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METASTATIC SQUAMOUS CELL CARCINOMA OF THE SALIVARY GLAND

Treatment and prognostic factors related to overall survival and recurrence

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ABSTRACT

Purpose:
This study aims to address treatment and prognostic factors related to metastatic salivary gland squamous cell carcinoma (SCC) overall survival and recurrence in a New Zealand hospital.

Methods:
10-year retrospective case series of patients with surgical management of metastatic salivary gland SCC. Data was collected on patient demographics, treatment and outcomes.

Results:
101 patients were diagnosed with metastatic SCC of the salivary glands, occurring primarily in the parotid (94%), in elderly (median 84 years) Caucasian (92%) males (72%). All patients were treated with parotidectomy with high rates of neck dissection (80%) and adjuvant radiation therapy (83%). Histology showed perineural invasion (PNI) (28%), cervical metastasis (53%) and extranodal extension (ENE) (28%) were common. Overall survival was reduced in patients with cervical metastasis, lymphovascular invasion (LVI) and PNI, while PNI was associated with disease recurrent and cervical node metastasis.

Conclusion:
This research provides insight into the high rates of metastatic salivary gland SCC in New Zealand. SCC of the salivary glands is an aggressive entity, with lower rates of survival related to PNI, LVI and cervical metastasis. Conservative surgical margins and adjuvant radiation therapy provide adequate oncological management, with reduced morbidity. While primary radiation therapy in cN0 patients may provide a potential alternative treatment modality.

Keywords:
salivary gland | squamous cell carcinoma

INTRODUCTION

Squamous cell carcinoma (SCC) of the salivary gland is rare, accounting for 1 to 5% of all salivary gland tumours.[1-3] SCC of the salivary glands is primarily metastatic involving intraparotid and periparotid lymph nodes, secondary to non-melanoma skin cancer (NMSC).[1,4,5] Five percent of NMSC metastasise, and in the head and neck the parotid gland acts as a metastatic basin providing first echelon lymph node drainage from the scalp, forehead and midface, which experience high rates of ultraviolet radiation.[6] In advanced disease, metastasis spreads to the cervical lymph nodes.[7,8]

Australasia has the highest rates of NMSC in the world, with SCC being the most common metastatic disease of the salivary glands, occurring primarily in Caucasian males in their eighth decade.[9,10] SCC of the submandibular gland account for around 20% of patients, with a heterogeneous etiology from lymph nodes draining both cutaneously and intraorally.[10,11] Primary SCC of the salivary glands is rare (<1%), with non-specific histological variation, absence of definitive pathogenesis, and often misdiagnosed metastatic SCC, or a diagnosis of clinical exclusion.[2,3] Metastatic SCC of the salivary gland is aggressive, with 30-50% having cervical node involvement, a five-year survival of 54-64% and a recurrence rate of 20-60%.[2,3,6,8,9]

There is a paucity of information relating to the management and prognostic factors of metastatic SCC of the salivary glands. Current guidelines do not address resection margins in metastatic disease, and it remains unknown whether margins surrounding lymph node disease influence survival. However, the National Comprehensive Cancer Network (NCCN) and National Institute of Health Care Excellence (NICE) recommend primary surgery with neck dissection, and adjuvant radiation therapy.[12,13]

Following our previous paper Mckenzie et al. (2022), which identified high rates of metastatic SCC in salivary glands in New Zealand, this paper aims to document the experience in the management of metastatic salivary gland SCC and identify prognostic factors in a New Zealand population via a retrospective case series.[10]

METHODS

Ethics consent was obtained by the New Zealand Health and Disability Commission and approved by the Waikato District Health Board. Data was collected between January 2010 to December 2020. Patients were included if they had a histological diagnosis of metastatic SCC of the salivary glands (WHO classification) that was primarily surgically managed.[14] All patients were presented at a specialist head and neck multidisciplinary meeting (MDM) for shared treatment planning.

The definition of margins, beyond nodal disease is not widely reported in the literature. We defined an involved margin as less than 1mm, a clear margin as greater than 5mm and a close margin as greater than 1mm and less than 5mm, as suggested by other authors.[15,16] Tumour excision was based on clinical assessment of facial nerve, pre-operative imaging, intra-operative findings and surgeon experience with preservation of the facial nerve if indicated. These margin definitions were selected to achieve consistency with reporting, and aligns with literature findings that more radical surgery does not improve disease free survival.[7,8,17,18]

Analysis of primary cutaneous tumour characteristics were not undertaken as this information is not readily available in New Zealand. This is due to treatment with topical chemotherapeutic agents, and the absence of mandatory histological reporting for cutaneous SCC. Furthermore, histological features such as primary tumour depth of invasion, grade, PNI or LVI are not routinely reported for cutaneous SCC, limiting prognostication of salivary gland metastasis from primary cutaneous SCC. Within our study cohort histological reporting did not indicate any cases of primary SCC of the salivary glands.

