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ORIGINAL ARTICLE

Facial nerve perineural spread from cutaneous squamous cell carcinoma of the head and neck: A single institution analysis of epidemiology, treatment, survival outcomes, and prognostic factors

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Abstract

Background: This study aimed to examine patients with facial nerve (VII) perineural spread (PNS) from cutaneous squamous cell carcinoma of the head and neck.

Methods: Retrospective analysis of patients managed by an Australian tertiary center between 2000 and 2019.

Results: Seventy three patients were included. Most presented with recurrent disease (89.0%) and simultaneous trigeminal nerve (V) involvement (67.1%). Of the 55 patients (75.3%) who received curative intent treatment, 48 received surgery plus/minus post-operative radiotherapy. In these patients, 5-year disease-free survival, disease-specific survival, and overall survival was 50.7%, 68.7%, and 58.1%, respectively. Pathological nodal disease, involved margins, increasing VII zonal extent, and concurrent zone 2 V PNS significantly worsened outcomes.

Conclusion: High rates of recurrent disease reflects the importance of adequate treatment of the primary. Surgery and post-operative radiotherapy remains the mainstay treatment. Outcomes are improved in early-stage disease and with clear surgical margins, reinforcing the need for prompt diagnosis and intervention.

KEYWORDS

cutaneous squamous cell carcinoma, facial nerve, perineural spread, radiation therapy, skull base surgery

1 | INTRODUCTION

Perineural spread (PNS) is a unique form of tumor metastasis, representing an advanced and potentially lethal consequence of head and neck malignancies. PNS in the head and neck can occur from tumors of cutaneous, mucosal, or salivary gland origin.[1] However, in Queensland (Australia), where keratinocyte cancer (KC) rates are one of the highest in the world, the experience is largely with cutaneous squamous cell carcinoma (cSCC).

Much of the confusion in the literature lies in the definitions of perineural invasion (PNI) and PNS. Incidental PNI is a histopathological feature detected in asymptomatic patients with a primary skin cancer.[1] In comparison, PNS or clinical PNI refers to the spread of cancer along larger caliber nerves away from the primary tumor, primarily in a retrograde direction toward the brain stem with eventual central failure if left untreated. In the head and neck, the trigeminal nerve (V; ophthalmic [V_1], maxillary [V_2], mandibular [V_3] branches) and facial nerve (VII) are the most commonly involved, with the latter being involved in 25%–35% of cases.[2–6]

PNS manifests radiologically, on dedicated magnetic resonance imaging (MRI), and/or clinically, with focal cranial neuropathy, often months to years after the primary cancer was treated.[1,7,8] As such, PNS can be easily misinterpreted as a benign cranial neuropathy such as trigeminal neuralgia or Bell's palsy, resulting in diagnostic and treatment delays, which may be costly to the patient.

To date, there have been no published studies that have exclusively examined VII PNS from cSCC of the head and neck (cSCCHN). Instead, the literature on head and neck PNS is comprised of articles that group involved nerves. These also often pool histopathological subtypes and include incidental PNI in their cohorts.

This report aims to describe our institution's experience of managing patients with VII PNS from cSCCHN, analyzing epidemiology, treatment, survival outcomes, and prognostic factors. Through this, we aim to further the reader's understanding and awareness of VII PNS from cSCCHN, which can secondarily improve outcomes through earlier detection and treatment of disease.

2 | MATERIALS AND METHODS

2.1 | Patient population

A retrospective review was conducted of consecutive patients diagnosed with VII PNS from cSCCHN and managed by the Head and Neck Tumor Board at the Princess Alexandra Hospital, Brisbane, Australia, between 2000 and 2019. Ethics approval was obtained from the Metro South Human Research Ethics Committee prior to commencing (LNR/2019/QMS/50709). Data was largely extracted from a prospectively maintained database of patients with VII PNS at our institution. Patient charts were also analyzed to ensure data was accurately recorded and to collect any missing information.

Inclusion required patients to either have pathological evidence of VII PNS or, if managed non-operatively, convincing clinical and/or radiological features consistent with VII PNS. Patients with PNS from tumors of non-cSCC histopathology were excluded. Patients who had tumors externally compressing or directly infiltrating VII (intra-tumoral PNI) *without* evidence of spread along the nerve away from the tumor mass were also excluded. Only patients who underwent curative intent surgery with or without post-operative radiotherapy (PORT) were included in the prognostic factor analysis.

Key demographical and clinical information was recorded for each patient, including age at diagnosis, gender, immune status, and presenting signs and symptoms.

2.2 | Disease extent

With the assistance of the head and neck radiologist (M.G.), all imaging at time of VII PNS diagnosis was analyzed. As standard at our institution, all patients underwent skull base 3T magnetic resonance (MR) neurography to evaluate PNS, as previously described.[9] Alternatively, contrast-enhanced computed tomography (CT) was performed if MRI was contraindicated. In addition, a whole-body positron emission tomography (PET) or CT was used to assess for regional and distant metastatic disease.

Data was collected on nerve(s) involved, extent of PNS, and presence of nodal disease. When images were not available to review, radiological reports were used as a surrogate. With this information, patients were retrospectively staged according to both the 8th edition American Joint Committee on Cancer (AJCC) system and the Williams et al. zonal classification.[10,11]

2.3 | Treatment

All patients were assessed through the institution's Head and Neck Tumor Board to determine best management and, if applicable, plan surgical intervention. Our surgical approach to PNS from cSCCHN was based on the nerve(s) involved and zonal extent of disease, as described previously.[12] Following oncological principles, the goal of surgery was to remove the involved nerve(s), its branches, and any associated tumor mass *en bloc* with clear margins. As the main aim was to halt the central progression of disease, we focused on achieving a clear central neural margin of at least 5 mm, routinely with frozen section control.

Curative intent surgery was offered to all patients with radiological zone 1 and 2 disease. Patients with radiological zone 3 disease were treated on a case-by-case basis, and only considered surgical candidates if resection could be achieved without dural breach, to avoid risk of leptomeningeal spread and drop metastases. Palliative surgery was considered in cases of advanced and unresectable disease associated with severe debilitating pain or extensive ulceration, for the purposes of improving symptom management and quality of life.

Given the low rate of nodal metastasis associated with PNS from cSCCHN seen in previous studies, neck dissection was performed for clinically positive nodal disease or if required to facilitate reconstruction.[6,12]

All patients treated with surgery were offered PORT, unless previous radiotherapy was given with no scope for further dosing. Curative or palliative intent radiotherapy was offered to patients who were medically unfit for surgery, refused surgery, or if their disease was deemed unresectable.

Data was collected on treatment intent (curative or palliative), operative details, and adjuvant therapy. Histopathology reports were reviewed to record nerve(s) involved and size, zonal extent of PNS, differentiation, lymphovascular invasion (LVI), surgical margin status, and pathological nodal disease.

