Original Article

Elective Neck Dissection Versus Observation in Patients With Head and Neck Cutaneous Squamous Cell Carcinoma

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BACKGROUND: The survival benefit of elective neck dissection (END) for patients with cutaneous squamous cell carcinoma (cSCC) of the head and neck and no evidence of regional metastasis (cN0) has never been reported. The aim of this study was to determine the effect of END on patient survival. **METHODS:** The authors included patients with head and neck cSCC who had undergone primary surgery from 1995 to 2017. The primary end point was survival, and the secondary end points were the incidence of occult regional disease and regional disease control. To assess the impact of END on survival, the authors used multivariable Cox proportional hazards models with propensity score and matching techniques for internal validation. **RESULTS:** A total of 1111 patients presented with no evidence of nodal disease; 173 had END, and 938 were observed. Adjuvant radiotherapy to the neck was administered to 101 patients (9%). END resulted in a 5-year overall survival rate of 52%, whereas the rate was 63% in the observation group (P = .003 [log-rank]). The 5-year disease-free survival rate for patients undergoing END was similar to that for the observation group (73% vs 75%; P = .429). A multivariate regression model showed that the performance of END was not associated with improved rates of overall, disease-specific, or disease-free survival; similarly, among patients with advanced disease (T3-4), those who underwent END did not have improved survival rates. **CONCLUSIONS:** Among patients with cSCC of the head and neck, observation of the neck nodes resulted in noninferior survival rates in comparison with END at the time of primary surgery. Further studies are required to elucidate the role of END in patients with advanced disease. ***Cancer* 2021;127:4413-4420**. © *2021 American Cancer Society*.

KEYWORDS: head and neck, lymph node, metastasis, neck dissection, skin, squamous cell carcinoma, survival.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) most commonly occurs in the head and neck region.[1] The majority of newly diagnosed cSCCs are early-stage tumors that can be successfully cured with surgical excision.[2] However, a subset of cSCCs is associated with high-risk features such as poor histologic differentiation; greater depth of invasion (≥2 mm); perineural, vascular, or lymphatic invasion; and patient immunosuppression. These high-risk cSCCs carry an increased risk for local recurrence and regional metastasis.[2-6] Although the management of regional cSCC metastases to the parotid gland and neck with therapeutic nodal dissection and optional adjuvant radiotherapy—and, in selective cases, chemoradiotherapy—is widely accepted, the optimal management of high-risk, node-negative head and neck cSCC remains controversial.[7,8] Depending on their age, morbidity, and clinical and pathologic risk factors, these patients may be managed by either a wait-and-see approach (observation) or elective neck dissection (END).[7] Furthermore, the impact of occult nodal metastasis on survival in cSCC remains to be established.[9] In this study, we wanted to determine the effect of END on patient survival in clinically node-negative head and neck cSCC. Secondary aims were to determine the incidence of occult regional disease and regional disease control.

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MATERIALS AND METHODS

Patients

On June 16, 2020, we searched the REDCap cSCC registry in the Department of Head and Neck Surgery of The University of Texas MD Anderson Cancer Center for patients with head and neck cSCC who had undergone primary surgery at our institution from 1995 to 2017. Inclusion criteria included no evidence of regional metastasis (cN0) on physical examination reports or imaging studies (ie, ultrasonography, computed tomography, positron emission tomography–computed tomography, or magnetic resonance imaging).[10] Patients with less than 6 months of follow-up were excluded unless an event (ie, disease-specific death or recurrence) was recorded within 6 months of surgery. Patients with prior neck regional dissection or radiotherapy were excluded. Staging was determined by physical examination, computed tomography, ultrasonography, magnetic resonance imaging, and/or positron emission tomography–computed tomography. All staging was completed according to the guidelines of the American Joint Committee on Cancer (8th edition).[11] All cases were presented at a multidisciplinary conference. Adjuvant radiotherapy with or without concurrent systemic therapy was administered to patients with T3-4 or N2-3 tumors, extranodal extension, involved margins, or perineural invasion. Indications for END were tumor extension to high-risk regions according to the National Comprehensive Cancer Network guidelines for cSCC (ie, central face, lips, preauricular and postauricular skin, temple, and ears), the presence of perineural or lymphovascular invasion on presurgical biopsy, and recurrence on presentation that required free flap reconstruction.[12] Univariate analysis followed by multivariate logistic regression analysis of patients undergoing END versus observation was used to confirm that in our cohort, a high-risk site ($P = .012$) and recurrence on presentation ($P = .034$) were significant determinants of neck management (Supporting Table 1). Observed cases were monitored with physical examination and neck computed tomography or ultrasonography every 1 to 3 months for year 1, every 2 to 4 months for year 2, and every 4 to 6 months for years 3 to 5.

