International Journal of Otorhinolaryngology and Head and Neck Surgery
Maldonado J et al. Int J Otorhinolaryngol Head Neck Surg. 2024 Dec;10(6):683-694
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20243508

Systematic Review

Management of cutaneous head and neck squamous cell carcinoma with trigeminal nerve involvement: a systematic review

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Received: 11 June 2024
Revised: 26 August 2024
Accepted: 02 September 2024

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ABSTRACT

Cutaneous head and neck squamous cell carcinoma (cHNSCC) is the second most common cancer worldwide, carrying a favorable prognosis. Perineural invasion/spread dramatically reduces survival outcomes. The trigeminal nerve (CNV) is most commonly affected, providing abundant opportunities for skull base and intracranial cavity invasion. Standard treatment includes surgery and radiotherapy (SRT). We intended to systematically review the literature on cHNSCC with CNV involvement and evaluate the effects of treatment modalities and pattern of CNV invasion/spread on outcomes. We performed a systematic review according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA). Kaplan-Meier curves were utilized to determine the impact of treatment and pattern of invasion/spread on disease-free survival (DFS) and overall survival (OS). Fifty-one studies were identified, generating a sample size of 172 patients with cHNSCC and CNV involvement. The most common treatment modality was SRT (n=90, 52.9%), and all three major CNV branches were affected with similar frequency (V1 33.7%, V2 33.7%, V3 32.6%). Cox proportional hazards regression models revealed significant differences in OS for V1 vs V2 involvement (HR 2.84 95% CI 1.02-7.89), skull base invasion (HR 3.90 95%CI 1.30-11.65), SRT vs RT alone (HR 5.77 95% CI 2.13-15.6), SRT vs other treatment (HR 6.21 95 CI 2.24-17.20). Only SRT and RT had a significant difference in DFS (HR of 3.90, 95%CI 1.30-11.65). In cHNSCC with CNV involvement, treatment modality and the pattern of CNV are crucial for locoregional control and mortality. V1 involvement and definitive RT are associated with significantly lower survival curves.

Keywords: Skull base surgery, Skull base oncology, Perineural invasion, Perineural spread, CNV, Skin cancer

INTRODUCTION

Cutaneous head and neck squamous cell carcinoma (cHNSCC) is the second most common cutaneous malignancy in the United States, with a rising annual incidence reaching 1.1 to 1.8 million cases/year.[1,2] Most cases are successfully treated with Mohs microsurgery, achieving a five-year survival rate of >90%.[1] However,

several high-risk features have been identified as portending a significantly worse prognosis, including local recurrence, nodal metastasis (NM), distant metastasis (DM), and disease-specific death (DSD). Perineural invasion is one of the most well-established poor prognostic indicators for cHNSCC, particularly when large caliber or named nerves (0.1 mm) are involved.[1,3]

Perineural invasion is the infiltration in, around, and through the peripheral nerves by tumor cells, and it occurs in 2.5%-14% of cHNSCC cases.[2] It is a microscopic finding, diagnosed exclusively by histologic staining. Perineural spread on the other hand, is a distinct entity, characterized by radiologically or clinically apparent extension of tumor along a nerve fiber. Both invasion and spread have been associated with increased recurrence and worsened survival.[1,3-5] Perineural invasion, in particular, has been associated with local recurrence rates ranging from 16%-45% and NM rates between 10% and 50%.[5] Moreover, DSD rates have reportedly been four times as high in patients with cSCC with perineural invasion compared to those without perineural invasion.[6] Indeed, two separate meta-analyses by Thompson et al and Zahkem et al demonstrated that perineural invasion was significantly associated with recurrence, metastasis, and DSD.[1,3]

In one meta-analysis of 17,248 patients with cSCC, the risk ratio for recurrence was highest among those with perineural invasion.[3] In another meta-analysis of 137,449 patients with primary cSCC, Zakhem et al demonstrated that perineural invasion had the largest risk ratio for metastasis compared to all other risk factors for poor outcome.[1] Of note, Zakhem et al also investigated which treatment outcomes were associated with improved outcomes, finding that patients treated with Mohs microsurgery (MMS) had the lowest risk of all poor outcomes.[1] This finding supports the recommendations for MMS as first-line treatment for high-risk cSCC with adjuvant radiotherapy (RT) added on in the presence of perineural invasion.[1]

cHNSCC typically arises in areas of high sun exposure (ie, scalp, cheek, ear, lips). Thus, nerves with an extensive cutaneous distribution in these areas are more likely to be impacted by perineural invasion/spread. The trigeminal (V1 ophthalmic, V2 maxillary, V3 mandibular divisions) nerve (CNV) is most frequently involved in perineural invasion/spread of cHNSCC.[6] V1 and V2 are purely sensory divisions, and V3 is a mixed nerve providing sensory innervation to the lower face and motor innervation to the masticatory muscles. While V2 is most often involved in perineural invasion/spread, V3 is associated with significantly worse outcomes.[2,7] One report found V1 involvement to be significantly associated with earlier recurrence compared to V2 and V3.[8] Thus, there is evidence suggesting that outcomes might differ by pattern of CNV involvement.