2.4 | Survival outcomes analysis

Post-treatment, patients were followed-up clinically and radiologically for recurrence. Patients were seen 3 months post-treatment with a baseline MRI (if not contraindicated) and then six monthly with an MR neurogram until year three. Patients were then reviewed clinically six monthly with annual MR scanning until 5 years post-treatment. If disease-free at this point, patients were considered cured and offered discharge from the clinic. Patients may have also decided to continue annual scanning beyond this point.

The primary end points of interest were disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) at 2- and 5-years after treatment, calculated using Kaplan–Meier survival analysis. Thus, we recorded time to recurrence(s) and location (local [central and/or peripheral], regional, and/or distant), time to death and cause, and time to last contact if recurrence or death had not occurred.

2.5 | Prognostic factor analysis

For patients treated with curative intent surgery, Kaplan–Meier analysis with log-rank testing and univariate Cox regression was performed for prognostic factors for all outcomes of interest. Variables analyzed included age, gender, immunosuppression, nerve(s) involved, zonal extent, involved nerve diameter, pathological nodal disease, LVI, differentiation, and surgical margin status.

Multiple Cox regression was subsequently performed. Variables with a p value <0.2 in univariate Cox analysis and/or of known clinical significance (i.e., age, immunosuppression) were shortlisted. The proportional hazards assumption was checked for each variable through inspection of survival curves and multicollinearity was assessed. The remaining variables were included in the preliminary Cox model, and through backward stepwise elimination based on likelihood ratios (entry p value <0.2, retention p value <0.1), the final Cox model was generated.

Results were considered statistically significant at a p-value of <0.05. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Patient population

Ninety nine patients with clinical and/or radiological findings consistent with VII PNS were assessed for enrolment. Nine cases managed surgically, including eight cSCC cases, had a large tumor mass and radiological findings consistent with concurrent VII PNS, but were excluded as there was a lack of pathological evidence of VII PNS spreading away from the tumor mass (a false positive rate of 9.1% for PNS). Of note, 44.4% of these patients ($n = 4/9$) did not have a pre-operative VII palsy. A further 17 patients were excluded due to non-cSCC histopathology, including 12 primary parotid malignancies. The remaining 73 cases of VII PNS from cSCCHN were analyzed for epidemiology and survival outcomes. Prognostic factor analysis was performed on 48 of these patients who underwent curative intent surgery. Refer to Figure 1 for the full flow diagram to determine the cohorts examined at each aspect of the study.

The average age at diagnosis was 67.6 years old (range, 37–88 years), with the majority being male (90.4%). Seven patients (9.6%) were immunosuppressed.

3.2 | Perineural spread characteristics

3.2.1 | Clinical features

Table 1 summarizes the clinical features of patients with VII PNS at time of diagnosis. The mean duration of

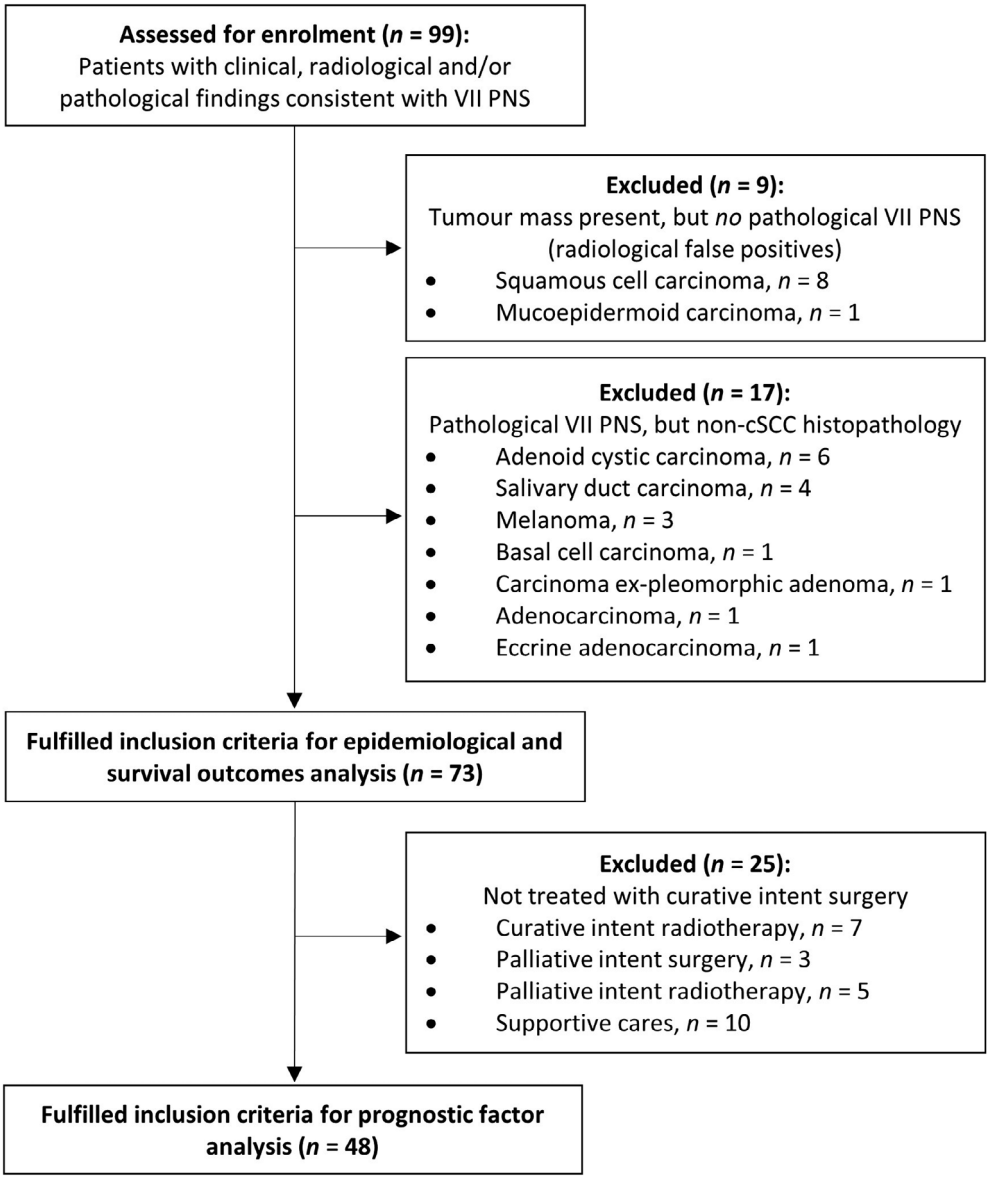

FIGURE 1 Flow chart demonstrating the study cohort. Abbreviations: VII PNS, facial nerve perineural spread; cSCC, cutaneous squamous cell carcinoma

symptoms to diagnosis of VII PNS was 8.9 months (median, 6 months; range, 0.5–48 months). 95.9% presented with unilateral VII palsy, with most patients (45.2%) experiencing a slowly progressive complete (House Brackmann [HB] grade VI) palsy, as opposed to a reported sudden onset (8.2%).[13] 41.1% of patients had a partial (HB II-V) palsy, mostly affecting multiple branches with some preserved power (27.1%). Palsy of a single VII branch, indicating early disease, was uncommon (8.6%). Three patients (4.1%) had completely intact VII function (HB I) at presentation, with two cases eventuating as pathological zone 1 disease, and one case as zone 3 disease.