Histopathologic Analysis

Both primary and neck dissection specimens underwent a standard pathologic evaluation by a certified dermatopathologist or head and neck pathologist. Specimens were dissected and tissues were sampled as recommended by the guidelines for the histopathologic evaluation of head and neck carcinoma.[13]

Statistical Analysis

We used the Kaplan-Meier method to calculate the rates of overall survival (OS; the time elapsed from the date of surgery to the date of death or censoring at last follow-up), disease-specific survival (DSS; the time elapsed from the date of diagnosis to death resulting from cSCC), disease-free survival (the time elapsed from the date of surgery to the first signs or symptoms of cSCC recurrence), and regional control (the time elapsed from the date of surgery to the first signs or symptoms of cSCC nodal recurrence). The log-rank test was used to assess the differences in survival and control rates.[14,15] The Cox proportional hazards regression model was used to compare the factors with prognostic potential.[16] We applied a process of several steps to develop a final model. The first step was to study the correlation between DSS or OS and each covariable via a univariable Cox proportional hazards regression model and then a preliminary multivariable Cox proportional hazards regression model. Thus, covariates with a univariable P value $< .2$ were included in the preliminary multivariable model. Variables that remained statistically significant ($P < .05$) were included in the final multivariable model. A 2-step matching process was implemented. First, all eligible controls were matched according to their age, sex, and T classification. In the second step, we applied 1:1 propensity score matching with the Mahalanobis distance. The variables included in the propensity score matching were age, sex, ethnicity, recurrence status on presentation, immunosuppression status, and T classification. $P < .05$ was defined as significant, and 2-sided statistical tests were used in all calculations using JMP (version 14; SAS Institute, Inc, Cary, North Carolina). The study was approved by the institutional review board committees of MD Anderson Cancer Center.

RESULTS

A total of 1582 patients were surgically treated consecutively for head and neck cSCC at our institution during the study period; 1111 of those patients presented with no evidence of nodal disease and were eligible for study inclusion (Fig. 1). One hundred seventy-three patients (16%) underwent END; 131 of these (12%) involved parotidectomy. The remaining 938 patients (84%) were managed with observation followed by therapeutic neck dissection at the time of regional recurrence.

Patients' demographic and clinical characteristics are summarized in Table 1. Of the 1111 patients included in this study, 952 (86%) were male, and 159 (14%) were female; the median age was 70 years (range, 19-97 years).

