognosis (5-8). Tumour subsite location within the oral cavity is also important when evaluating treatment outcomes with higher mortality rates seen in cancers involving the oral tongue, buccal region and floor of mouth (8). Smoking and alcohol use are synergistic in oral carcinogenesis and increased consumption impacts overall survival and the incidence of second primary tumours (8-12). The role of human papillomavirus in the development of OCC is still unclear although there is well established evidence of the virus' causality in oropharyngeal SCC (13,14).

The global incidence of OCC is estimated at 300,000 cases annually and although incidence has declined over the past few decades, OCC still remains one of the top ten most common cancers worldwide (8,15,16). More concerning is the minimal improvement in mortality rates for OCC despite advances in treatment and technology (8,17-20). OCC diagnosed at an early stage is associated with good survival outcomes. Local OCC of the lip, tongue and floor of mouth all have 5-year survival rates >75%, however, when diagnosed at a later stage with regional metastases, survival diminishes to between 38–63% (depending on site) (21). Unfortunately only a minority (approximately 30%) of OCC are diagnosed at an early stage so despite favourable prognosis in these cases, mortality remains high (22). Surgical resection is the mainstay of treatment for OCC and if indicated, the optimal time frame from surgical resection to post-operative radiotherapy should be less than 6 weeks (23,24).

OCC is a common malignancy worldwide and there is an abundance of literature regarding the presentation, work-up, diagnosis and management of OCC. OCC outcomes over the last 5 years in Australia are poorly described and so the aim of this study was to evaluate the treatment outcomes of OCC treated at a tertiary hospital in WA.

Methods

We conducted a retrospective cohort study at Sir Charles Gairdner Hospital (SCGH) in Perth, WA, one of the largest tertiary hospitals in the state. The hospital-based cancer registry was used as a primary source of data, including cases presented between January 2012 and December 2016. Review of medical records was performed for those patients with missing data. One hundred and one patients were included that were treated for OCC during this 5-year period. Patients identified as having OCC recurrence with previous malignancy prior to January 2012 were excluded.

Lip malignancies were also not included in this dataset. The study was approved by the Institutional Safety Board (ISB) in accordance with the hospital regulations (SCGH).

Patient characteristics were recorded and included: age, gender, alcohol consumption, smoking history, evidence of recurrence, time between treatment and recurrence, and deceased status. Disease specific data was also recorded and included: tumour site and size, pathology, grade, pathological stage, resection margins, evidence of lymphovascular/neural/bony invasion, cancer progression, primary treatment modality, adjuvant therapy and surgical reconstruction.

The primary outcome was overall survival. Secondary outcomes included disease-specific survival (DSS) and recurrence. Nodal status was defined as the presence of metastasis on neck lymph nodes on clinical presentation, imaging investigations or pathology results. We calculated 3-year survival rates due to the fact that the last patients included had a follow-up of only one year at the time of the analysis and so 5-year estimates were not available for all patients. We included all consecutive patients during that period of time.

As a part of standard of care at SCGH, every patient with OCC is discussed in a multi-disciplinary head and neck oncology meeting (MDT), regarding indication for primary and adjuvant treatment, as well as surveillance and palliative-care.

Statistical analyses

Variables were analysed using Stata12, with mean and standard deviation for normal-distributed continuous variables and relative and absolute frequencies for categorical variables. Fisher's exact test was used for association between categorical variables. Kaplan-Meier curves were used for survival analysis, and log-rank test for assessing differences among variables. For all analysis we considered an alpha of 5%.

Results

A total of 101 patients with primary diagnosed OCC received treatment during the 5-year period (*Table 1*) and were included in the study. The majority of patients were male (55.6%) and the mean age at diagnosis was 64 years. The most common primary site of malignancy was oral tongue (66%) followed by the retromolar trigone (9%).

Of all patients, 89.1% were treated primarily with

Table 1 Patient and disease specific characteristics

Patient characteristics	N=101 (%)
Male	56 (55.6)
Female	45 (44.4)
Age at diagnosis (years), [mean (range)]	64.4 [19–94]
Primary tumour location	
Tongue	67 (66.0)
Retromolar trigone	10 (10.0)
Floor of mouth	9 (9.0)
Gingiva (upper or lower)	9 (9.0)
Buccal	4 (4.0)
Hard palate	2 (2.0)
Tumour size (mm), [mean (range)]	26.9 [0.5–84]
Recurrence	26 (25.7)
Locoregional	23 (88.5)
Distant	3 (11.5)
Time to recurrence (months), [mean (range)]	11 [1–48]
Histopathology	
Squamous cell carcinoma	99 (98.0)
Adenoid cystic carcinoma	1 (1.0)
Verrucous carcinoma	1 (1.0)
Smoking history	
Current smoker	26 (25.7)
Ex-smoker	30 (29.7)
Non-smoker	20 (19.8)
Unknown	25 (24.8)
Alcohol consumption history	
Heavy	17 (16.8)
Moderate	10 (9.9)
Light	19 (18.8)
Non-drinker	15 (14.9)
Unknown	40 (39.6)
Margin status	
Involved resection margins	16 (15.8)
Unknown margins	22 (21.8)
Average closest margin (mm), n=63	3.8 [0.1–12]

