Survival outcomes of perineural spread in head and neck cutaneous squamous cell carcinoma

Daniel Phung, Navid Ahmadi, Ruta Gupta, Jonathan R. Clark, James Wykes, Sydney Ch’ng, Michael S. Elliott, Carsten E. Palme, Kerwin Shannon, Raymond Wu, Jenny H. Lee and Tsu-Hui (Hubert) Low

*Department of Head and Neck Surgery, Chris O’Brien Lifehouse, Sydney, New South Wales, Australia
†Sydney Medical School, The Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia
‡Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia
§The Royal Prince Alfred Institute of Academic Surgery, Sydney Local Health District, Sydney, New South Wales, Australia
¶Department of Head and Neck Surgery, Wollongong Hospital, New South Wales, Australia
∥Department of Radiation Oncology, Chris O’Brien Lifehouse, Sydney, New South Wales, Australia
**Department of Medical Oncology, Chris O’Brien Lifehouse, Sydney, New South Wales, Australia and
††Faculty of Medicine and Health Sciences, Macquarie University, Sydney, New South Wales, Australia

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Correspondence
Dr Tsu-Hui (Hubert) Low, Chris O’Brien Lifehouse, 119-143 Missenden Rd, Camperdown NSW 2050, Australia.
Email: hubert.low@lh.org.au

D. Phung MBBS, N. Ahmadi MBBS, MPh; R. Gupta MBBS, MD, FRCPA; J. R. Clark MBBS, FRACS; J. Wykes MBBS, FRACS; S. Ch’ng MBBS, FRACS; M. S. Elliott MBBS, FRACS; C. E. Palme MBBS, FRACS; K. Shannon MBBS, FRACS; R. Wu MBBS, FRANZCR; J. H. Lee MBBS, FRACP; T.-H. Low MBBS, FRACS.

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Abstract

Aim: To present an institution’s experience and survival outcomes for patients with head and neck cutaneous squamous cell carcinoma (HNcSCC) and perineural spread (PNS).

Method: Retrospective study of patients with HNcSCC and PNS treated between January 2010 and August 2020 from the Sydney Head and Neck Cancer Institute database, Sydney, Australia: a high-volume, tertiary, academic head and neck centre. Patient demographics, primary site, involved cranial nerves, treatment modality, loco-regional failure and survival data were obtained.

Results: Forty-five patients were identified, of which 32 patients were male (71%). Mean age at diagnosis was 68.7 years (range 43–90). Median follow-up was 16.1 months (range 1–107). The trigeminal nerve was most frequently involved (n = 30, 66.6%) followed by facial nerve (n = 13, 28.9%). Most patients underwent surgery followed by radiotherapy (n = 33, 73%) and eight received definitive radiotherapy. The median overall survival (OS) was 4.5 years (95% CI 3.71–5.38), median disease-specific survival 5.1 years (95% CI 4.21–5.97) and median disease-free survival (DFS) was 1.7 years (95% CI 1.11–2.22). The estimated 5-year OS and DFS were 45% and 25%, respectively. Patients treated with surgery and adjuvant radiotherapy with a clear proximal nerve margin had favourable DFS (P = 0.035) and trended towards better OS (P = 0.134) compared with patients with an involved nerve margin. Patients treated surgically with involved proximal nerve margins had similar outcomes compared with patients with treated definitive radiotherapy (HR 0.80, 95% CI 0.29–2.22, P = 0.664).

Conclusion: The likelihood of achieving a clear proximal nerve margin should be a strong consideration in the selection of appropriate patients for primary surgery.
Introduction
Non-melanoma skin cancers account for 80% of new cancer cases every year in Australia with an estimated 570,000 new diagnoses in 2020. Sun-exposed areas are at particular risk of developing skin cancers and as such, the incidence is often highest in the head and neck. Several pathologic features are associated with a poor prognosis of head and neck cutaneous squamous cell carcinoma (HNCSCC), one of which is perineural invasion (PNI) and is present in 2.4–14% of cases.1–3

The presence of perineural invasion in HNCSCC is associated with worse disease-specific survival and overall survival, and is an independent predictor of developing nodal metastases.6,7 As a result, patients with HNCSCC with multifocal or large-nerve PNI are generally treated more aggressively, with the aim of a complete local resection followed by adjuvant radiotherapy.8 Historically, there has been confusion regarding the pathway of tumour spread through neural tissue. Within the neural microenvironment, there is a complex and reciprocal interaction between tumour cells, stromal cells and neural cells that influence PNI.9