While cHNSCC with perineural invasion/spread has been extensively studied, there have not been any systematic reviews focusing specifically on outcomes in patients with cHNSCC and CNV involvement. Given the frequency with which CNV is involved in perineural invasion/spread and the evidence suggesting that the pattern of invasion/spread influences outcomes, a systematic evaluation of cHNSCC with CNV involvement is of paramount importance. Thus, the following paper sought to characterize both patterns of treatment and invasion/spread in patients with cHNSCC and CNV involvement and the effect of treatment modality and pattern of spread on DFS and OS.

METHODS

The following systematic review was performed according to the PRISMA guidelines.[9] Institutional review and informed consent was not required as this study relied on already published publicly available data.

Data sources and strategy

A comprehensive electronic review of the literature was performed between December 2022 and January 2023, using PubMed, Cochrane, and GoogleScholar databases. Articles published from database inception to January 1, 2023 were included in the search. The following search terms and phrases were used: "perineural spread" “trigeminal nerve” “Gasserian ganglion” AND "squamous cell carcinoma", “head and neck squamous cell carcinoma” AND “trigeminal nerve”, “cutaneous squamous cell carcinoma” AND” trigeminal nerve invasion”, “perineural invasion” AND “head and neck squamous cell carcinoma”. Selected articles were exported to Endnote (v20.4) (Thompson Reuters, Carlsbad, California, USA).

Eligibility criteria

Studies were assessed for eligibility based on the following inclusion criteria: (1) SCC was cutaneous and arose from the head and neck region; (2) Radiographic and/or histologic evidence confirming the presence of CNV involvement; (3) Treatment was reported for at least one patient with cHNSCC and CNV involvement. Studies were excluded if (1) the identity of the involved nerve was not specified; (2) treatment modality was not specified; (3) review article, abstract, errata, poster presentation, conference proceeding, or textbook chapters; (4) data on patients with c-HNSCC could be separated from ineligible information. No minimum follow up time was established since this varies widely in the literature. The presence of CNV symptoms without histologic and/or radiologic confirmation of perineural invasion/spread was not considered definitive involvement, and these cases were excluded.[7]

Study selection and extraction

Titles and abstracts were assessed based on our criteria by two independent blinded reviewers (JM, SL). The full text was sought for titles and abstracts in which there was insufficient information to render a decision. The reference list of every article was examined for additional studies. Decisions were compared between authors and discrepancies resolved by third author arbitration (EP, JMR). The full text was obtained for the remaining articles, and their eligibility was determined based on our inclusion criteria. Four authors (JM, SL, AR, TA) performed data abstraction. The quality of included studies was assessed independently by two authors (SV, EP) using the Joanna Briggs institute (JBI) for case studies, case reports, and cohort studies.

The primary outcome variables were mortality (no evidence of disease [NED], alive with disease [AWD], DOD, dead from other cause [DOC]), recurrence (yes, no), DFS, and OS. DFS was calculated from the date of treatment to the date of first recurrence, or to the date of death or last follow up if recurrence did not occur. OS was determined based on the date of treatment to the date of death from any cause (all-cause mortality) or last follow up.

Statistical analysis

All statistical analyses were performed with IBM SPSS software package version 29.0 (Armonk, NY, IBM Corp). The Kolmogorov–Smirnov was used to verify the normality of distribution of variables. Qualitative data were presented in numbers (%). Normally distributed quantitative data were described using mean ± standard deviation (SD), while skewed were described using median (interquartile range [IQR]). Differences between categorical variables were assessed using the X^2 and Fisher exact tests. Survival statistics were calculated using the Kaplan-Meier curves to determine the effect of the pattern of invasion/spread and treatment modality on the outcome variables. Differences in survival were calculated using the log-rank test. Effect sizes were estimated using hazard ratios (HR) from Cox proportional hazards models with a single covariate. Separate models were fitted to compare survival between trigeminal branches and by treatment modality. A $p<0.05$ was considered statistically significant for all analyses.

RESULTS

An initial pool of 3195 articles was gathered from the primary literature search. After removing duplicates and non-English sources, 2475 titles and abstracts were screened. A total of 2084 studies were excluded based on the irrelevance of the topic and insufficient information provided. The full texts of the remaining 391 studies were sought for retrieval, and 340 were excluded based on our exclusion criteria. The final number of studies was 51, consisting of 40 case reports, 9 cases series, and 2 retrospective cohort studies.[6-8,11-58] A depiction of the study selection process is illustrated in Figure 1. Study characteristics and JBI risk assessment scores are summarized in Table 1.

Table 1: Summary of included studies reporting treatment and pattern of spread for cHNSCC with CNV involvement.