surgery and 66.3% received adjuvant or palliative radiation therapy. Pathological staging was as follows (% patients): I: 37.6; II: 11.9; III: 8; IV/IVA: 39.7; IVB: 1.9; IVC: 0.9. Thirty-five patients (34.7%) had pathologically positive lymph nodes and only one patient had distance metastases at diagnosis. Resection margins were involved in 15.8% of patients. Lymphovascular invasion (LVI) was present in 11 patients, perineural invasion present in 31 and bony invasion present in five. The decision to treat patients with adjuvant therapy (radiotherapy or chemoradiotherapy) was made after discussion at MDT with post-operative histopathological results available.

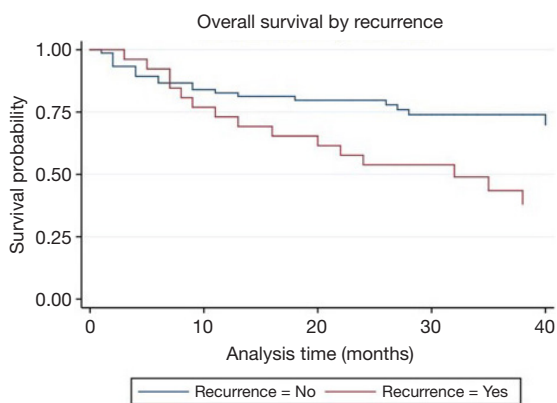
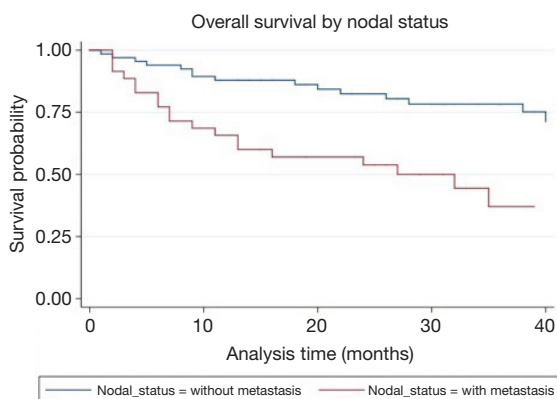
Forty-four patients (43.6%) received microvascular free flap reconstruction, the most common being anterolateral thigh (ALT) (n=16) and radial forearm (RFFF) (n=15).

Sixty-seven patients (66%) received radiotherapy at some part of their treatment. Of these, 56 underwent primary surgery and the received adjuvant post-operative radiation therapy, and a small proportion of patients (n=10) received radiotherapy without any surgical intervention. Of the series, 33 patients (32.6%) underwent surgery with no need for post-operative radiotherapy. There was one patient that did not receive any surgery or adjuvant therapy due to death soon after initial diagnosis (within 2 weeks). The majority of patients received surgery with post-operative radiotherapy as curative intent treatment, however six patients received palliative radiotherapy and no surgical intervention. These patients all had large tumour burdens and were at least staged IVA. Twenty-eight patients (27.7%) received adjuvant chemotherapy in addition to radiotherapy and the most common agent used was cisplatin. Management of the neck varied and was dependent on discussion at the MDT and with the patient. A majority of patients received comprehensive neck dissections (77%) if appropriate although patient factors and co-morbidities precluded some patients from surgical management of the neck.

One quarter of the patients (25.7%, n=26) developed a recurrence during the follow up, with a median time to recurrence of 11 months (range, 1–48). Locoregional metastatic recurrence was most common (n=23). Of the patients with recurrence, 73% (19/26) died and subsequent analysis identified that recurrence was associated with significantly worse overall survival (P=0.001). The presence of LVI was significantly associated with recurrence (P=0.02) however PNI was not (P=0.052). There were no significant associations between gender and recurrence (P=0.50),

Table 2 Three-year disease-specific survival according to stage in patients with OCC

Stage	Survival (%)	95% CI (%)
I	93.5	76.5–98.3
II	75	40.8–91.1
III	84.7	33.4–97.8
IVA	73.2	43.4–88.9

**Figure 1** Overall survival by recurrence on a series of patients with OCC (log-rank $P=0.001$).**Figure 2** Overall survival by nodal status on a series of patients with OCC (log-rank $P=0.004$).

pathological stage and recurrence ($P=0.41$) or tumour site and recurrence ($P=0.68$). There was no difference in the mean age between patients with recurrence and for those that did not develop recurrence ($P=0.84$).

