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Elective Neck Dissection for Head and Neck Cutaneous Squamous Cell Carcinoma with Skull Base Invasion

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Abstract

Objectives. Skull base invasion from cutaneous squamous cell carcinoma (cSCC) via perineural spread affects survival and the rate of regional metastasis. Our objective is to investigate the factors associated with elective neck dissection (END) in this population and the survival difference with END compared with observation for patients with a cN0 neck.

Study Design. Case series with chart review.

Setting. Academic.

Subjects and Methods. Patients were treated surgically for head and neck cSCC with skull base invasion via perineural spread with a cN0 neck from 2004 to 2014. Clinicopathologic data were collected and analyzed. Primary outcomes were disease-free survival (DFS) and overall survival (OS).

Results. Fifty-nine patients met inclusion criteria: 28 underwent an END and 31 underwent neck observation. Free tissue transfer reconstruction was significantly associated with END ($P < .001$). Patients treated with an END had significantly improved 5-year DFS (57% and 32%, $P = .042$) and OS (60% and 37%, $P = .036$) compared with those who were observed and a significantly reduced rate of regional recurrence (9% and 37%, $P = .024$). The rate of occult nodal metastasis identified with END was 36% and is approximately equal to the regional failure rate of the neck observation group (37%).

Conclusion. END was more commonly used in cases requiring free tissue transfer. The use of END for head and neck cSCCs that have invaded the skull base is not routinely performed but was found to be associated with a survival advantage and reduced regional recurrence rate.

Keywords

cutaneous squamous cell carcinoma, skin cancer, head and neck, skull base invasion, elective neck dissection, perineural spread, risk factors, survival outcomes

Cutaneous malignancy is the most common cancer worldwide and often occurs in the head and neck.[1] Overall cure rates exceed 95% for several different treatment modalities; however, more aggressive tumors are responsible for approximately 2500 deaths per year.[2] Poor prognosis for head and neck cutaneous squamous cell carcinoma (cSCC) is associated with known high-risk features: larger tumor size, H-zone of the face, greater depth of invasion, immunosuppression, recurrent tumor, poor differentiation, lymphovascular invasion, and perineural invasion (PNI).[3-6] These high-risk features of the primary tumor are incorporated into the T classification under the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system for cSCC.[7] For cSCC, the overall incidence of regional metastasis is less than 5%,[3] but high-risk and advanced T classification tumors have an increased regional metastasis rate between 15% and 40%,[2,3,8] depending on criteria used, which is an independent risk factor for increased recurrence and mortality.

Lymph node involvement is also an important part of the AJCC staging system: classifying tumors N0 to N3. Clinically and radiographically, N0 (cN0) tumors have no evidence of regional lymph node metastasis prior to treatment. Elective

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neck dissection (END) and sentinel node biopsy have been used in high-risk patients to stratify and identify those patients with occult regional metastasis and pathologic positive neck disease (pN1-3), but currently there is a lack of consensus for the management of the cN0 neck. Based on final pathologic staging, recent studies have identified patients who benefit from adjuvant radiotherapy or chemoradiotherapy, including those with positive neck disease, to improve survival in these at-risk patients.[9]

Skull base invasion due to cSCC occurs by perineural spread from the skin along a cranial nerve toward the intracranial cavity or by direct extension through the underlying tissue and, by definition, is advanced-stage T4 disease.[7] We restricted our analysis to patients with perineural spread. Skull base invasion of cSCC is associated with increased morbidity and mortality, but this clinical entity is not well defined in the literature. We have described skull base invasion patterns and survival outcomes of nonmelanoma skin cancers and found that the route and extent of skull base invasion significantly affect disease-specific and overall survival.[10] For these patients, the success of initial surgical treatment relies heavily on accurate clinical judgment of the magnitude of disease spread to achieve resection with negative margins.[11] Magnetic resonance imaging (MRI) can delineate large nerve perineural spread classified according to the degree of skull base involvement[12] and is valuable for determining zonal classification: peripheral (zone 1), skull base (zone 2), and central (zone 3).[13,14] This classification correlates with disease-specific and overall survival.[10]

Rates of regional metastasis after skull base invasion due to cSCC are not well studied, and the benefit of an END in these patients is not known. Our goal is to identify factors associated with END and to investigate the survival difference in these patients treated with an END compared with observation for the cN0 neck.