Most patients (70%) with histologically-confirmed PNI are asymptomatic with no sensory or motor deficit; hence, termed incidental PNI (iPNI). This must be contrasted with perineural spread (PNS) which presents as either MRI evidence of named nerve disease or clinically apparent cranial neuropathy.11 It is important to distinguish PNS from histologic PNI as it is associated with significantly poorer outcomes; 5-year local and regional control of iPNI was 72% versus 50% and 90% versus 54–57% and 70–72% versus 50–51%, respectively.3,12

Apart from the studies by Panizza et al.,15–16,22 there is limited literature regarding the optimal management and clinical outcomes of this particularly high-risk subset of patients with HNCSCC and PNS. In this retrospective review, we present our institution’s experience with HNCSCC with PNS.

Methods
Local ethics approval was obtained from the relevant institutional human research ethics committee (HREC/16/RPAH/510). We conducted a retrospective study of patients with HNCSCC with clinical and radiologic evidence of perineural spread treated between January 2010 and August 2020 identified from the Sydney Head and Neck Cancer Institute (SHNCI) database, Sydney, Australia, a high-volume, tertiary, academic head and neck centre. Patient demographics, primary site of SCC, age at PNS diagnosis, involved cranial nerves, primary and adjuvant treatment, loco-regional failure and survival data were obtained. We utilized the zonal classification for large nerve perineural involvement in head and neck malignancy,17,18 which divides PNS into peripheral (Zone 1), central/skull base (Zone 2) and cisternal (Zone 3). For those with incomplete data, files were retrieved from either hospital medical records or surgeon notes.

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM, Chicago). Survival statistics were calculated using the Kaplan–Meier method.19 Disease-free survival (DFS) calculated from the date of treatment to the date of first disease recurrence, or to the date of death or last follow-up if there was no disease recurrence. Disease-specific survival (DSS) was calculated from the date of treatment to the date of death from the disease or last follow-up. Overall survival (OS) was calculated from the date of treatment to the date of death or last follow-up if patients are alive. For non-surgical patients, survival was calculated from the date of commencement of radiotherapy or immunotherapy to the date of death or last follow-up. Differences in survival were calculated using the log-rank test and hazard ratios calculated using the Cox proportional hazards model.20

Results
Clinicopathological characteristics
A total of 45 patients with HNCSCC and PNS were included in this study. The clinicopathological data are summarized in Table 1. The mean age was 68.7 years (range 43–90) and 71% of patients were male. The most frequent primary sites were cheek, forehead and nose. Four patients had unknown primary sites with a history of multiple HNCSCC and actinic keratosis. The trigeminal nerve was most frequently involved (n = 30, 67%), of which the maxillary division was the most common (17/30 patients, 56.6%). The facial nerve alone was involved in 13 patients (29%), with two patients presenting with both trigeminal and facial nerve involvement (4%). The median follow-up was 16.1 months (range 1–107).

The majority of patients underwent surgery (n = 33, 73%), all of whom received adjuvant radiotherapy with a dose range between 60 and 66 Grey in 30 fractions. Eight patients received definitive radiotherapy alone and four patients were treated with radiation and hypoglossal recurrent.
immunotherapy, of which two patients declined surgery and radiotherapy, and two were considered not suitable for surgery or radiotherapy due to advanced zone three disease affecting cranial nerves V, VII, X and XII and brainstem involvement.

Survival outcomes and patterns of relapse

Of the 45 patients, 34 patients were alive at the time of data collection. There were 23 patients (51%) who developed local recurrence, of whom 18 (78%) had intracranial recurrence. Five patients (11%) developed regional recurrence and two patients (4%) developed distant disease. The median overall survival (OS) was 4.5 years (95% CI 3.71–5.38), median disease-specific survival (DSS) was 5.1 years (95% CI 4.21–5.97) and median disease-free survival (DFS) was 1.7 years (95% CI 1.11–2.22). The estimated 5-year OS and DFS were 45% and 26%, respectively (Fig. 1).

Zonal disease and proximal (central) nerve margin

The extent of perineural disease is documented in Table 2. Of the 33 patients who underwent surgical resection, 20 had trigeminal nerve involvement, 12 had facial nerve involvement and one had both facial and trigeminal nerve involvement. Clear margins were achieved in 13 patients (76%) with Zone 1 disease compared with five patients (33%) with Zone 2 disease (P < 0.001, chi-squared test).