A total of 38 patients died during the follow-up (37.6% of the group), with a 3-year overall survival of 66.3% (95% CI,

55.2–75.2%), and a 3-year DSS of 83.2% (95% CI, 72.2–90.1%). The 3-year DSS for patients with stage I was 93.5%, while for patients with stage IVA was 73.2% (Table 2). LVI and PNI were not associated with poorer overall survival ($P=0.23$ and $P=0.07$ respectively). Gender was not associated with overall survival ($P=0.83$), and there was no difference in age between survivors and non-survivors ($P=0.29$). However, there was a statistically significant association between tumour site and survival ($P=0.04$), with 100% mortality in those with primary buccal site malignancies ($n=4$). Forty percent of both the tongue and retromolar trigone tumour location patients died whilst mortality was lower for tumours of the floor of mouth and gingiva (22.2% and 11.1% respectively). All patients with hard palate tumours survived. When analysing survival, there was a statistically significant difference in overall survival according to recurrence ($P=0.001$) (Figure 1) and nodal status ($P=0.004$) (Figure 2). There was no difference in DSS according to recurrence or nodal status, and there was no difference in recurrence depending on nodal status.

Discussion

Oral cancer poses a significant disease burden and global 5-year overall survival rates are estimated at 50% (25). There is however, significant variation in treatment outcomes worldwide. In North America, OCC survival continues to improve, whereas in other regions survival rates have remained stable or declined. The main proposed causes for improvement include more advanced adjuvant therapy options (superior radiation therapy, standardised protocols and enhanced knowledge of adjuvant therapy), access to greater reconstruction options that allow more comprehensive resections, improved imaging technology which offers more accurate staging prior to treatment, and regionalisation of services (26–28). The global incidence of OCC also appears to be steadily declining however there is some evidence that incidence in younger individuals may in fact be increasing. Our study assessed OCC treatment outcomes at a tertiary hospital in Perth, WA and our findings are in align with data from North America demonstrating improvement in overall survival in patients suffering from OCC.

Warnakulasuriya's review in 2009 revealed an increasing incidence of oral cancer in Western Europe and Japan during the last 20 years and higher mortality rates in Eastern Europe (8). There was also an increase in mortality and incidence of OCC among younger individuals. Data

released by Cancer Research UK demonstrated similar results with increasing age-standardised mortality rates by up to 21% during the last decade and predicted increases of up to 35% by 2035 (28). Conversely, Gupta *et al.* and Montero *et al.* recently revealed an overall downward trend in mortality for those with oral cancer in the USA (27,29). In fact overall 5-year survival rates increased from 52.7% in 1975 to 68.8% as of 2010 (28,30). The reduction in smoking habits has likely contributed to the overall decline in global incidence of OCC. However, an ageing population in addition to an increase in alcohol consumption particularly amongst the younger generation may be partly responsible for the global variation in mortality rates.

In Australia, there have been several large epidemiological studies published assessing OCC incidence, trends and mortality between the 1980's and mid 2000's. Sugerma *et al.* assessed over 2,000 patients with OCC. The most common sites of malignancy being the lip followed by tongue, occurring more frequently in males and in those above the age of 60 (30). Incidence remained stable during the study period with some variation between anatomical site (increase in lip and decrease in floor of mouth cancers). Mortality rates in lip and tongue malignancies in the study decreased (30). Farah *et al.* reported similar findings between 1982 and 2008 assessing over 60,000 new cancer cases (lip, oral cavity and oropharynx). Overall incidence and mortality remained stable however there was a small increase in incidence of tongue cancer which was also associated with poorer outcomes as compared to the other oral cancer anatomical sites (31). Although difficult to draw conclusions in our cohort given the absence of lip and oropharyngeal malignancies, it is important to acknowledge the significant burden of tongue specific oral cancer.

Abreu conducted a retrospective epidemiological study in WA between 1982 and 2006 demonstrating highest mortality rates in malignancies involving the tongue however overall mortality rates were down-trending. Incidence also remained stable (32). The results of this study closely resemble ours in that OCC is seen most frequently in elderly men and responsible for higher mortality rates when involving the tongue. In contrast to the European data, Australian statistics are suggestive of an overall reduction in incidence of OCC and stable or down-trending mortality rates.