Authors	Year	JBI	Study design	Total	No. included	Outcome(s)
Ali et al[11]	2014	7/8	CR	1	1	NED
Alonso et al[12]	1995	7/8	CR	2	2	AWD
Anderson et al[13]	1990	7/8	CR	1	1	NED
Bagatin et al[14]	1995	7/8	CR	4	2	NED, DOD
Bard et al[6]	2022	6/8	CR	1	1	Unknown
Barnett et al[15]	2013	8/10	CS	55	6	NED, AWD, DOD
Bhat et al[16]	2015	7/8	CR	1	1	AWD
Bhatnagar et al[17]	2005	7/8	CR	1	1	AWD
Brennard-Roper et al[18]	2010	7/8	CR	1	1	NED
Califano et al[19]	1995	7/8	CR	1	1	DOD
Chalfant et al[20]	2021	6/8	CR	1	1	Unknown
Chan et al[21]	2008	6/8	CR	1	1	Unknown
Clouston et al[22]	1990	9/10	CS	5	5	NED, AWD, DOD, AWD
Cottel et al[23]	1982	9/10	CS	17	15	NED
De Keizer et al[24]	1997	8/8	CR	1	1	DOD
Erkan et al[8]	2017	10/10	CS	21	20	-
Esmaeli et al[25]	2000	8/8	CR	1	1	AWD
Esmaeli et al[26]	2003	8/8	CR	230	2	NED
Farah et al[27]	2020	8/8	CR	1	1	NED
Fowler et al[28]	2005	9/10	CS	5	3	NED, DOD
Hagiga et al[29]	2021	7/8	CR	1	1	AWD
Hell et al[30]	1987	7/8	CR	3	2	DOC, NED
Kalil et al[31]	2022	7/8	CR	1	1	NED
Kumar et al[32]	1993	7/8	CR	2	1	NED

Continued.

Authors	Year	JBI	Study design	Total	No. included	Outcome(s)
Lane et al[33]	2010	7/8	CR	1	1	DOC
Leach et al[34]	2008	10/10	CS	6	4	NED, DOD
Limawararut et al[35]	2007	8/8	CR	1	1	AWD
Mattox et al[36]	1982	8/8	CR	2	1	AWD
McNab et al[37]	1997	10/10	CS	2	2	DOD
MeHanna et al[38]	2007	8/8	CR	5	2	DOD
Mickalites et al[39]	1978	7/8	CR	1	1	AWD
Moore et al[40]	1962	7/8	CR	2	2	DOD, Unknown
Morris et al[41]	1983	8/8	CR	5	2	AWD
Notz et al[42]	2014	8/8	CR	1	1	NED
Okholm et al[43]	2018	8/8	CR	3	1	DOD
Panizza et al[7]	2012	11/11	Cohort	21	19	NED, DOD
Phan et al[44]	2009	8/8	CR	1	1	NED
Schifter et al[45]	1993	8/8	CR	2	2	AWD
Shah et al[46]	2017	7/8	CR	2	1	Unknown
Shah et al[47]	2013	8/8	CR	1	1	AWD
ten Hove et al[48]	1997	8/8	CR	7	4	NED
Trobe et al[49]	1982	8/8	CR	2	2	NED
van Vugt et al[50]	2017	8/8	CR	1	1	DOC
Veness et al[51]	2000	8/8	CR	4	2	NED, DOD
Warden et al[52]	2009	8/8	CR	3	2	DOD
Weisberg et al[53]	2000	8/8	CR	1	1	NED
Wilcsek et al[54]	2000	8/8	CR	1	1	DOC
Williams et al[55]	2001	11/11	Cohort	35	26	NED, AWD
Wu et al[56]	2022	10/10	CS	11	11	AWD, DOD, DOC
Zhu et al[57]	2004	8/8	CR	1	1	AWD
Zupi et al[58]	1998	10/10	CS	12	8	AWD, DOD

cHNSCC-cutaneous head and neck squamous cell carcinoma; CNV-trigeminal nerve; CR-case report; CS-case series; JBI-Joanna Briggs Institute; NED-no evidence of disease; AWD-alive with disease; DOD-dead of disease; dead other cause.