Most patients ($n = 48$, 65.8%) also presented with progressive neuropathic symptoms from concurrent V or other cranial nerve involvement, including numbness (50.7%), dysesthesia (pain, burning; 38.4%), and paresthesia (pins and needles, formication; 38.4%). In addition, 41.1% presented with a subcutaneous mass, representing either extraneural anterograde extension of cancer along the course of an involved nerve with PNS ($n = 19$, 26.0%), or a metastatic nodal deposit or subcutaneous recurrence ($n = 11$, 15.1%).

Four patients (5.5%) presented with PNS in conjunction with the primary skin cancer. Four patients (5.5%) had no history of any cSCCHN and presented solely with PNS. Fifty three patients (72.6%) had locally recurrent disease leading to VII PNS, where the average time from treatment of the primary to PNS diagnosis was 20.3 months (median, 12 months; range, 1–89 months). In these 61 patients who had local disease (primary or recurrent) as cause for VII PNS, seven (11.5%) had clinical nodal disease, with the distribution by nodal station as follows: parotid or periparotid ($n = 6$, 9.8%), level I ($n = 1$, 1.6%), and level II ($n = 3$, 4.9%).

TABLE 1 Clinical features of perineural spread at diagnosis

Clinical features	No. of patients ($n = 73$)	%
Signs and symptoms		
VII palsy	70	95.9
Pre-existing	1	1.4
Partial	30	41.1
Complete	39	53.4
Sudden	6	8.2
Progressive	33	45.2
Mean duration to diagnosis, months (range)	7.3 (0.25–48)	
Other		
Numbness	37	50.7
Subcutaneous mass	30	41.1
Dysesthesia	28	38.4
Paresthesia	28	38.4
Pain (non-neuropathic)	15	20.5
Trismus	8	11.0
Skin lesion	7	9.6
Headache	1	1.4
Otorrhea	1	1.4
Discharge	1	1.4
Clinical TNM classification (AJCC 8th ed.)		
T		
rTx	5	6.8
rT1	3	4.1
rT2	1	1.4
T3	1	1.4
rT3	20	27.4
T4b	7	9.6
rT4b	36	49.3
N		
N0	54	74.0
N2b	3	4.1
N3b	16	21.9
M		
M0	73	100.0

Abbreviations: AJCC, American Joint Committee on Cancer; VII, facial nerve.

The remaining 12 patients (16.4%) had regionally recurrent disease as the cause of VII PNS. This was in the form of involved parotid lymph nodes with extranodal extension (ENE), including three cases of PNS resulting from recurrences in the parotid bed. A radiological example of this is provided in Figure 2.

3.2.2 | Radiological features

As outlined in Table 2, VII PNS was detected radiologically in the majority ($n = 60$, 82.2%), and was reported negative in 13 (17.8%). For imaging detected VII PNS, disease involved zone 1 in 41.7%, zone 2 in 51.7%, and zone 3 in 6.7%. Of the 10 imaging negative VII PNS cases managed surgically, eight had pathological early zone 1 disease and two had zone 2 disease, including one patient who had contraindications to MRI and had biopsy confirmed zone 2 disease before surgery. Multiple nerve involvement (67.1%) occurred more commonly than VII PNS alone (15.1%), with simultaneous VII and V_3 PNS the most frequent (58.9%), largely via its auriculotemporal branch.

3.3 | Treatment

Fifty five patients (75.3%) in the cohort underwent curative intent treatment. This included those treated with curative surgery ($n = 48$, 65.8%) with or without PORT, and curative radiotherapy alone ($n = 7$, 9.6%), with an average dose of 63 Gray (Gy) (range, 54–70 Gy) in 32 fractions (range, 27–35 fractions). Eight patients (11.0%) were treated with a palliative intent, including three (4.1%) managed with palliative surgery and five (6.8%) with palliative radiotherapy alone, with an average dose of 56 Gy (range, 30–66 Gy) in 27 fractions (range, 10–33 fractions). The remaining 10 patients (13.7%) received supportive cares only.

The operative details for those who had surgical treatment ($n = 51$) are outlined in Table 3. All patients underwent some form of parotidectomy, with most undergoing a radical parotidectomy (80.4%). Temporal bone resection (TBR) was required in 80.4%, most commonly in the form of a lateral TBR (56.9%). Given the high proportion of concurrent V_3 PNS, 66.7% of patients had resection of their temporomandibular joint and/or mandible, and 60.8% had infratemporal fossa resection. A lateral craniotomy was required in 19 patients (37.3%) to gain access to and resect the Gasserian ganglion for cases of concurrent zone 2 V_3 PNS ($n = 17$), or zone 2 V_2 PNS ($n = 2$) where a trans-facial approach would not have been possible to clear disease.

VII was resected in its intratemporal course in 76.5% of patients, most commonly at either the second genu (41.2%) or first genu/geniculate ganglion (31.4%) via a trans-temporal approach. In select cases of early zone 1 disease (17.6%), preservation of at least one peripheral VII branch was possible.

There were no peri-operative deaths. Surgical complications included: free-flap failure requiring return to theater ($n = 7$), wound hematoma or infection requiring

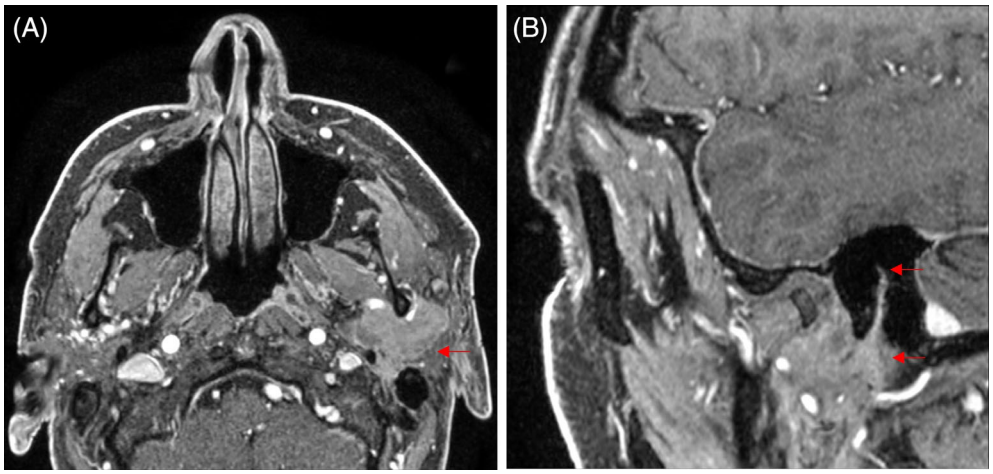

FIGURE 2 T1 fat-suppressed post-contrast magnetic resonance imaging demonstrating facial nerve (VII) perineural spread developing from a left parotid nodal mass with extranodal extension in the axial (A) and sagittal planes (B), with VII enhancement extending away from the tumor mass into the stylomastoid foramen and mastoid segment of VII (red arrows) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Radiological features of perineural spread at diagnosis

Radiological features	No. of patients ($n = 73$)	%
Nerve(s) involved with PNS		
VII alone	11	15.1
VII + V_2	5	6.8
VII + V_3	43	58.9
VII + V_2 + V_3	1	1.4
V alone (VII imaging negative)	7	9.6
Imaging negative	6	8.2
VII zone[a]		
1	25	41.7
2	31	51.7
3	4	6.7
Max V zone[b]		
1	20	29.9
2	32	47.8
3	4	6.0

Abbreviations: PNS, perineural spread; VII, facial nerve; V, trigeminal nerve; V2, trigeminal nerve maxillary branch; V3, trigeminal nerve mandibular branch.