Unfortunately, a vast majority of OCC diagnoses are made at a later stage with patients presenting with nodal disease. This is especially important given nodal involvement is the most important prognostic factor

with regards to OCC outcomes (33,34). The prognosis of advanced stage disease remains poor, in contrast to relatively high survival rates in patients with early stage disease. There is limited data in Australia assessing these outcomes specifically, so the present study contributes significantly in this regard.

In this cohort, just over 50% (n=51) of the patients were initially diagnosed with at least pathological stage III disease, which is in keeping with the US National Cancer Institute SEER data demonstrating regional disease in 47% of OCC malignancies (22). The survival outcomes vary significantly between early and advanced disease with 5-year survival rates estimated at 83.7% for localised disease compared to 64.2% in regional disease (22). A recent publication out of the Memorial Sloan Kettering Cancer Center assessed 1,800 patients with OCC revealing a 5-year overall survival rate of 62.5% and overall survival by stage: I: 78.5%; II: 68.4%; III: 64.5% and IV: 34.5% (28). The results from our study are certainly comparable with this data demonstrating good prognosis with early stage cancers without nodal involvement but marked deterioration in survival associated with regional disease (*Figure 2*). Interestingly, there was no significant correlation between pathological stage and recurrence in our cohort despite strong evidence supporting nodal disease and factors (including size, number, ratio) as predictors of recurrence (35-37). There was however a statistically significant association between tumour site and overall survival with 100% mortality for buccal tumour site malignancies. Although there were only four cases of buccal site tumours in our cohort, it is well acknowledged that this subsite is associated with aggressive disease and higher mortality (38-40).

Recurrence was low in our cohort (25%) and more often than not occurring within 18 months of initial diagnosis. This can be likened to recurrence patterns demonstrated in the literature (41-44). Our study also explored the associations between histopathological factors, recurrence and overall survival. Perineural invasion is widely accepted as a predictive prognostic indicator of recurrence and increased mortality however our study was in contrast to this, with no significant associations demonstrated (40,45-47). LVI is also recognised as a marker of prognosis given the potential for nodal metastases however to what extent remains largely unclear (48-51). Adel and Chen *et al.* papers concluded that although strongly correlated with poorer overall survival, LVI is not an independent prognostic factor in those with early stage OCC (51,52).

This study adds to the existing literature supporting

improvements in mortality rates over the past 20–30 years especially in comparison to Europe and the UK. Our results are similar to that of North America demonstrating relatively good prognosis in early stage disease but poorer prognosis with more advanced disease. Three-year overall survival in our cohort was 66.3% which is certainly comparative to that of North America and significantly better than outcomes from some of the larger studies worldwide (28). Survival according to stage in our study was encouraging compared to previous data with overall excellent 3-year DSS of 93.5% for stage I and 73.2% for stage IVA malignancies. Unfortunately nodal metastases drastically reduced overall survival in our cohort and this is well known based on previous literature. Recurrence was low (25.7%) but significantly associated with an increase in overall mortality in this cohort, analogous to other published papers (28,41,53).

The study utilises a relatively large sample size and includes comprehensive analysis of current data relating to oral cavity SCC which has been lacking in recent years in Australia. This study has several limitations including the retrospective nature of the study design which inherently introduces biases and that data was collected at a single centre institution. Depth of tumour invasion was not available in this cohort which was unfortunate given the importance of the role of adjuvant therapy and potential recurrence in patients with greater depths of invasion. Smoking and alcohol consumption history where available was collected but poorly captured in the hospital-based cancer registry and/or medical notes and so analyses of these variables was not performed. Similarly, resection margins were unknown in almost a quarter of the cohort so multi-variate analysis was not performed in order to prevent potential bias and invalid conclusions.

Conclusions

OCC continues to be a therapeutic challenge for the head and neck surgeon despite advances in surgical treatments and adjuvant therapies. Incidence appears to be decreasing slowly worldwide although emerging data suggests geographical variation. Fortunately, in Australia, mortality rates have improved as demonstrated by several large epidemiological studies over the past 20–30 years. Our study supports this notion through analysis of up-to-date treatment outcomes in those with OCC in a large tertiary hospital in Western Australia. Given the relatively asymptomatic nature of early disease, OCC diagnosed at

a late stage is not uncommon therefore positive lymph-nodes are important when evaluating survival. Tumour location and histopathological markers are also significant in determining overall prognosis in patients with OCC. This study is one of few in recent years in Australia assessing OCC treatment outcomes and these results, whilst encouraging, highlight the importance of prevention and early detection of OCC in otolaryngology.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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