Statistical analysis was completed with SPSS (Version 26.0, IBM, Somers, USA). Medians and interquartile ranges were used for non-parametric data. Chi-squared (Chi-sq) tests were used to assess disease characteristics. Kaplan Meier analysis and log-rank tests were used to assess univariate factors for survival. Close and clear margins were combined for Kaplan-Meier analysis due to the small number of patients with clear margins. Kaplan Meier analysis and log-rank tests were used to assess univariate factors for survival. Cox regression was used for multivariate analysis. A p-value of 0.05 was statistically significant.

RESULTS

A total of 101 patients were diagnosed with metastatic SCC of the salivary glands. The median age of patients was 84 years (IQR: 71-97 years). Eighty-three (83/101, 72%) patients were male with a median age of 82 years (IQR 70-94 years), with 18 (18/101, 18%) being female with a median age of 91 years (IQR 79-103 years) (p=0.04, Chi-sq). Ninety-three (93/101, 92%) patients were Caucasian, with three (3/101, 3%) being Māori and five (5/101, 5%) other European. Ninety-five (95/101, 94%) tumours occurred in the parotid gland, with six (6/101, 6%) occurring in the submandibular gland. Of the patients with SCC of the submandibular gland three (3/6, 50%) of these patients were female, and two (2/6, 33%) were Māori, with a median age of 63 years (IQR = 59-68 years), which was statistically younger (p=0.001) than patients with SCC of the parotid gland (median = 83 years, IQR = 83-86 years).

Eleven (11/101, 11%) patients underwent surgery alone, with six (6/101, 6%) patients receiving adjuvant chemoradiation therapy, and 84 (84/101, 83%) patients receiving adjuvant radiation therapy. Patients who underwent parotidectomy but did not undergo neck dissection, were treated with adjuvant radiation therapy, none had recurrence. Seventy-five percent (15/20) of patients who did not undergo neck dissection were misdiagnosed on fine needle aspirate, and were cN0. Histologically the majority of patients had positive cervical lymph nodes (54/101, 53%). Occult nodal disease was identified in 28 (28/101, 28%) patients. Twenty-eight (28/101, 28%) patients had extranodal extension (ENE), while 15 (15%) and 28 (28%) patients were positive for lymphovascular infiltration (LVI) and perineural invasion (PNI), respectively. For patients with submandibular SCC, six (6/6, 100%) had neck dissection with four (4/6, 67%) having positive cervical lymph nodes, with two (2/6, 33%) patients having ENE and PNI, respectively.

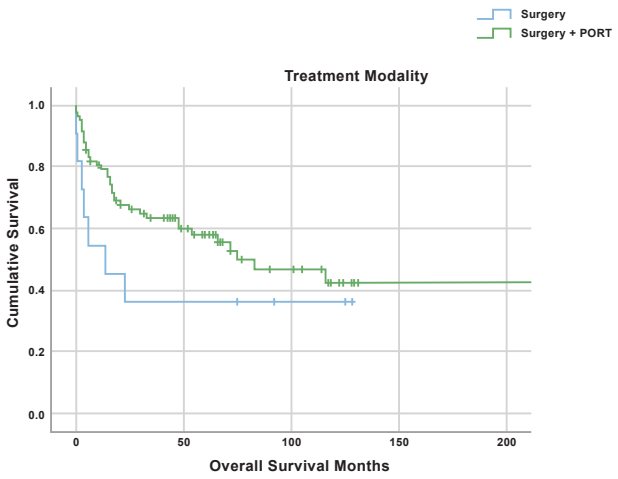
Involved margins were found in 51 (51/101, 51%) patients, 41 (41/101, 41%) patients had close margins and nine (9/101, 9%) had clear margins. Of the patients with involved margins 40 (40/51, 78%) had adjuvant radiation therapy and four (4/51, eight%) had adjuvant chemoradiation therapy. Of patients with involved margins 40 (40/51, 78%) had neck dissection, with 28 (28/51, 55%) having positive nodal disease and 15 (15/28, 54%) having ENE.