[a]Percentages are reflective of only those who had imaging positive VII PNS ($n = 60$).

[b]Percentages are reflective of only those who had imaging positive PNS ($n = 67$).

washout and antibiotics ($n = 4$), deep vein thrombosis or pulmonary embolism ($n = 2$), and vagal nerve injury requiring vocal cord medialization ($n = 1$).

Most patients (82.4%) treated surgically received PORT, with an average dose of 60 Gy (range, 50–63 Gy) in 30 fractions (range, 25–30 fractions). This included 83.3% ($n = 40/48$) of curative intent and 66.7% ($n = 2/3$) of palliative intent surgical cases. Of the nine patients (17.6%) who did not receive PORT, five had previously received radiotherapy with maximal dosage, two declined, and one died shortly after surgery.

Long term complications following radiotherapy included: osteoradionecrosis of the external auditory canal ($n = 2$) and mandible ($n = 2$), temporal lobe radionecrosis ($n = 1$), and dysphagia with enteral feeding tube dependency ($n = 1$).

3.4 | Pathological outcomes

The pathological features of the 51 patients who underwent surgical intervention are detailed in Table 4. According to the 8th ed. AJCC system, the majority of patients were pathologically classified T3 (23.5%) or T4b (58.8%), given the system attributes T3 status as a minimum for the presence of PNS, and upstages to T4b once the skull base is transgressed. Twelve patients (23.5%) had pathological N3b disease, with most of these ($n = 9$) representing VII PNS cases arising from parotid nodal metastases with ENE or parotid bed recurrences. Of the patients who underwent surgery for PNS from local disease ($n = 42$), five (11.9%) had pathological nodal disease, with the distribution by nodal station as follows: parotid or periparotid ($n = 4$, 10.8%), level II ($n = 2$, 5.4%), level III ($n = 1$, 2.7%), and level IV ($n = 1$, 2.7%).

Most tumors were moderately differentiated (56.9%) and had absence of LVI (37.3%). The average maximal diameter of involved nerve with PNS was 3.2 mm (median, 2.5 mm; range, 0.5–15 mm). For patients who had curative intent surgery ($n = 48$), surgical margins were reported as clear in 37.5%, close (<5 mm) in 27.1%, and involved in 35.4%. Of the 17 patients with involved margins, the location of involved margin was most commonly peripheral ($n = 9$), or both peripheral and central ($n = 6$).

TABLE 3 Operative details in patients who underwent surgical intervention

Treatment	No. of patients ($n = 51$)	%
Parotidectomy	51	100.0
Superficial	8	15.7
Total conservative	2	3.9
Radical	41	80.4
Temporal bone resection	41	80.4
Mastoidectomy	11	21.6
Lateral	29	56.9
Total	1	2.0
TMJ ± mandible resection	34	66.7
TMJ/condyle	2	3.9
Ascending mandible	29	56.9
Hemimandible	3	5.9
ITF resection	31	60.8
Craniotomy	19	37.3
VII resection	51	100.0
Branch or upper/lower division	9	17.6
Trunk/stylomastoid foramen	3	5.9
Second genu	21	41.2
First genu/geniculate ganglion	16	31.4
Internal auditory canal	2	3.9
V_2 resection	8	15.7
Pterygopalatine fossa	1	2.0
Foramen rotundum	1	2.0
Gasserian ganglion	6	11.8
V_3 resection	31	60.8
Retromandibular/ITF (ATN)	4	7.9
Foramen ovale	10	19.6
Gasserian ganglion	17	33.3
Neck dissection	20	39.2
Elective	14	27.5
Therapeutic	6	11.8
Selective	16	31.4
Modified radical	4	7.8

Abbreviations: ATN, auriculotemporal nerve; ITF, infratemporal fossa; TMJ, temporomandibular joint; VII, facial nerve; V2, trigeminal nerve maxillary branch; V3, trigeminal nerve mandibular.

3.5 | Survival outcomes

For the entire cohort, the 2- and 5-year DSS rate was 74.8% and 55.7%, and OS was 65.9% and 47.5%. Survival rates by treatment intent are outlined in Table 5, and the Kaplan–

TABLE 4 Pathological features of perineural spread in patients who underwent surgical intervention

Pathological features	No. of patients ($n = 51$)	%
Pathological TNM classification (AJCC 8th ed.)		
T		
Tx	4	7.8
T1	3	5.9
T2	1	2.0
T3	12	23.5
T4b	31	60.8
N		
N0	37	72.5
N1	2	3.9
N3b	12	23.5
M		
M0	51	100.0
PNS features		
Nerve(s) involved		
VII alone	14	27.5
VII + V_2	8	15.7
VII + V_3	28	54.9
VII + cervical plexus	1	2.0
VII zone		
1	22	43.1
2	26	51.0
3	3	5.9
Max V zone		
1	17	33.3
2	19	37.3
3	0	0.0
Histopathological features		
Differentiation		
Well	4	7.8
Moderate	29	56.9
Poor	13	25.5
Unknown	5	9.8
LVI		
No	19	37.3
Unknown	21	41.2
Yes	11	21.6
Surgical margin[a]		
Clear	18	37.5
Close	13	27.1

(Continues)

TABLE 4 (Continued)

Pathological features	No. of patients ($n = 51$)	%
Involved	17	35.4
Peripheral	9	18.8
Central	2	4.2
Both	6	12.5
PNS mean max nerve diameter, mm (range)	3.2 (0.5–15.0)	

Abbreviations: AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; PNS, perineural spread; VII, facial nerve; V, trigeminal nerve; V2, trigeminal nerve maxillary branch; V3, trigeminal nerve mandibular branch.

[a]Percentages are reflective of only those who received curative intent surgery ($n = 48$).

Meier plot for DSS is presented in Figure 3. Within the curative intent group, patients treated with radiotherapy alone compared to surgery and PORT had worse 5-year DFS (26.8% versus 54%), but this trend was not statistically significant ($p = 0.489$). Four patients (5.5%) were lost to follow-up during the 5 years post-treatment.