Table 2 Zonal extent of perineural disease in patients with PNS

| Zone | Surgical patients | Non-surgical patients | Total |
|------|-------------------|-----------------------|-------|
|      | Proximal nerve margin status |                      |       |
|      | Clear             | Involved              |       |
| 1    | 13 (72.2%)        | 4 (22.2%)             | 1 (5.6%) | 18 |
| 2    | 5 (23.8%)         | 10 (47.6%)            | 6 (28.6%) | 21 |
| 3    | 0 (0%)            | 1 (16.7%)             | 5 (83.3%) | 6 |

Of the surgical patients with Zone 1 disease, 40% of patients (n = 2) with facial nerve involvement had a positive nerve margin compared with 17% of patients (n = 2) with trigeminal nerve involvement. Of note, the two patients who had positive central trigeminal nerve margins also had significant locally-invasive soft tissue disease in addition to large nerve perineural disease and positive soft tissue margins. One patient had orbital extension of tumour with ophthalmic nerve PNS and the other had a large mass within the maxillary sinus and infraorbital nerve PNS, extending into the foramen rotundum.

Amongst patients with Zone 2 disease, 71% patients (n = 5) with facial nerve involvement had a positive nerve margin compared with 62% patients (n = 5) with trigeminal nerve involvement. Most patients with Zone 3 disease in this series were not offered surgical treatment, except one patient, in whom a clear nerve margin was not achieved.

A clear proximal nerve resection margin predicted improved DFS

Of the 33 patients treated with surgery and adjuvant radiotherapy, 18 patients achieved a clear proximal nerve margin. Patients with a clear proximal nerve margin had favourable 2 and 5-year DFS compared with patients with involved proximal nerve margins (81% vs. 24% and 49% vs. 16%, P = 0.035) and trended towards better OS (2-year 90% vs. 52% and 5-year 77% vs. 77% respectively, P = 0.134). Surgery with involved proximal nerve margins did not confer a significant improvement in survival compared with patients treated with definitive radiation at 2 and 5 years (DFS 24% vs. 34% and 16% vs. 0% respectively, P = 0.625). Patients with clear proximal nerve margins had better outcomes compared with those treated with definitive radiotherapy with a 2 and 5-year DFS of 81% and 49% compared with 34% and 0% (P = 0.009), as well as 2 and 5-year OS of 90% and 52% compared with 54% and 0% (P = 0.032) (Fig. 2).
Survival outcomes by zonal distributions and named cranial nerve

The zonal distributions for this cohort were 18, 21 and 6 patients for Zones 1, 2 and 3, respectively. There was no significant difference in DFS for patients with Zone 1 disease (2 and 5-year DFS 60% and 43%), compared with Zone 2 (43% and 21%) and Zone 3 (30% and 0%). Likewise, no significant difference in DSS was observed (2 and 5-year DSS for Zone 1 93% and 56% respectively, Zone 2 69% and 60%, respectively and Zone 3 67% and 0% respectively). There was no significant difference in OS when comparing Zone 1 disease to Zone 2 and Zone 3 disease (2 and 5-year OS Zone 1 93% and 56%; zone 2 65% and 49%; Zone 3 67% and 0% P = 0.201) (Fig. 3). Although there was no statistical significance found a trend was observed with respect to reduced outcomes in Zone 2 and Zone 3 compared with Zone 1.

The Kaplan–Meier’s survival analysis showed no difference in OS and DFS for patients with trigeminal versus facial nerve involvement (P = 0.859 and P = 0.317, respectively) (Fig. 4).

Discussion

In this retrospective review of 45 patients with HNcSCC and PNS, we have demonstrated that clear proximal nerve margins following surgery is a predictor of significantly improved DFS and that Zone 2 disease is associated with lower rate of a clear proximal margin, compared to Zone 1 disease. The estimated 5-year DFS and OS in this series were 26% and 45% for all patients. Surgery followed by adjuvant radiotherapy was associated with a superior outcome to definitive radiotherapy and remains the standard of care at our centre. Locoregional failure was more frequent than distant metastatic
disease, supporting previous arguments that appropriate surgical resection, with acceptable morbidity, followed by radiotherapy to the primary site and local disease may confer favourable survival outcomes.\textsuperscript{14,21}

In a recent systematic review, Karia \textit{et al.} found PNS to be associated with a higher overall risk of local recurrence compared with incidental histological PNI (37\% vs. 17\%, \(P < 0.001\)).\textsuperscript{21} There was no significant difference in risk of nodal and distant metastases. Furthermore, patients presenting with PNS had worse mean 5-year recurrence-free-survival and disease-specific survival compared with those with iPNI (RFS 76\% vs. 61\%; \(P = 0.009\); DSS, 88\% vs. 70\%; \(P = 0.002\)).