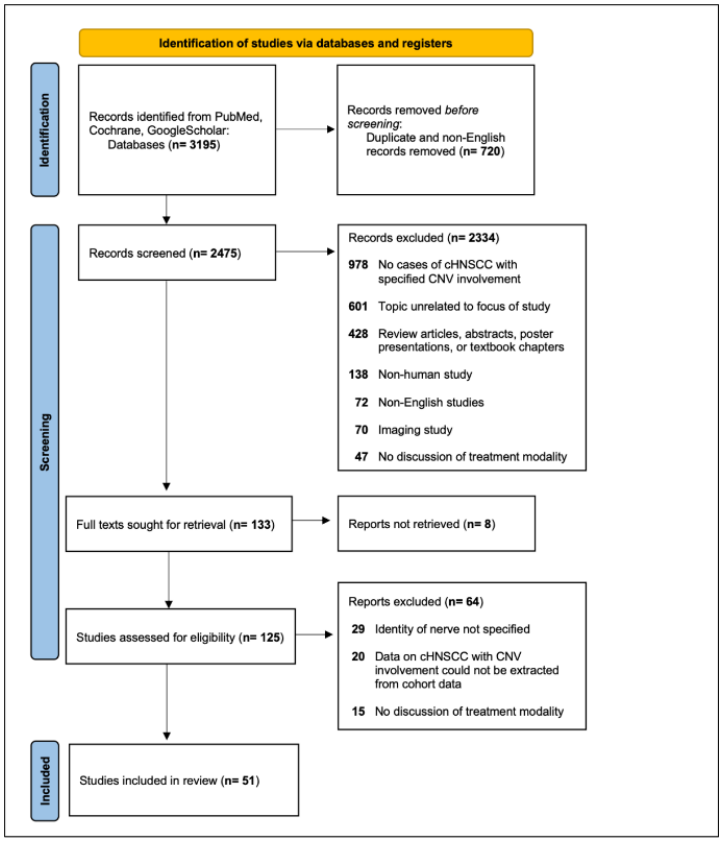

Figure 1: PRISMA flow diagram depicting methodology and literature search on treatment and pattern of spread in cHNSCC with CNV involvement.

Table 2: Characteristics of cHNSCC with CNV Involvement at time of diagnosis.

Characteristics	N (%)/ median (IQR)
Gender	
Male	115 (77.7%)
Female	33 (22.3%)
Median age (in years)	66 (18)
Primary site	
Not identified	37 (21.5%)
Forehead/brow	27 (15.7%)
Cheek/ nasolabial fold	22 (12.8%)
Lip	19 (11.0%)
Periorbital region	14 (8.1%)
Nose/ cheek-nose angle	13 (7.6%)
Temple/scalp	11 (6.4%)
Ear/ external auditory canal	7 (4.1%)
Jaw	2 (1.2%)
Not reported	20 (11.6%)
Point of diagnosis	
Disease recurrence	60 (69.8%)
Disease progression	15 (17.4%)
Initial presentation	11 (12.8%)
Sx of CNV involvement	
Yes	132 (79.0%)
No	35 (21.0%)
Symptom duration (m)	
Median	8.0 (20.0)
Pathology	
Poorly differentiated	18 (48.6%)
Moderately differentiated	10 (27.0%)
Well-differentiated	9 (24.3%)
Metastasis	
None	142 (92.8%)
Locoregional	8 (5.2%)
Distant	2 (1.3%)
Nodal	1 (.7%)

cHNSCC-cutaneous head and neck squamous cell carcinoma; CNV-trigeminal nerve

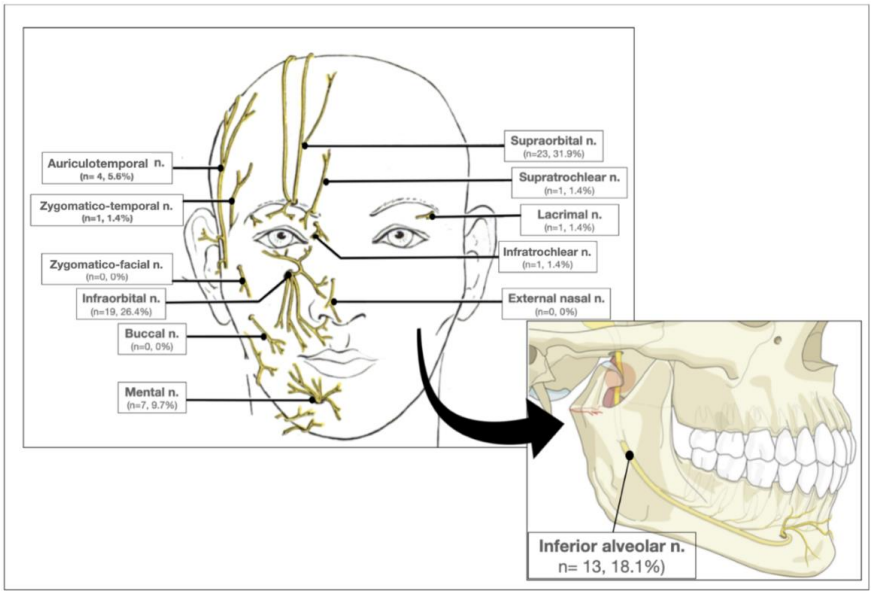

Figure 2: Peripheral CNV branches affected by cHNSCC.