Materials and Methods

Approval was granted from the University of Utah Institutional Review Board (IRB 00045048). Our database was retrospectively reviewed to identify patients with cSCC in the head and neck with radiographic evidence of perineural skull base invasion (zonal classification 2 and 3)[13] and a cN0 neck treated with surgical curative intent at our tertiary care hospital based on treatment recommendations of the multidisciplinary Head and Neck Treatment Planning Conference between 2004 and 2014. Patients with evidence of neck disease underwent a therapeutic neck dissection and were excluded from this analysis, as well as those treated with definitive chemoradiation or palliative therapy. Clinicopathologic data, treatments received, extent of skull base invasion, and survival outcomes were collected and analyzed. All comparisons were made between patients with a cN0 neck that underwent observation of the neck vs those treated with END.

Statistical analysis was performed using XLSTAT (version 2015.6.01; Addinsoft, New York City, New York, USA). A Fisher exact test was used on 2×2 contingency tables for categorical variables. The Kaplan-Meier method was used to calculate survival curve estimates, and comparisons between these groups were then performed using the log-rank test. Multivariate survival analysis was performed using the Cox proportional hazard regression model, using all variables to control for confounding covariates. Primary outcomes were disease-free survival (DFS) and overall survival (OS), and results were considered significant at $P \leq .05$.

Results

Fifty-nine patients met inclusion criteria: 28 underwent an END and 31 underwent neck observation. The most common END performed was levels 1 to 3 (n = 16), which was performed for any anterior lesion that did not involve the parotid. For a posterior lesion that did not involve the parotid, an END levels 1 to 4 was performed (n = 7). If the parotid was involved with the primary tumor, then a parotidectomy was performed as well as an END levels 1 to 4 (n = 5). Elective parotidectomy was not performed. There were no cases of posterior scalp lesions with invasion of the skull base via perineural spread. The mean follow-up time was 42 months, and 81% of patients were male. The average age at skull base invasion diagnosis was 69.1 years (range, 44-93 years), average age for the END cohort was 68.0 years, and the average age for the neck observation cohort was 70.1 years (P = .557). Clinicopathologic data, neck treatment groups, and complications are summarized in **Table 1**. Other factors associated with survival outcomes are compared between neck treatment groups: neck observation and END in **Table 2**. Free tissue transfer reconstruction ($P < .001$) and orbital invasion (P = .018) were significantly associated with utilization of END. No other significant difference between treatment groups was identified for factors including recurrent tumors, immunosuppression, extent of skull base involvement based on the zonal classification, cranial nerve involved, positive margin, and adjuvant therapy.

Patients treated with an END had significantly improved mean DFS and mean OS compared with those that were observed (67 vs 35 months, P = .042; 78 vs 44 months, P = .036, respectively), as well as 5-year DFS and OS (57% and 32%, P = .042; 60% and 37%, P = .036, respectively) (**Figure 1**). The rate of nodal metastasis identified in the N0 neck was 35.7% or 10 of 28 patients. Positive nodal disease was identified in the parotid alone (20%; n = 2), level 2 alone (30%; n = 3), level 3 alone (20%; n = 2), or multiple levels (30%; n = 3). No level 4 nodal metastasis were identified.

Multivariate analysis demonstrated that age at skull base invasion diagnosis, active immunosuppression, orbital involvement, and extent of skull base invasion based on the zonal classification, as well as END, were all independent factors associated with DFS and OS ($P < .05$) (**Table 3**).

The patterns of failure for those patients who recurred after treatment with an END were 64% (n = 7) with a central or local recurrence, 9% (n = 1) with a regional recurrence, and 27% (n = 3) with distant metastatic disease. The patterns of failure for those patients who recurred after neck observation were 16% (n = 3) with a central or local recurrence, 37% (n = 7) with a regional recurrence, and 47% (n = 9) with distant metastatic disease. These were significantly different between

Table 1. Patient and Tumor Characteristics, Neck Treatment Groups, and Complications (N = 59).