39.6% of curative intent surgical cases ($n = 19/48$) had recurrences during the follow-up period at an average of 18.8 months post-surgery (median, 14 months; range 4–53 months). Of these 19 recurrences, 82.4% were locoregional, including recurrences peripherally in the skin or subcutaneous tissues (57.9%), centrally (26.3%), and/or in regional nodes (5.3%). Four patients had distant recurrences. Two patients had more than one location of disease recurrence.

TABLE 5 Survival by treatment intent

	DFS		DSS		OS	
Intent	2Y, %	5Y, %	2Y, %	5Y, %	2Y, %	5Y, %
Curative[a] ($n = 55$)	66.7	50.7	88.0	68.7	77.1	58.1
Palliative[b] ($n = 8$)			37.5	18.8	37.5	18.8
Supportive cares ($n = 10$)			29.6	0.0	26.7	0.0
Overall ($n = 73$)			74.8	55.7	65.9	47.5

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival; 2Y, 2-year; 5Y, 5-year.

[a]Curative intent includes curative surgery ± post-operative radiotherapy (PORT) ($n = 48$), and curative radiotherapy (RT) alone ($n = 7$).

[b]Palliative intent includes palliative surgery ± PORT ($n = 3$), and palliative RT alone ($n = 5$).

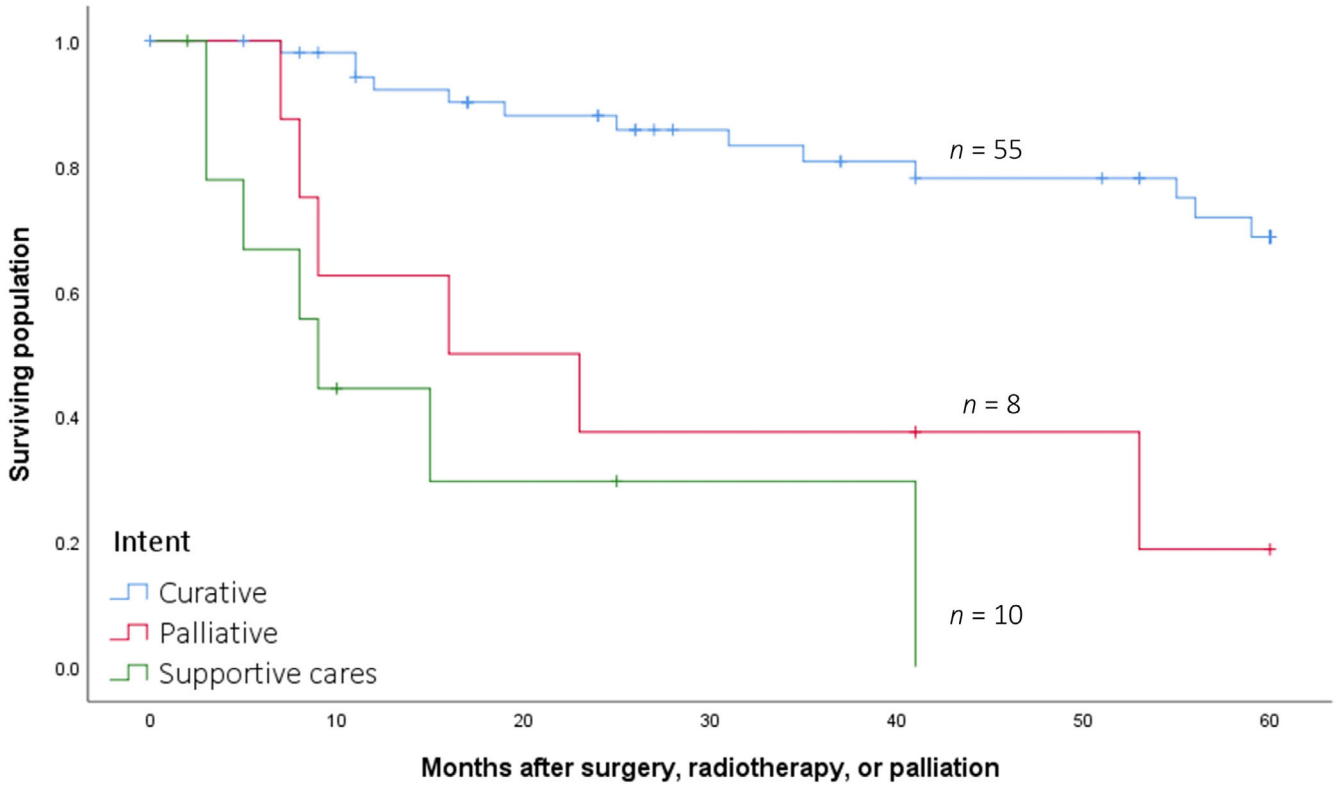

FIGURE 3 Disease-specific survival by treatment intent [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 6 Univariate Cox regression for prognostic factors for all survival outcomes in patients who underwent curative intent surgery ($n = 48$)

	DFS			DSS			OS		
Prognostic factor	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age (continuous)[a]	1.01	(0.97–1.06)	0.538	0.98	(0.94–1.03)	0.520	1.01	(0.97–1.06)	0.609
Gender									
Male	Ref			Ref			Ref		
Female	1.82	(0.42–7.94)	0.424	1.46	(0.19–11.42)	0.720	0.95	(0.13–7.25)	0.964
Immunosuppression[a]									
No	Ref			Ref			Ref		
Yes	2.30	(0.66–7.96)	0.189	2.60	(0.56–12.09)	0.223	2.56	(0.73–9.06)	0.144
Pathological nerve(s) involved									
VII alone	Ref			Ref			Ref		
VII + V	1.00	(0.38–2.64)	1.000	2.41	(0.53–11.01)	0.257	2.23	(0.64–7.79)	0.207
Pathological VII zone[a]									
Zone 1	Ref			Ref			Ref		
Zone 2	1.07	(0.41–2.77)	0.891	1.10	(0.34–3.62)	0.871	1.18	(0.44–3.16)	0.747
Zone 3	15.39	(2.57–92.02)	**0.003**	7.27	(0.76–69.18)	0.084	3.84	(0.45–32.83)	0.220
Pathological max V zone[a]									
Nil	Ref			Ref			Ref		
Zone 1	0.57	(0.16–2.03)	0.386	1.90	(0.35–10.40)	0.459	2.22	(0.57–8.59)	0.249
Zone 2	1.51	(0.53–4.24)	0.439	2.93	(0.59–14.54)	0.189	2.25	(0.58–8.72)	0.241
Nil or Zone 1	Ref			Ref			Ref		
Zone 2	1.96	(0.79–4.83)	0.144	2.00	(0.64–6.22)	0.230	1.38	(0.53–3.64)	0.510
pN[a]									
pN0	Ref			Ref			Ref		
pN+	3.11	(1.26–7.68)	**0.014**	4.92	(1.55–15.57)	**0.007**	3.04	(1.17–7.92)	**0.023**
Max nerve diameter									
<2.5 mm	Ref			Ref			Ref		
2.5–5 mm	1.02	(0.38–2.75)	0.965	0.59	(0.15–2.28)	0.442	0.54	(0.17–1.73)	0.298
>5 mm	0.48	(0.10–2.22)	0.346	0.61	(0.13–2.93)	0.534	0.65	(0.18–2.38)	0.517
LVI									
No	Ref			Ref			Ref		
Yes	2.00	(0.67–6.01)	0.217	3.41	(0.81–14.33)	0.093	1.71	(0.52–5.60)	0.379
Differentiation									
Well	Ref			Ref			Ref		
Moderate	0.80	(0.10–6.20)	0.827	0.43	(0.05–3.57)	0.432	0.32	(0.07–1.47)	0.142
Poor	0.67	(0.08–5.78)	0.718	0.38	(0.04–3.68)	0.405	0.19	(0.03–1.15)	0.070
Surgical margin[a]									
Clear	Ref			Ref			Ref		
Close	2.20	(0.49–9.84)	0.302	1.75	(0.35–8.73)	0.494	0.96	(0.28–3.29)	0.946
Involved	7.05	(1.97–25.19)	**0.003**	2.84	(0.71–11.39)	0.141	1.18	(0.40–3.52)	0.768
Clear or close	Ref			Ref			Ref		
Involved	4.84	(1.89–12.42)	**0.001**	2.23	(0.72–6.93)	0.166	1.20	(0.44–3.25)	0.723