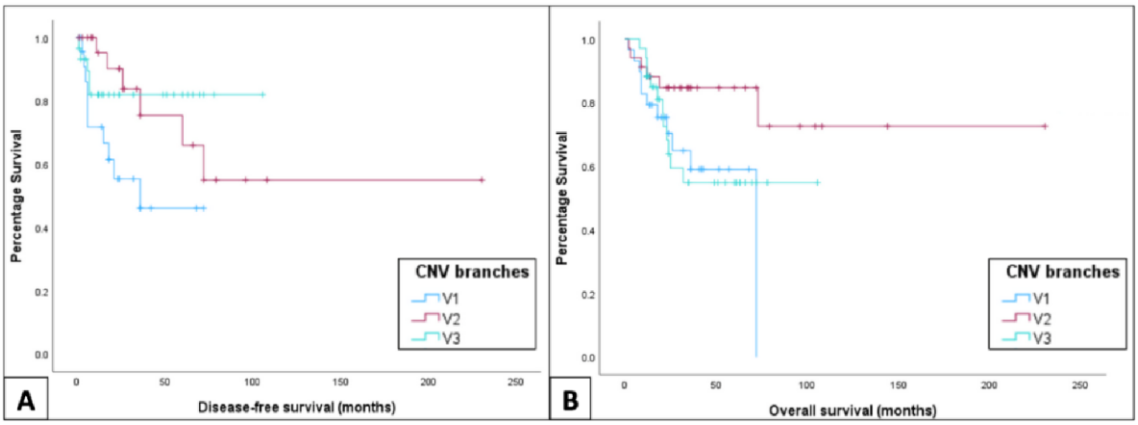

Figure 3 (A and B): Kaplan-Meier curve for DFS (A) and OS (B) according to pattern of invasion/spread in cHNSCC with CNV involvement.

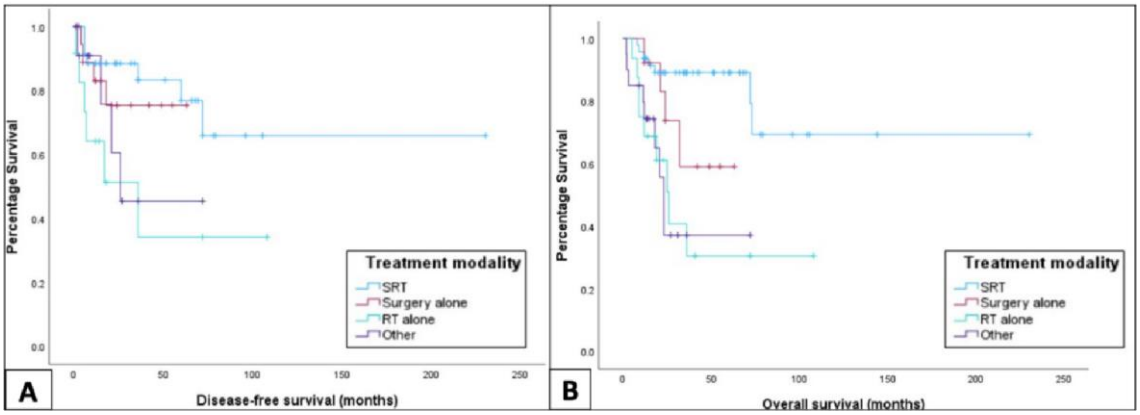

Figure 4 (A and B): Kaplan-Meier curve for DFS (A) and OS (B) according to treatment of cHNSCC with CNV involvement.

Patient and disease characteristics

The total sample consisted of 172 patients with cHNSCC and CNV involvement. Most patients were male (n=115, 77.7%), the median age was 66 (18) years, and 69.8% of patients developed CNV involvement on recurrence of prior cHNSCC. CNV symptoms were reported in 79.0% (n=132) cases, and the median symptom duration was 8 (20) months. The forehead/brow was the most commonly identified primary site (n=27, 15.7%), but the primary site was unidentified in 21.5% (n=37) cases. Poorly differentiated cHNSCC (n=18, 48.6%) was the most common differentiation, but most cases did not report tumor differentiation (Table 2).

Pattern of CNV involvement

V1 and V2 were each involved in 33.7% of cases, and V3 was involved in 32.6% of cases (Table 3). The most common peripheral branch involved was the supraorbital nerve (n=23, 39.7%), followed by the infraorbital nerve (n=19,32.8%), and the inferior alveolar nerve (n=13, 23.2%) (Figure 2). In 34 (19.8%) cases, more than one CNV branch was affected. Skull base invasion was present at the time of diagnosis in 70.2% (n=113) of cases, and intracranial spread was present in 5.6% (n=9) of cases. Zonal classification was estimated for 91 cases. Sixty (65.9%) cases were classified as zone 1, 23 (25.3%) cases as zone 2, and 8 cases as zone 3 (Table 3).

Table 3: Pattern of CNV involvement in cHNSCC with CNV, trigeminal nerve.

Characteristic	N (%)
CNV branch affected	
V1	58 (33.7%)
V2	58 (33.7%)
V3	56 (32.6%)
Skull base invasion	
Yes	113 (70.2%)
No	48 (29.8%)
Intracranial extension	
No	152 (94.4%)
Yes	9 (5.6%)
Zonal classification	
Zone 1	60 (65.9%)
Zone 2	23 (25.3%)
Zone 3	8 (8.8%)

V1-ophthalmic nerve; V1-maxillary nerve; V3-mandibular nerve

Treatment

SRT was the most common treatment (n=90, 52.9%), followed by surgery alone (n=27, 15.9%), and definitive RT (n=24, 14.1%). Twenty-nine patients received other forms of treatment, which can be summarized as follows: Eleven (6.5%) patients received immunotherapy, eight (4.7%) patients received surgery with chemoradiotherapy, six (3.5%) patients received chemoradiotherapy, two (1.2%) patients received definitive chemotherapy, and two (1.2%) patients received palliative care. Clear surgical margins were achieved in 50.4% (n=63) of cases. The median RT dose was 60 Gy (10.9 Gy). The median follow up time was 34.4 months (49.6 months) (Table 4).