Patient and Tumor Characteristics	No. (%) of Patients
Male	48 (81)
Female	11 (19)
Preauricular	10 (17)
Scalp	9 (15)
Temple	9 (15)
Forehead	7 (12)
Cheek	7 (12)
Ear	5 (8)
Eyebrow	4 (7)
Postauricular	4 (7)
Nose	2 (3)
Midface	1 (2)
Lip	1 (2)
Well differentiated	10 (17)
Moderately differentiated	17 (29)
Poorly differentiated	24 (41)
Histologic grade unknown	8 (14)
Recurrent tumor	43 (73)
Immunosuppression	9 (15)
Orbital invasion	11 (19)
Skull base perineural zone II	30 (51)
Intracranial perineural zone III	29 (49)
Cranial nerve V involved	43 (73)
Cranial nerve VII involved	16 (27)
Elective neck dissection	28 (40)
Neck observation	31 (44)
30-day mortality	1 (2)
Stroke	0 (0)
Myocardial infarction	1 (2)
Cerebrospinal fluid leak	3 (5)
Reconstructive regional flap partial failure	1 (2)
Hematoma	3 (5)

Table 2. Patient and Tumor Characteristics Associated with Neck Treatment and Survival Outcomes Comparing Observation vs Elective Neck Dissection for Cutaneous Squamous Cell Carcinoma (cSCC) with Skull Base Invasion and a cN0 Neck.[a]

Patient and Tumor Characteristics	Neck Observation (n = 31)	Elective Neck Dissection (n = 28)	*P* Value
Recurrent tumor			
Yes	20 (47)	23 (53)	.153
No	11 (69)	5 (31)	.153
Immunosuppression			
Yes	4 (44)	5 (56)	.723
No	27 (54)	23 (46)	.723
Orbital invasion			
Yes	2 (18)	9 (82)	**.018**
No	29 (60)	19 (40)	**.018**
Extent of skull base invasion			
Perineural zone II	18 (60)	12 (40)	.301
Perineural zone III	13 (45)	16 (55)	.301
Cranial nerve			
V involved	22 (51)	21 (49)	.777
VII involved	9 (56)	7 (44)	.777
Adjuvant treatment			
Radiation	23 (44)	29 (56)	.687
Chemoradiation	2 (29)	5 (71)	.687
Histologic grade			
Well differentiated	4 (40)	6 (60)	.807
Moderately differentiated	9 (53)	8 (47)	.807
Poorly differentiated	14 (58)	10 (42)	.807
Unknown	4 (50)	4 (50)	.807
Surgical margin			
Negative	29 (55)	24 (45)	.409
Positive	2 (33)	4 (67)	.409
Reconstruction			
Free tissue transfer	4 (14)	24 (86)	**<.001**
Local flap/graft	27 (87)	4 (13)	**<.001**
Mean disease-free survival, mo	35	67	**.042**
Mean overall survival, mo	44	78	**.036**

[a]Values are presented as number (%) unless otherwise indicated. $P < .05$ in bold.

the 2 treatment cohorts and are summarized in the **Table 4** ($P = .024$).

To prevent surgical wound complications, establish a barrier between intracranial structures, and limit cerebrospinal fluid (CSF) leaks and ascending infections, patients were reconstructed after surgical resection with a variety of techniques. Different types of vascularized and nonvascularized flaps and grafts were used for reconstruction: bony free tissue transfer (n = 15), soft tissue free tissue transfer (n = 24), regional pedicled flaps (n = 9), free fascia lata and mucosal grafts (n = 18), and free autologous split calvarial bone grafts (n = 4). The primary decision for free tissue transfer can be categorized as exposed dura (17.9%; n = 5), CSF leak repaired (17.9%; n = 5), orbital exenteration (32.1%; n = 9), large soft tissue defect (17.9%; n = 5), and bony reconstruction (14.3%; n = 4). Surgical complications were 30-day mortality (1.7%; n = 1), myocardial infarction (1.7%; n = 1), CSF leak (6.8%; n = 4), regional nasoseptal flap partial failure (1.7%; n = 1), and hematoma (3.4%; n = 2). Reconstructive method and neck treatment received were not significantly associated with complications, DFS, or OS.