Note: Bolding indicates statistical significance (p value < 0.05).

Abbreviations: CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; LVI, lymphovascular invasion; OS, overall survival; pN, pathological nodal disease; V, trigeminal nerve; VII, facial nerve.

[a]Prognostic factors shortlisted for inclusion in multiple Cox regression.

TABLE 7 Final multiple Cox regression models for prognostic factors for all survival outcomes in patients who underwent curative intent surgery ($n = 48$)

	DFS			DSS			OS		
Prognostic factor	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
pN									
pN0	Ref			Ref			Ref		
pN+	8.81	(2.49–31.18)	**0.001**	12.46	(2.82–55.12)	**0.001**	4.29	(1.44–12.76)	**0.009**
Pathological max V zone									
Nil or Zone 1	Ref			Ref			Ref		
Zone 2	3.88	(1.19–12.61)	**0.024**	6.44	(1.48–27.93)	**0.013**	2.37	(0.79–7.13)	0.125
Surgical margin									
Clear or Close	Ref								
Involved	5.46	(1.90–15.67)	**0.002**						
Pathological VII zone									
Zone 1	Ref								
Zone 2	2.17	(0.74–6.36)	0.158						
Zone 3	10.06	(1.52–66.57)	**0.017**						

Note: Bolding indicates statistical significance (p value < 0.05).
Abbreviations: CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; pN, pathological nodal disease; V, trigeminal nerve; VII, facial nerve.

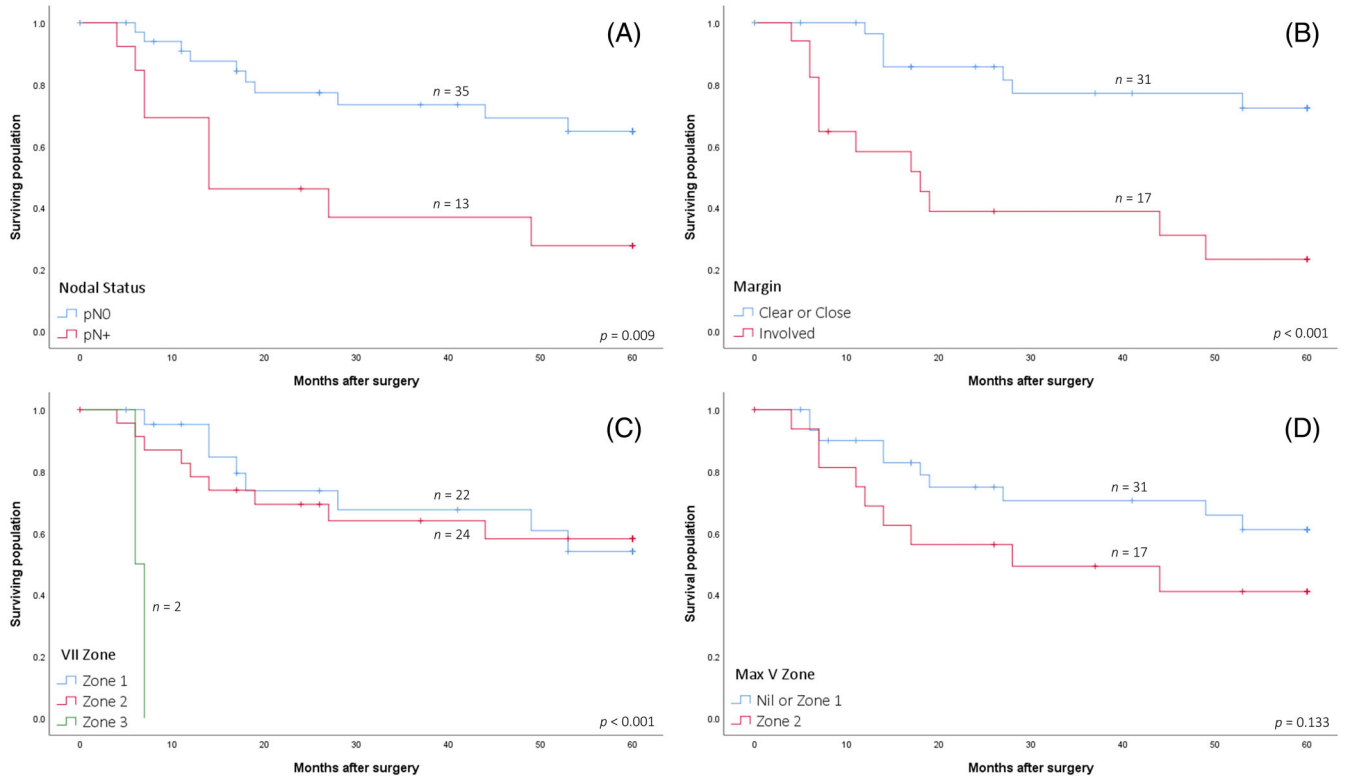

FIGURE 4 Disease-free survival in curative intent surgical cases ($n = 48$), stratified by (A) pathological nodal disease (pN), (B) surgical margin status, (C) facial nerve (VII) zonal extent, and (D) maximal trigeminal nerve (V) zonal extent [Color figure can be viewed at wileyonlinelibrary.com]

3.6 | Prognostic factors

The results of univariate Cox regression analysis for prognostic factors for DFS, DSS, and OS is detailed in Table 6. The final models generated by multiple Cox regression are outlined in Table 7.