Eight (8/101, 8%) patients had recurrence. Of patients with recurrence, five (7/8, 88%) had involved margins, five (5/8, 63%) had PNI and four (4/8, 50%) had ENE and nodal positivity, respectively.

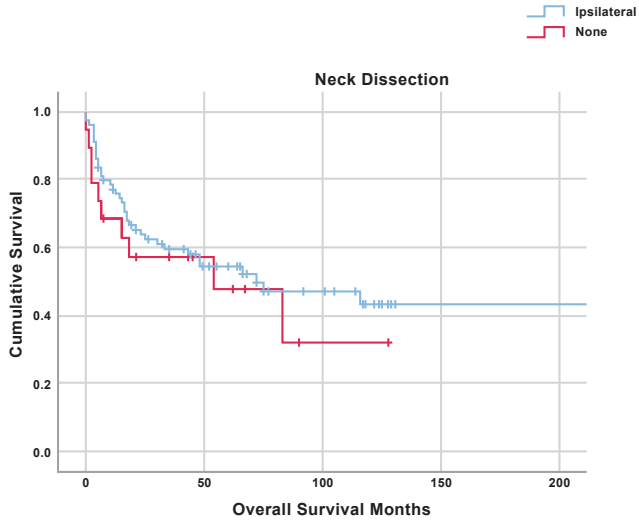
The median time of survival for all patients was 35 months (IQR = 9-68 months), this was reduced in patients with recurrence (25 months, IQR 4-45 months), but was not statistically significant (p=0.24). While patients had an overall five-year survival of 53%. Parotid gland SCC median survival was 32 months (IQR = 19-48 months) compared to the submandibular gland of 44 months (IQR = 39-114), but this was not statistically significant (p=0.16, Chi-sq).

Kaplan-Meier analysis showed overall survival was reduced in patients with cervical metastasis (p=0.04) ***(Graph 4)***, LVI (p<0.001) ***(Graph 6)*** and PNI (p<0.001) ***(Graph 7)***. Survival benefit was found in patients treated with adjuvant radiation therapy ***(Graph 1)***. No statistically significant differences were identified for margins, neck dissection or ENE ***(Graphs 2-3, 5)***.

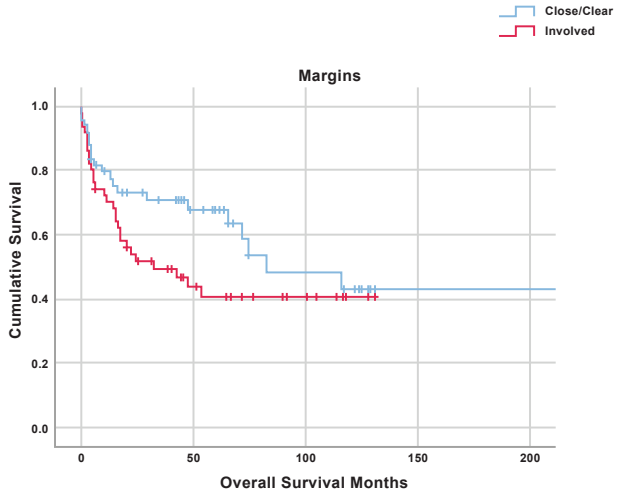
Cox regression for overall survival showed worse outcomes for patients with PNI (HR = 2.5, p=<0.01) and LVI (HR = 2.3, p=0.04), but not ENE (HR = 1.0, p=0.9), margins (involved HR = 1.1 p=0.3; close HR = 1.2 p=0. 8), or cervical metastasis (HR = 1.1, p=0.7). For disease recurrence only PNI was statistically significant (HR 2.1, p=0.03), with margins (involved HR = 0.8, p=0.6; close = 0.58, p=0.1), ENE (HR = 1.1, p=0.7) LVI (HR = 1.3, p=0.5), and nodal positivity (HR = 1.1, p=0.8) not reaching significance. While for cervical node metastasis PNI (HR 1.9, p=0.04) was the only factor statistically significant.



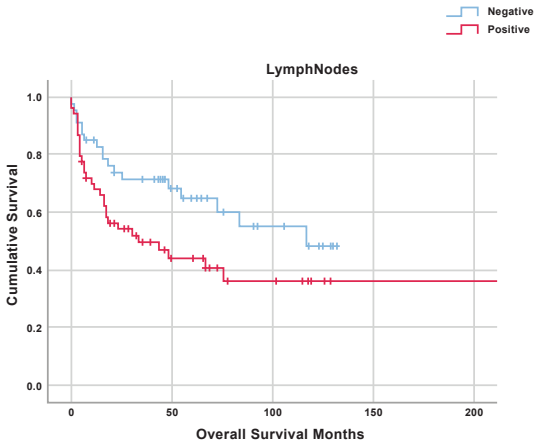
Graph 1
Treatment modality Kaplan-Meier survival. Surgery median survival 14 months (IQR = 3-83 and surgery with radiation therapy median survival 75 months (IQR = 20-130 months). (p=0.02).