Discussion

Despite the frequency of cSCC, advanced tumors that have invaded the skull base are rare, and this clinical entity's survival outcomes are not well defined. The current body of literature is heterogeneous with incomplete data reporting, with individual series defining their results based on the type of surgical resection performed, area or cranial nerve

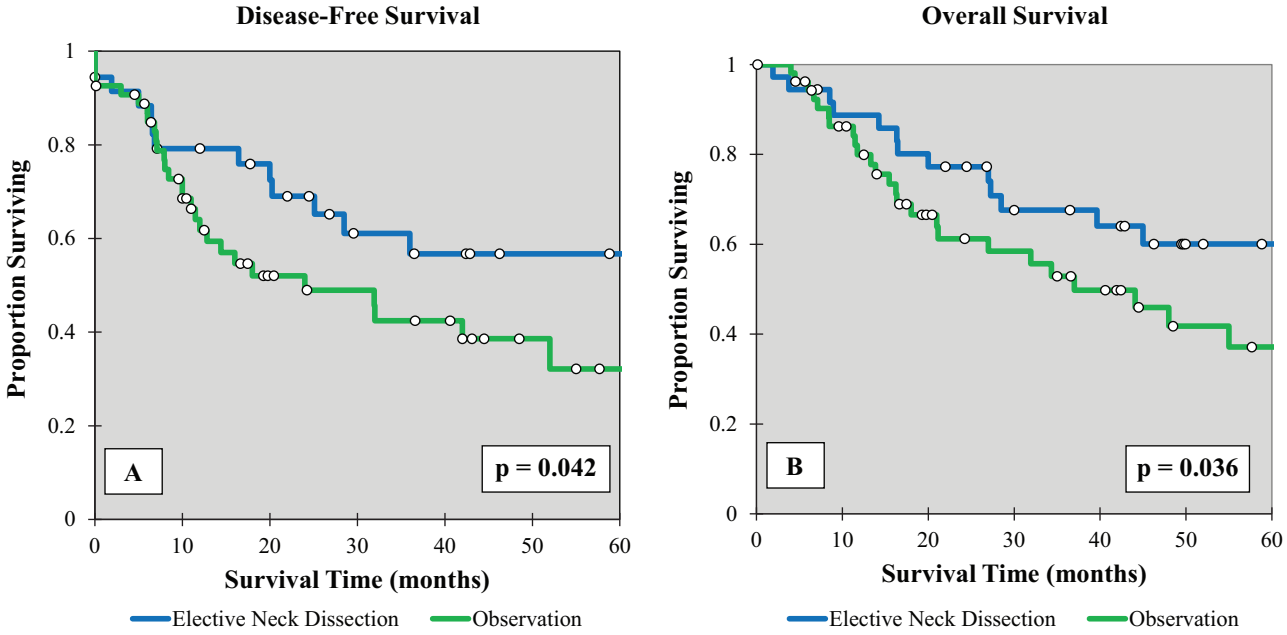

Figure 1. (A) Disease-free and (B) overall survival for cutaneous squamous cell carcinoma (cSCC) with skull base invasion with a cN0 neck, comparing patients treated with an elective neck dissection (n = 28) to those who were observed (n = 31).

Table 3. Multivariate Analysis of Factors Affecting Disease-Free Survival and Overall Survival Reported as Proportional Hazard Ratios with 95% Confidence Intervals.[a]

	Disease-Free Survival		Overall Survival	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age at diagnosis	1.311 (1.005-1.570)	**.039**	1.290 (1.020-1.065)	**.013**
Active immunosuppression	1.795 (1.026-2.324)	**.025**	1.434 (1.130-1.987)	**.041**
Orbital invasion	1.401 (1.292-1.798)	**.040**	1.677 (1.399-1.819)	**.036**
Skull base invasion zonal classification	2.113 (1.818-2.516)	**.013**	2.210 (1.191-3.012)	**.012**
Neck dissection	1.859 (1.059-3.604)	**.026**	1.936 (1.160-2.767)	**.015**

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]$P < .05$ in bold.

involved, histology, microscopic PNI vs large nerve PNI, or perineural spread, and classifying the extent of disease involvement is not consistent, so interpreting survival outcomes is a significant challenge.