In the multivariate model for DFS, pathological nodal disease, margin status, VII zonal extent, and maximal V zonal extent all retained independent prognostic significance. Kaplan–Meier plots for these factors are provided in Figure 4. Patients with pathological nodal disease had a significantly greater hazard of recurrence than those without (HR: 8.81 [95% CI: 2.49–31.18], $p = 0.001$). Involved margins compared to clear or close margins significantly increased risk of recurrence (HR: 5.46 [95% CI: 1.90–15.67], $p = 0.002$). Zone 3 VII disease demonstrated worse DFS compared to zone 1 disease (HR: 10.06 [95% CI: 1.52–66.57], $p = 0.017$). Zone 2 VII disease also showed a trend toward increased recurrence risk, but this did not reach statistical significance ($p = 0.158$). The presence of concurrent zone 2 V PNS, compared to nil or zone 1 V disease, increased the risk of recurrence by over three times (HR: 3.88 [95% CI: 1.19–12.61], $p = 0.024$).

Multiple Cox regression models for DSS and OS showed that pathological nodal disease significantly increased the risk of death from disease (HR: 12.46 [95% CI: 2.82–55.12], $p = 0.001$) and all-cause mortality (HR: 4.29 [95% CI: 1.44–12.76], $p = 0.009$). Zone 2 V PNS also significantly worsened DSS (HR: 6.44 [95% CI: 1.48–27.93], $p = 0.013$), and demonstrated a non-significant trend toward worse OS rates ($p = 0.125$).

4 | DISCUSSION

Despite significant advances made over the last decade, PNS from cSCCHN remains an often-misunderstood disease that can have potentially devastating impacts on patient prognosis. Past reports on head and neck PNS are generally limited in their accuracy and external validity through pooling of nerves and histopathological subtypes, small cohort numbers, lack of multivariate analysis, varying treatment methodologies, and unclear definitions on what constitutes PNS. As more relevant data is obtained with appropriate and clear subgrouping, we analyzed a cohort comprised entirely of patients with VII PNS from cSCCHN.

Consistent with our previous studies, the vast majority of patients (89.0%) had recurrent disease at time of VII PNS diagnosis, with the primary being treated on average almost 2 years prior.[1,6] Only ~5% of cases presented with PNS in conjunction with the primary lesion, and these patients had large, neglected tumors present for months or years. The small group of remaining patients had no previous history of cSCCHN, indicating subclinical disease or potential immune-mediated regression of the primary. In this respect, PNS can be considered a unique metastatic process as there is often no physical connection to the primary tumor.

Adding complexity to reaching a diagnosis of VII PNS is the slowly progressive nature of the disease, with symptoms being present on average almost 9 months before diagnosis, and up to 4 years in some. The hallmark presentation in this cohort was of a steadily worsening VII palsy, generally starting in one branch and progressing to affect the entire nerve as centripetal spread occurred. This differentiates VII PNS from conditions such as Bell's palsy, which is typically of rapid onset and recovery. Of note, a small proportion of patients (4.1%) had radiological VII PNS in absence of VII palsy, reflecting that subclinical disease is rare but possible. In contrast to the often difficult to interpret neuropathic symptoms that accompany V PNS, the clear clinical sign of a progressive VII palsy should give clinicians a high degree of suspicion for VII PNS, and such patients should be offered dedicated MR neurography.

A relatively high proportion (26.0%) of patients in this cohort presented with clinical nodal disease, largely owing to the 16.4% of VII PNS cases resulting from parotid lymph nodes with ENE or nodal bed recurrences. This reflects that, in addition to local invasion at terminal nerve endings, regionally recurrent disease in the parotid is an additional way in which tumor cells can gain access to VII and develop PNS, not generally observed in cases of V PNS.[1,14] Like other cSCCs, nodal disease remains important prognostically in these cases of VII PNS, significantly reducing DFS, DSS, and OS when present.[15,16]

Early recognition and diagnosis of VII PNS is crucial, as these results showed that progression along the nerve significantly increased chances of recurrence, and more advanced disease with concurrent Zone 2 V PNS worsened DFS and DSS. V3 was the most commonly involved V branch, an expected finding given its known anastomotic connection to VII via ATN in the retromandibular window.[9,17,18] These findings are consistent with previous reports on all nerve PNS from cSCCHN from our unit and others, with increasing zonal extent and multiple nerve involvement correlating with poorer prognosis.[2,7,19,20]

Detection of early zone 1 PNS is a recognized deficit in MR neurography, and this is reflected in the distribution of our patients with imaging negative disease.[9,21] More recently, however, improved MRI techniques, resolution, and assessment has led to an increased ability in detecting PNS involving peripheral branches of VII, and improved accuracy in determining zonal extent. For now, a low threshold should be had for clinically suspicious MRI negative cases with either close interval follow-up

imaging (6–8 weeks), or imaging guided or open biopsy of the nerve at question.[9]

Given the technical challenges associated with surgical resection, several authors have proposed radiotherapy as an alternative to manage PNS from cSCCHN.[3,20,22,23] However, despite a lack of direct comparative studies and standardized treatment protocol, surgery and PORT currently forms the mainstay of treatment in the literature, reporting to afford patients the best survival outcomes with justifiable perioperative risks.[1,12,17,19,24] This remains the case in this study of VII PNS from cSCCHN. Our results showed that curative intent radiotherapy had higher recurrence rates compared to curative surgery and PORT, although non-statistically significant differences were seen. Furthermore, it is possible that false positive VII PNS cases (up to 10%) were treated with radiotherapy given there was no pathological confirmation of disease, potentially artificially improving survival outcomes in this group. This remains an issue in other studies quoting outcomes with radiotherapy alone.[3,20,22,23]

Nonetheless, long term outcomes for patients with VII PNS from cSCCHN remain relatively poor despite treatment with a curative intent, with 5-year DSS and OS of 68.7% and 58.1%, respectively. These results also suggest that VII PNS may be more difficult to control than V PNS, with survival outcomes being slightly worse than our previous report on head and neck PNS from cSCC (5-year DSS and OS of 75% and 64%, respectively), comprised primarily (60%) of V PNS cases.[19] Dundar et al. also demonstrated poorer outcomes for VII PNS, but this study pooled histopathological subtypes.[2]

As seen in previous studies on PNS, surgical margin status was found to be a highly significant prognostic factor for VII PNS from cSCCHN, with involved margins increasing the chances of recurrence over five times.[7,17] Thus, an *en bloc* clear margin surgical resection should ideally be aimed for to optimize patient outcomes. However, this can be difficult to achieve in this anatomically complex region in terms of access, exposure, and radicality required to clear disease. As seen in our cohort, 35% of patients had involved margins, with just under half of these being central at the skull base. In these patients, despite designing operations to obtain a clear margin, intra-operatively, disease was found to extend beyond what was predicted, likely due to a combination of underestimation of disease extent on MRI and disease progression between the time of scanning and surgery. In these circumstances, decisions need to be made during surgery as to whether the resection will be extended, with considerations made to the patient, their medical status, and maintaining acceptable functional outcomes. Resection beyond the Gasserian or geniculate ganglion is usually not performed to avoid disturbing dural barriers and risk of inadvertent spread of disease, which makes designing PORT volumes difficult. Given these complexities, it is essential that patients are managed by a multidisciplinary surgical team, including an experienced skull base and plastic and reconstructive surgeon, with neurosurgical support available for cases where combined approaches are required.