Graph 2
Neck dissection Kaplan-Meier survival. Ipsilateral neck dissection median survival 35 months (IQR = 11-72 months) and no neck dissection median survival 21 months (IQR = 5-58) (p=0.33).

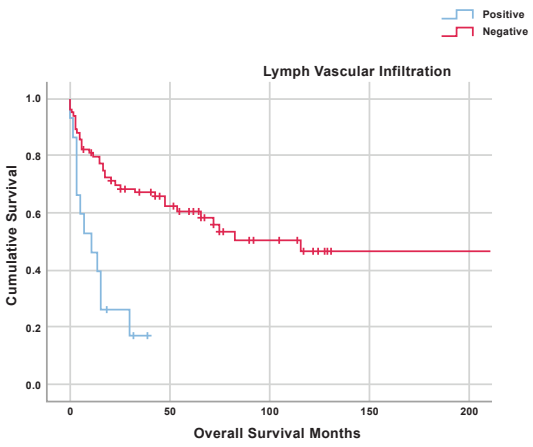


Graph 3
Margins Kaplan-Meier survival. Involved margin median survival was 23 months (IQR = 7-65 months) with close/clear margins having a median survival of 83 months (IQR = 29-136 months) (p=0.12).



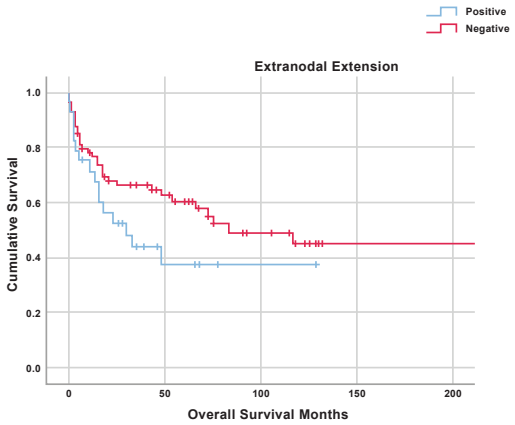
Graph 4

Cervical lymph node positivity Kaplan-Meier survival. Node positive median survival 22 months (IQR = 5-65) vs. node negative median survival 46 months (IQR = 15-83) (p=0.04).



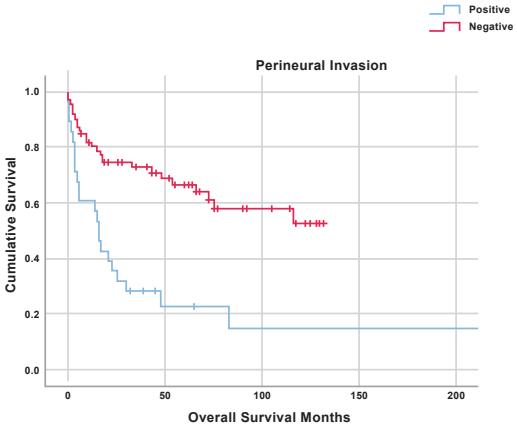
Graph 6

Lymphovascular infiltration (LVI) positivity Kaplan-Meier survival. LVI positive median survival 11 months (IQR = 4 -19 months), vs LVI negative median survival 45 months (IQR = 14-75) (p=<0.001).



Graph 5

Extranodal extension (ENE) positivity Kaplan-Meier survival. ENE positive median survival 24 months (IQR = 6-47 months) vs extranodal extension negative median survival 44 months (IQR = 11-75 months) (p=0.11).



Graph 7

Perineural invasion (PNI) positivity Kaplan-Meier survival. PNI positive median survival 16 months (IQR = 4-35 months), vs PNI negative median survival 46 months (IQR = 15-75) (p=<0.001).