We present our survival outcomes for cSCC with skull base invasion and cN0 neck based on the neck treatment received: observation vs END. Positive neck disease strongly correlates with recurrence and decreased survival; therefore, identifying these patients and triaging them to appropriate adjuvant therapy is critical. In our series, END was associated with improved survival outcomes compared with neck observation. Free tissue transfer reconstruction and orbital invasion were both significantly associated with utilization of END. To control for cofounding variables, a multivariate analysis was performed, including factors known to be associated with survival outcomes, and END was found to be an independent predictor of survival. In addition, we analyzed several other factors known to be associated with survival outcomes and found that none were associated with the type of neck treatment received for patients with a cN0 neck.

It is common practice at our institution to perform an END to aid in isolation of donor vessels for microvascular anastomosis for free tissue transfer, although the impact on disease outcomes was not known. In addition, patients with orbital invasion were most often treated with an orbital exenteration, and this defect was reconstructed with free tissue transfer. These practice patterns explain why these factors were associated with END; however, we had hypothesized that they were associated with worse survival outcomes, and our results were therefore unexpected.

This data illustrates that END for cSCC with skull base invasion is associated with identifying occult nodal disease in greater than a third (36%) of patients with a cN0 neck

Table 4. Patterns of Recurrence and Treatment Failure for Cutaneous Squamous Cell Carcinoma (cSCC) with Skull Base Invasion with a cN0 Neck, Comparing Patients Treated with an Elective Neck Dissection (n = 28) to Those Who Were Observed (n = 31).[a]

	Patterns of Recurrence and Treatment Failure, No. (%)			
Neck Treatment	Local/Central	Regional	Metastatic	*P* Value
Elective neck dissection	7 (64%)	1 (9%)	3 (27%)	**.024**
Neck observation	3 (16%)	7 (37%)	9 (47%)	**.024**

[a]$P < .05$ in bold.

and with a significant survival advantage. The rate of occult nodal disease identified is approximately equal to the regional failure rate of the neck observation group (37%). The reason for this survival difference is unclear. Although the rates of adjuvant therapy were not significantly different between the observation and END groups in our study, the observed survival benefit could be related to appropriately treating with adjuvant therapy based on pathology. More patients in the END treatment group received adjuvant radiation (29% vs 23%) and chemoradiation (5% vs 2%), and this could account for some of the survival benefit, but multivariate analysis demonstrated that adjuvant therapy was not an independent factor associated with DFS and OS. The effect of surgically clearing occult nodal disease could also be part of the survival benefit, as this is thought to significantly improve survival outcomes for squamous cell carcinoma from the oral cavity, oropharynx, and supraglottic larynx.[15-20] A recent prospective, randomized, controlled trial evaluated the effect of END on survival for lateralized stage T1 and T2 oral squamous cell carcinomas and found significantly higher rates of overall and disease-free survival compared with observation followed by a therapeutic node dissection for nodal relapse.[17] This high-level evidence for head and neck oral cavity squamous cell carcinomas suggests both improved patient stratification to adjuvant therapy and occult disease eradication can significantly improve survival outcomes.

Several limitations should be considered when interpreting the results of this study. The data were retrospectively obtained and are a single institution's experience. Physician and patient selection of treatment type was not standardized or randomly assigned, and the patients within each cohort had different comorbid conditions. Further multi-institution or population-level research or a clinical trial is needed to fully evaluate the efficacy of END in this rare disease entity and validate our findings.

Conclusions

The use of END for head and neck cSCC with invasion of the skull base via perineural spread is not routinely performed but appears to be associated with an increase in both disease-free and overall survival. END was significantly associated with utilization of free tissue transfer and orbital invasion, as these procedures were routinely performed in conjunction, but was not significantly related to other potential confounding variables associated with survival outcomes.

Author Contributions

Richard B. Cannon, study design, acquisition, analysis, and interpretation of the data, drafting the work, and final approval; **Yusuf Dundar**, study design, acquisition and interpretation of data, drafting the work, and final approval; **Andrew Thomas**, study design, analysis and interpretation of data, drafting the work, and final approval; **Marcus M. Monroe**, study design, analysis and interpretation of data, drafting the work, and final approval; **Luke O. Buchmann**, study design, analysis and interpretation of data, drafting the work, and final approval; **Benjamin L. Witt**, study design, analysis and interpretation of data, drafting the work, and final approval; **Aleksandra M. Sowder**, study design, analysis and interpretation of data, drafting the work, and final approval; **Jason P. Hunt**, study design, analysis and interpretation of data, drafting the work, and final approval.

Disclosures

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