The limitations of this study were largely in its retrospective design and relatively small cohort size, owing to the single institution nature of the study and rarity of disease. Some results may therefore be limited in accuracy and subject to information bias, given existing records were relied upon. Radiological analysis was also subject to potential inaccuracies, given the evolving techniques and quality of MRI over the course of the study and the potential for reporting bias. Thus, best attempts were made to remain blinded and consistent when assessing imaging. A strength of the study was the consecutive inclusion of patients utilizing our prospectively maintained database, whereby all patients presenting to our institution with VII PNS are recorded. As such, there was also a relatively low amount of missing data. Only four patients were lost to follow-up and most had complete data sets, with only certain prognostic factors, such as tumor differentiation and LVI, succumbing to missed data and reduced statistical power.

5 | CONCLUSION

This study represents the first in the literature to exclusively examine a cohort of patients with VII PNS from cSCCHN. Almost 90% of patients had recurrent disease as the cause for VII PNS, including 16% of cases resulting from parotid nodal metastases with ENE, reflecting the importance of adequate treatment of primary lesions to improve disease control in the first instance.

Most patients also experienced considerable delays to diagnosis, with symptoms being present a median of 6 months prior to diagnosis. Thus, VII PNS should always be considered in those presenting with progressive VII palsy and investigated with dedicated MR neurography. The clinician should also be aware of the often-coexistent V involvement, which must be closely examined clinically and radiologically, and included in any treatment planning.

Surgical resection and PORT remains the mainstay treatment for VII PNS from cSCCHN at our institution. Although survival outcomes remain relatively poor, they are improved in the earlier stages of disease and with clear surgical margins. Thus, prompt diagnosis and treatment of VII PNS is crucial, and this is expected to improve with increasing disease awareness and advancing imaging technology.

Given the complex nature of VII PNS from cSCCHN, it is imperative that patients are managed in a

multidisciplinary setting, with close collaboration between an experienced skull base surgeon, radiation oncologist, and radiologist. One must also always be aware of the risks of surgical morbidity and mortality, and weigh these carefully against potential survival benefit.

AUTHOR CONTRIBUTIONS

Michael J. C. Schachtel: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing-original draft, writing-review & editing. **Mitesh Gandhi**: conceptualization, data curation, investigation, methodology, project administration, supervision, validation, writing-review & editing. **James J. Bowman**: conceptualization, investigation, methodology, project administration, supervision, validation, writing-review & editing. **Sandro V. Porceddu**: conceptualization, investigation, supervision, validation, writing-review & editing. **Benedict J. Panizza**: conceptualization, data curation, investigation, methodology, project administration, supervision, validation, visualization, writing-original draft, writing-review & editing.

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CONFLICT OF INTERESTS

The author declares that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Panizza BJ. An overview of head and neck malignancy with perineural spread. *J Neurol Surg B Skull Base*. 2016;77:81-85.
2. Dundar Y, Cannon RB, Monroe MM, Buchmann LO, Hunt JP. Skull base invasion patterns and survival outcomes of nonmelanoma skin cancers. *J Neurol Surg B Skull Base*. 2017;78:164-172.
3. Balamucki CJ, Mancuso AA, Amdur RJ, et al. Skin carcinoma of the head and neck with perineural invasion. *Am J Otolaryngol*. 2012;33:447-454.
4. Goepfert H, Dichtel WJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. *Am J Surg*. 1984;148:542-547.
5. Mendenhall WM, Amdur RJ, Williams LS, Mancuso AA, Stringer SP, Price Mendenhall N. Carcinoma of the skin of the head and neck with perineural invasion. *Head Neck*. 2002;24:78-83.
6. Warren TA, Whiteman DC, Porceddu SV, Panizza BJ. Insight into the epidemiology of cutaneous squamous cell carcinoma with perineural spread. *Head Neck*. 2016;38:1416-1420.
7. Warren TA, Nagle CM, Bowman J, Panizza BJ. The natural history and treatment outcomes of perineural spread of malignancy within the head and neck. *J Neurol Surg B Skull Base*. 2016;77:107-112.
8. Warren TA, Panizza B. Managing perineural and skull base involvement. In: Riffat F, Palme CE, Veness M, eds. *Non-melanoma skin cancer of the head and neck*. Springer India; 2015:117-130.
9. Gandhi M, Sommerville J. The imaging of large nerve Perineural spread. *J Neurol Surg B Skull Base*. 2016;77:113-123.
10. Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys*. 2001;49:1061-1069.
11. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.
12. Solares CA, Mason E, Panizza BJ. Surgical management of perineural spread of head and neck cancers. *J Neurol Surg B Skull Base*. 2016;77:140-149.
13. House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg*. 1985;93:146-147.
14. Panizza B, Warren TA, Solares CA, Boyle GM, Lambie D, Brown I. Histopathological features of clinical perineural invasion of cutaneous squamous cell carcinoma of the head and neck and the potential implications for treatment. *Head Neck*. 2014;36:1611-1618.
15. Porceddu SV, Veness MJ, Guminski A. Nonmelanoma cutaneous head and neck cancer and merkel cell carcinoma: current concepts, advances, and controversies. *J Clin Oncol*. 2015;33:3338-3345.
16. Hasan Z, Palme C, Riffat F. Evaluation, staging and prognostication. In: Riffat F, Palme CE, Veness M, eds. *Non-melanoma skin cancer of the head and neck*. Springer India; 2015:25-36.
17. Erkan S, Savundra JM, Wood B, Acharya AN, Rajan GP. Clinical perineural invasion of the trigeminal and facial nerves in cutaneous head and neck squamous cell carcinoma: outcomes and prognostic implications of multimodality and salvage treatment. *Head Neck*. 2017;39:1280-1286.
18. Stambuk HE. Perineural tumor spread involving the central skull base region. *Semin Ultrasound CT MR*. 2013;34:445-458.
19. Warren TA, Panizza B, Porceddu SV, et al. Outcomes after surgery and postoperative radiotherapy for perineural spread of head and neck cutaneous squamous cell carcinoma. *Head Neck*. 2016;38:824-831.
20. Lin C, Tripcony L, Keller J, Poulsen M, Dickie G. Cutaneous carcinoma of the head and neck with clinical features of perineural infiltration treated with radiotherapy. *Clin Oncol (R Coll Radiol)*. 2013;25:362-367.
21. Gandhi MR, Panizza B, Kennedy D. Detecting and defining the anatomic extent of large nerve perineural spread of malignancy: comparing "targeted" MRI with the histologic findings following surgery. *Head Neck*. 2011;33:469-475.

22. McCord MW, Mendenhall WM, Parsons JT, et al. Skin cancer of the head and neck with clinical perineural invasion. *Int J Radiat Oncol Biol Phys*. 2000;47:89-93.
23. Jackson JE, Dickie GJ, Wiltshire KL, et al. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head Neck*. 2009;31:604-610.
24. Panizza B, Solares CA, Redmond M, Parmar P, O'Rourke P. Surgical resection for clinical perineural invasion from cutaneous squamous cell carcinoma of the head and neck. *Head Neck*. 2012;34:1622-1627.

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