Similar Australian series have described outcomes from HNcSCC with PNS treated with surgery and adjuvant radiotherapy. In their cohort, Panizza \textit{et al.}\textsuperscript{14} reported survival outcomes in a cohort of 21 patients who had surgical resection followed by adjuvant radiotherapy for cSCC with PNS. The 5-year OS was 67.9\%, 5-year DSS 64.3\% and 5-year RFS 58.6\% in this group. Warren \textit{et al.}\textsuperscript{16} examined 50 patients who had the same treatment for PNS with reported 5-year OS of 64\%, 5-year DSS of 75\% and RFS of 62\%. Our study found, in those who underwent surgery and radiotherapy, a higher proportion of recurrences centrally, in contrast to the Panizza and Warren series where the majority of failures occurred peripherally\textsuperscript{14,16,22} as small subcutaneous deposits. This may be explained by surgical resection planning where a clear central nerve margin was paramount and more often achieved compared with our group.

Previous studies have demonstrated that a lower zone of PNS is associated with improved survival. Warren \textit{et al.}\textsuperscript{22} in their series of 120 cases, reported 5-year DSS for Zone 1 at 84\%, Zone 2 at 63\% and Zone 3 at 16\% compared with our data which found DSS for Zone 1 at 56\%, Zone 2 at 60\% and Zone 3 at 0\%. This observation of worse outcomes within our cohort is likely due to the small number of patients, coupled with pooling of different treatment modalities.

Our series reported that trigeminal and facial nerves were the most commonly involved named nerves, consistent with the literature.\textsuperscript{5} There was no difference in survival between facial and trigeminal nerve involvement. Patients with Zone 1 disease in this study were likely to achieve clear resection margins, especially the proximal nerve margin (72.2\%). In our series of patients with Zone 1 facial nerve disease, 40\% had a positive central nerve margin which is likely explained by the cohort spanning over 10 years where earlier in the decade, patients with disease extending into the mastoid segment of the facial nerve were treated with radiotherapy so clear nerve margins were not aggressively chased. In more recent years, there has been a paradigm shift towards surgery where a clear proximal nerve margin is sought when appropriate. This was achieved through multidisciplinary pre-operative work-up, thorough evaluation of MRI with a dedicated head and neck radiologist and careful surgical planning for these patients.

In this series, patients treated with definitive radiotherapy demonstrated worse outcomes than those who underwent primary surgery. This outcome is likely in part due to this selection bias as the eight patients who received definitive radiotherapy had disease considered non-resectable at a multidisciplinary meeting by the surgical team, the common reasons being intracranial disease extent or multi-nerve disease whereby clear surgical margins were not deemed possible.

Our study is limited by its retrospective nature spanning over 10 years, small patient numbers, in addition to heterogenous treatment modalities, and pooled surgical approaches by several different surgeons. Specifically, the degree to which skull-base disease was chased varied amongst our group depending on familiarity with anterior and lateral skull-base techniques. The relatively short median follow-up (16.1 months) should also be taken into account as a limitation of our study.

\textbf{Conclusion}

Our data suggests that perineural spread of cutaneous head and neck SCC managed with surgical resection aiming for clear proximal nerve margin and adjuvant radiotherapy may be associated
with improved survival outcomes in carefully selected patients. The prognostic significance of a clear proximal nerve margin should be recognized in the consideration for patients to undergo comprehensive primary surgery by the appropriate team, with acceptable morbidity.

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Conflict of interest

None declared.

Author contributions

Daniel Phung: Data curation; investigation; writing – original draft; writing – review and editing. Navid Ahmadi: Writing – original draft; writing – review and editing. Ruta Gupta: Writing – review and editing. Jonathan R. Clark: Writing – review and editing. James Wykes: Writing – review and editing. Kerwin Shannon: Writing – review and editing. Michael S. Elliott: Writing – review and editing. Sydney Ch’ng: Writing – review and editing. Carsten E. Palme: Writing – review and editing. Raymond Wu: Writing – review and editing. Jenny H. Lee: Formal analysis; writing – review and editing. Tsu-Hui (Hubert) Low: Conceptualization; data curation; formal analysis; methodology; supervision; writing – review and editing.

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