DISCUSSION

Consistent with previous findings, metastatic SCC of the salivary glands occurred predominantly in older Caucasian males within the parotid gland.[7,8,16,19,20] The majority of patients were treated with surgery involving a neck dissection and adjuvant radiation therapy. Occult nodal disease was identified in 28% of patients, and the majority (53%) of patients had positive cervical nodes, with high rates of ENE (28%). Metastatic SCC of the salivary glands demonstrated high rates of LVI (15%) and PNI (28%), but low rates (8%) of recurrence compared to other studies.[2,3,6,8,9] Overall, there was a median survival of 35 months (IQR = 9-68 months) and five-year absolute survival of 53%, consistent with existing literature.[8,20–22] Overall survival was improved in patients without LVI or PNI, with PNI also implicated in recurrence ***(Graphs 4, 6-7)***. Patients had improved outcomes if treated with adjuvant radiation therapy, but margins, staging and neck dissection were not found to influence overall survival ***(Graphs 2-3, 5)***.

Involved margins were found in 51% of patients (51/101) with no differences in survival found compared to close or clear margins. Positive margin rates of 16-29% have been found in the literature related to the presence of LVI, PNI and proximity to the facial nerve.[16,19] However, definitions of margins vary significantly, making comparison difficult.[17,23] Principles of oncological resection in parotid tumours are compromised by preservation of the facial nerve.[19] Radical parotidectomy with facial nerve transection is indicated in patients with pre-operative facial nerve palsy, but in the absence of this, guidelines recommend the preservation of the facial nerve, often resulting in close or involved margins.[19,24] Our research supports the stance of preserving the facial nerve, as the presence of close or involved margins did not reduce overall survival. We hypothesis marginal status doesn't influence overall survival due to disease encapsulation within the node (72%) and high rates of adjuvant radiation therapy, which in our study improved overall survival and is supported by the wider literature.[19,20,25]

Within our study the majority of patients had positive cervical lymph nodes (53%), with a rate of occult nodal disease (28%), which is consistent with previous findings (20-30%, and 16-35%, respectively).[8,22,26] Metastasis to the cervical lymph nodes has been associated with PNI and LVI, which were highly prevalent in our patient cohort. Other factors such as differentiation, tumour size (>2 cm) and an immunocompromised host have been shown to increase the risk of nodal metastasis.[20,21] Given the high rates of cervical metastasis authors and guidelines have recommend selective neck dissection for all patients with salivary gland SCC.[13,22,27] Interestingly neck dissection within our study was not statistically significant regarding overall survival, however few patients were treated with primary radiation therapy (20%). Patients who underwent primary radiation therapy were often misdiagnosed initially (75%) and cN0. Following MDM, primary RT was undertaken based on patient preference. Given the absence of recurrence, and improved overall in patients treated with neck dissection, primary RT may provide appropriate management of the cN0 neck, however further research is required.

Within our study 8% of patients had disease recurrence, lower than what has been reported (20-60%).[8,20,25,28] Recurrences commonly occur within the parotid bed, in skin pre-auricularly or in the ipsilateral neck.[9,20] Overall survival is reduced in patients with recurrence as seen within our study, however this was not statistically significant. Recurrence rates have been associated with PNI as found in our study, along with positive margins, increased nodal burden, ENE, staging and differentiation.[8,28] Our low rates of recurrence maybe associated with population factors such as age of diagnosis and death from other factors or sample size.

SCC of the submandibular gland is a rare entity. In our study patients with SCC of the submandibular gland were younger and more likely to be Māori compared to patients with parotid SCC. This potentially correlates with oral metastatic SCC to the submandibular gland, but no primary lesions were identified. Case reports of SCC of the submandibular gland have high rates of cervical metastasis and ENE as found in our study.[29,30] Five-year disease specific survival for submandibular SCC is 25-30%, with high rates of recurrence of up to 60%, however with in our study, no cases of recurrence were found.[29,30] Given the aggressiveness of the tumour, authors have advocated for surgery, adjuvant radiation and chemotherapy.[13,27,29,30]

Summarising, these findings, this research demonstrates the demographics of metastatic salivary gland SCC in a New Zealand hospital. Marginal status should preserve the facial nerve if clinically able, and adjuvant radiation therapy is indicated, especially for patients with PNI and LVI. Neck dissection was not found to improve survival within our study cohort, but has categorically been shown to improve patient survival previously, and is currently indicated by head and neck cancer guidelines.[12,13,22,27] However, interestingly within our study cohort primary radiation therapy of the neck in patients who were cN0 did not have reduced overall survival and no patients developed recurrence. Therefore, primary radiation therapy to the neck may provide an alternative treatment modality, however further research is required.

Conflict of interest statement

The author(s) declare that there is no conflict of interest. The author(s) received no financial support for the research, authorship, and/ or publication of this article.

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