Table 4: Breakdown of treatment modality and outcomes in cHNSCC with CNV involvement.

Treatment/outcome	N (%)/ median (IQR)
Treatment modality	
SRT	90 (52.9%)
Surgery alone	27 (15.9%)
RT alone	24 (14.1%)
Immunotherapy	11 (6.5%)
Surgery+ CRT	8 (4.7%)
CRT	6 (3.5%)
Chemotherapy alone	2 (1.2%)
Palliative radiation	2 (1.2%)
Surgical margins	
Positive	62 (49.6%)
Negative	63 (50.4%)
Median RT dose (Gy)	60.0 (10.9)
Median follow-up (m)	34.4 (49.6)
Outcomes	
NED	74 (48.7%)
AWD*	35 (23.0%)
DOD	31 (20.4%)
Dead, other cause	7 (4.6%)
Unknown	5 (3.3%)
Recurrence	
Yes	25 (20.7%)
No	96 (79.3%)
Median DFS (m)	21.0 (30.5)
Posttreatment metastasis	
None	140 (85.4%)
Locoregional	17 (10.4%)
Nodal	4 (2.4%)
Distant	2 (1.2%)

CNV-trigeminal nerve; SRT-surgery+ radiotherapy; RT-radiotherapy; CRT-chemoradiotherapy; NED-no evidence of disease; DOD-dead of disease; OS-overall survival; DFS-disease-free survival. *Includes patients with reported disease progression (n=10, 6.7%).

Outcomes

Seventy-two (48.7%) patients had NED, 35 (23.0%) patients were AWD, 31 (20.4%) patients were DOD, and seven (4.6%) patients were DOC. Five cases did not provide enough information to determine the outcome. Twenty-five (20.7%) patients had recurrence of cHNSCC with CNV involvement. Locoregional metastasis occurred in 10.4% of cases, NM occurred in 2.4%, and distant metastasis occurred in 1.2% (Table 4).

Survival analysis by pattern of CNV involvement

The log rank test did not demonstrate a statistically significant difference in DFS (p=0.52) based on pattern of CNV involvement (p=0.52). One-year DFS for V1, V2, and V3 involvement was 78.3%, 100%, and 92.9%, respectively. Two-year DFS for V1, V2, and V3 was 60.0%, 95.20%, and 73.0%, respectively. Lastly, the five-year DFS for V1, V2, and V3 was 22.2%, 63.6%, and 61.5%, respectively (Figure 3 A).

Table 5: Hazard ratios for survival curves.

Variables	Hazard ratios for survival (95% confidence interval)	
	Overall	**Disease-free**
CNV branch		
V1	2.84 (1.02-7.89)	2.71 (0.97-7.56)
V2	Ref	Ref
V3	2.47 (1.79-6.68)	0.92 (0.28-3.02)
Treatment modality		
Surgery+ RT	Ref	Ref
Surgery alone	2.67 (0.77-9.28)	1.53 (0.44-5.33)
RT alone	5.77 (2.13-15.61)	3.95 (1.32-11.83)
Other	6.21 (2.24-17.20)	2.68 (0.78-9.24)
Skull base invasion	1.58 (0.66-3.80)	3.90 (1.30-11.65)
Intracranial spread	7.08 (2.79-17.97)	2.26 (0.52-9.79)
Surgical margins positive	0.72 (0.23-2.24)	8.34 (1.08-64.12)

CNV-Trigeminal nerve; V1-ophthalmic branch; V2-maxillary branch; V3-mandibular branch; RT-radiotherapy.

Similarly, the log rank test for OS by pattern of CNV involvement did not reveal any statistically significant differences (p=0.96). (Figure 3 B). One-year OS was 79.3% (V1), 87.9% (V2), and 85.3% (V3), and the two-year OS was 65.2% (V1), 82.9% (V2), and 56.0% (V3). Lastly, the five-year OS was 16.7% (V1), 60.0% (V2), and 45.0% V3) (Figure 3 B). A Cox proportional hazards regression model revealed significant differences in the OS of patients with V1 versus V2 involvement (HR 2.84 95% CI 1.02-7.89). However, there was no significant difference in OS between V2 and V3 (HR 2.47 95% CI 0.92-6.68) (Table 5).

Skull base invasion was significantly associated with a lower DFS curve (p=0.008). The one-, two- and five-year DFS or patients with skull base invasion were 87.5%, 69.4%, and 48.0%, respectively. A Cox proportional

hazards regression model revealed a HR of 3.90 (95%CI 1.30-11.65) (Table 5).

Survival analysis by treatment modality

Treatment modality demonstrated a marginally significant relationship with DFS (p=.058) (Figure 4 A). One-year DFS according to treatment modality was 92.3% (SRT), 92.9% (surgery alone), and 78.6% (RT alone). Two-year DFS was 90.9% (SRT), 90.0% (surgery alone), and 36.4% (RT alone). Lastly, five-year DFS was 72.2% (SRT), 50.0% (surgery alone), and 25.0% (RT alone). The Cox proportional hazards regression model demonstrated a significant difference between SRT and RT alone (HR of 3.90, 95% CI 1.30-11.65) (Table 5).

There was a statistically significant relationship between treatment modality and OS (p<0.001) (Figure 4 B). Compared with SRT, RT alone showed a HR of 5.77 (95% CI 2.13-15.6), while the group of other treatment modalities showed a HR of 6.21 (95% CI 2.24-17.20). The comparison between ST and surgery alone did not show a statistically significant increase in risk with a HR of 2.67 (95% CI 0.77, 9.28). One-year OS according to treatment modality was 93.8% (SRT), 92.3% (surgery alone), and 62.5% (RT alone). Two-year OS was 87.5% (SRT), 72.7% (surgery alone), and 41.7% (RT alone). Lastly, five-year OS was 76.2% (SRT), 20.0% (surgery alone), and 18.2% (RT alone).

DISCUSSION

Perineural involvement is an ominous finding that significantly reduces OS and DFS. CNV is most often affected by perineural invasion/spread often presenting with spread to both the skull base and intracranial cavity. This review addressed this phenomenon, highlighting the influence of treatment and pattern of spread on recurrence and mortality. Following an extensive review of the literature, we identified 172 cases of cHNSCC with CNV involvement. SRT was significantly associated with OS, demonstrating superior survival curves to RT and other treatment modalities. While CNV was not significantly associated with OS or DFS, we found a statistically significant difference in OS between V1 and V2 such that patients with V1 involvement had a significantly lower survival curve.

Previous studies have shown that the pattern of perineural invasion/spread is associated with outcomes.[5] For example, involvement of large caliber nerves (>0.1mm) and/or named nerves is associated with poorer outcomes.[2,5] V2 is most commonly involved in cutaneous malignancies, although it carries minimal morbidity; additional studies suggest that V3 involvement is associated with much poorer outcomes.[2,4,7] Solares et al reviewed 36 patients with cHNSCC and perineural invasion to identify specific variables that predict worse outcomes.[2] V3 involvement was associated with a much lower survival curve and median survival compared to those without V3 involvement.[2] Five-year survival rates for V3 involvement were 16.3% compared to 50.6% in those without involvement. Panizza et al found five-year recurrence-free survival to be much lower in patients with V3 involvement (0%) than those without V3 involvement (66.7%).[7] However, this finding did not reach statistical significance (p=0.21). Alternatively, Erkan et al performed a retrospective review on 21 patients with cHNSCC and perineural spread to compare outcomes between primary treatment with multimodal therapy and treatment for recurrence with salvage therapy.[8] Patients with V1 involvement had significantly earlier recurrence compared to V2, V3, and CNVII. The median time to recurrence was 12 months for V1, 33 months for V2, and 36 months for V3.[8]

Our review found that V1 consistently had the worse survival curve and had the highest HR. Compared to V2, V1 had a statistically significantly worse survival curve, indicating that patients with V1 involvement are more likely to die from their disease compared to patients with V2 involvement. V1 is the smallest division of CNV, existing the skull base via the superior orbital fissure to supply sensory innervation to the forehead, scalp, dorsum of the nose, and eye. It branches while in the orbital apex into the frontal, lacrimal and nasociliary nerves. Thus, aggressive, high-risk tumors in these regions can invade and spread along V1 and any one of its branches. Treatment for V1 involvement is complicated by the components of the orbit, which are particularly susceptible to RT damage, potentially resulting in irreversible optic neuropathy. To avoid complications, often RT doses must be adjusted, increasing the risk of inadequate coverage and potential for recurrence.

V2 exits the skull base via the foramen rotundum, crossing the pterygopalatine fossa to reach the orbit, where it exits to the splanchnocranium via the inferior orbital fissure. It supplies the eye, nose, scalp and forehead. Most of the area supplied by V2 are exposed to sun to a greater extent than the rest of the face and are the regions from which cSCC most commonly arises. Thus, this is consistent with V2 being most frequently involved with high-risk cHNSCC.[2] V3 is not only the largest division of CNV, but it is the only branch that carries mixed sensory and motor innervation. Its path is much more complex than V1 and V2, exiting the foramen ovale to the parapharyngeal masticator space, where it divides into its four main sensory branches: buccal, auriculotemporal, lingual and inferior alveolar nerves. Compared to V2, which branches upon entering the pterygopalatine fossa, V3 branches at several additional points along its path, which can make disease significantly harder to clear once it is involved.

Management of cHNSCC with CNV is highly variable across institutions, reflecting a paucity of high-level evidence addressing optimal management of perineural invasion/spread.[2,7,8,10,56] The goal of surgery is en bloc resection of the involved nerve with clear margins. This

approach requires multidisciplinary expertise (ie, neurosurgery, otolaryngology, dermatology, and plastic surgery) and appropriate planning. Williams et al devised a zonal system that classifies patients based on the extent of perineural spread.[55] For CNV, zone 1 refers to spread along any one of its branches to the superior orbital fissure (V1), foramen rotundum (V2), and/or foramen ovale (V3). Zone 2 refers to perineural spread up to the Gasserian ganglion, and zone 3 describes spread to the brainstem. Zone 1 and 2 are generally treated with multimodal SRT. Zone 3 disease is managed on a case-by-case basis, however, it is generally considered too extensive for surgery and treated with definitive RT.

Several studies have reliably shown improved outcomes with SRT compared to other treatments.[7,10,20,56] In one cohort of patients with cHNSCC and perineural involvement, Panizza et al found that careful surgical planning followed by RT led to improved five-year OS and DFS at 67.9% and 58.6%, respectively.[7] A more recent review of 45 patients found that SRT with clear margins yielded significantly better OS and DFS compared to definitive RT, highlighting the importance of surgical margins in disease control.[10] Despite no randomized clinical controlled trial comparing SRT to single modal therapy, the NCCN recommends SRT as primary therapy for patients with cHNSCC and perineural invasion.

Our findings support prior studies and the established guidelines, as SRT consistently demonstrated superior survival curves for both OS and DFS. OS at one, two, and five years was consistently higher for the SRT group (93.8%, 87.5%, 76.2%) compared to surgery alone (92.3%, 72.7%, 20%) and RT alone (62.5%, 41.7%, 18.2%). Moreover, positive surgical margins were significantly associated with a significantly lower DFS curve, demonstrating that negative margins are essential to locoregional control. Taken together, these findings highlight the effectiveness of SRT in achieving greater locoregional control and survival outcomes for patients.

Some advocate for definitive RT as it avoids the challenges and morbidity associated with surgery.[2,7] Interestingly, when compared to SRT, definitive RT demonstrated significantly lower OS and DFS with HR at 6.21 and 3.95, respectively. Prior studies have Prior studies have demonstrated similar results. Phung et al found that patients treated with definitive RT had significantly worse outcomes and a two- and five-year DFS of 34% and 0%; OS at two and five years was 54% and 0%. This outcome can be partially explained by a relatively small sample size compared to surgery and SRT. However, it is also likely that this finding reflects selection bias as patients treated primarily with RT are more likely to have more advanced disease deemed nonresectable. Thus, outcomes were worse due to the advanced nature of the disease.[10]

Although our review focused on more established treatment methods for cHNSCC with CNV involvement, it is imperative to address emerging alternatives such as immunotherapy. Immune checkpoint blockade and other forms of T-cell-based immunotherapy have recently been established as another form of treatment for a variety of solid tumors. cSCC has a high tumor mutational burden, with a high rate of response to immune checkpoint blockade.[59] We have noted anecdotally that perineural invasion can improve upon treatment with immune checkpoint blockade, and this has been reported in small case series, including one series of 11 patients that was found in our database search.[56] In that study, clinical benefit defined by radiographic response or stable disease was noted in 9 of 11 patients treated for cHNSCC with perineural invasion. In a similar series of 12 patients with cHNSCC and cranial nerve involvement, 83% demonstrated clinical evidence of response to the anti-PD-1 antibodies pembrolizumab or cemiplimab.[60] Although these studies are promising, further research is needed to define the role of T-cell-based immunotherapy in the treatment of cHNSCC with CNV involvement. A clinical trial in development at NRG Oncology (HN014), a phase III study that will randomize patients with high-risk cHNSCC to standard surgery versus neoadjuvant cemiplimab followed by response-adapted surgery and adjuvant therapy as indicated, is likely to help define the role of immune checkpoint blockade in this context.

Limitations

There are several limitations to this review that should be addressed. Due to the specificity of our topic, we were unable to include a large number of studies that addressed cHNSCC with perineural invasion/spread but did not specify CNV involvement. Similarly, many of the studies we excluded had pooled data from which we were unable to separate the data relevant to our study. However, despite this limitation, we were able to gather a good number of high-quality articles as determined by the JBI. An inherent limitation of systematic reviews is the potential for selection bias, which we avoided by implementing a rigid set of inclusion criteria and utilizing a standardized critical appraisal tool (JBI).

CONCLUSION

This is the first systematic review to investigate the roles of both CNV involvement and treatment modality on survival outcomes in cHNSCC patients. Survival outcomes differ according to the identity of the involved CNV branch as well as by treatment. V1 involvement and definitive RT are associated with significantly lower survival curves.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Maldonado J, Lohana S, Barrow E, Vuncannon J, Pradilla I, Zohdy Y, et al. Management of cutaneous head and neck squamous cell carcinoma with trigeminal nerve involvement: a systematic review. Int J Otorhinolaryngol Head Neck Surg 2024;10:683-94.