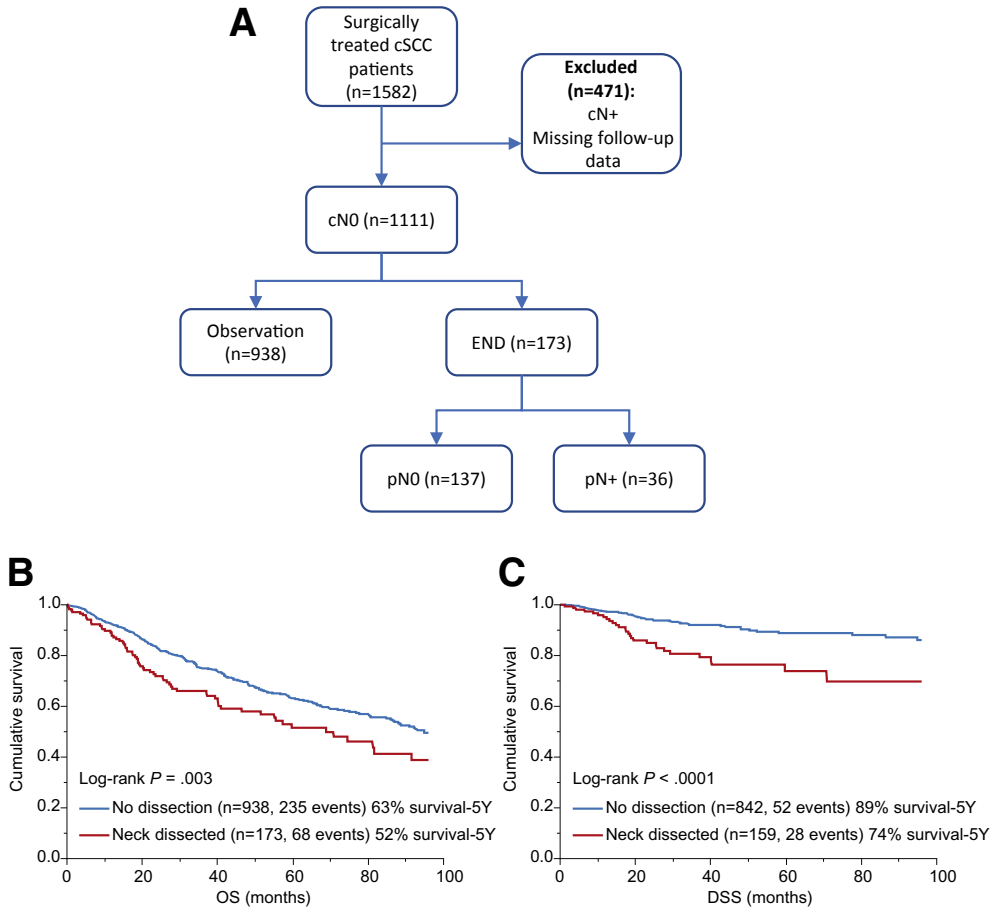

Figure 1. Patient population and Kaplan-Meier analysis. (A) Consolidated Standards of Reporting Trials flowchart of the study population. (B) Five-year OS and (C) DSS calculated by the Kaplan-Meier method according to the neck management status. cSCC indicates cutaneous squamous cell carcinoma; DSS, disease-specific survival; END, elective neck dissection; OS, overall survival.

The distribution of the patients according to ethnicity was as follows: White, 1055 (95%); Asian, 34 (3%); and Hispanic, African American, or other, 22 (2%). Chronic immunosuppression was present in 256 patients (23%), hematologic malignancies (eg, chronic lymphocytic leukemia) were present in 86 (8%), and organ transplantation was performed in 38 patients (3%).

Advanced disease (T3-4) was more common in the patients who underwent END (58% vs 25%; $P < .001$). Fifty-four patients (31%) in the END group received adjuvant therapeutic-dose irradiation to the lateral neck fields, whereas 47 (5%) did in the no-END group ($P < .001$). Total radiation doses ranged from 50 to 70 Gy, with no difference in the mean doses (52 ± 1.24 and 52 ± 1.33 Gy in the END and no-END groups, respectively; $P = .798$).

The 5-year OS rate was 52% for patients who underwent END and 63% for patients who did not ($P = .003$ [log-rank]; Fig. 1). The 5-year DSS rate was 74% for patients who underwent END and 89% for patients who did not ($P < .001$ [log-rank]; n = 1001 [the cause of death was not available for 110 patients]). At 5 years, the disease-free survival rates were similar in the END and observation groups (73% vs 75%; $P = .429$).

Throughout the study period, there were 34 recurrences (14 of which were regional) and 97 deaths in the END group and 155 recurrences (49 of which were regional) and 282 deaths in the observation group. The 5-year regional recurrence rates did not differ between patients who underwent END (8%) and those who did not (5%; $P = .138$; Fig. 2). Notably, 41 of the 49 patients (84%) who developed regional recurrence after observation were treated with therapeutic neck dissection for their relapse; only 6 patients with regional recurrence treated with therapeutic neck dissection died of head and neck cSCC.

The overall rate of occult nodal metastasis among patients who underwent END was 21% (36 of 173). A

TABLE 1. Patient Demographic and Clinical Characteristics

Variable	Elective Neck Dissection	No Neck Dissection	*P*
No. of patients (%)	173 (16)	938 (84)	
Recurrence on presentation, No. (%)	90 (52)	257 (27)	<.001
Age, mean ± SD, y	69 ± 11	70 ± 12	.732
Sex, No. (%)			.365
Male	152 (88)	800 (85)	
Female	21 (12)	138 (15)	
Immunosuppression, No. (%)			.826
None	134 (77)	714 (77)	
IDDM	21 (12)	74 (8)	
Hem/Onc	4 (2)	82 (9)	
Organ transplant	8 (5)	39 (3)	
Steroid use	4 (2)	20 (2)	
AID	1 (<1)	15 (2)	
HIV/AIDS	0 (0)	3 (<1)	
Other	4 (2)	19 (2)	
Pathologic T classification, No. (%)			<.001
T1	36 (21)	607 (65)	
T2	37 (21)	101 (11)	
T3	75 (43)	183 (19)	
T4	25 (15)	47 (5)	
Pathologic N classification, No. (%)		N/A	
N0	137 (79)		
N1	17 (10)		
N2	9 (5)		
N3	10 (6)		
Lateral neck irradiation: yes, No. (%)	54 (31)	47 (5)	<.001
Adjuvant chemotherapy: yes, No. (%)	36 (21)	34 (4)	<.001
Follow-up, median (range), mo	26 (6-217)	24 (2-254)	.7518

Abbreviations: AID, autoimmune disease; Hem/Onc, hematologic/oncologic; IDDM, insulin-dependent diabetes mellitus; N/A, not applicable.

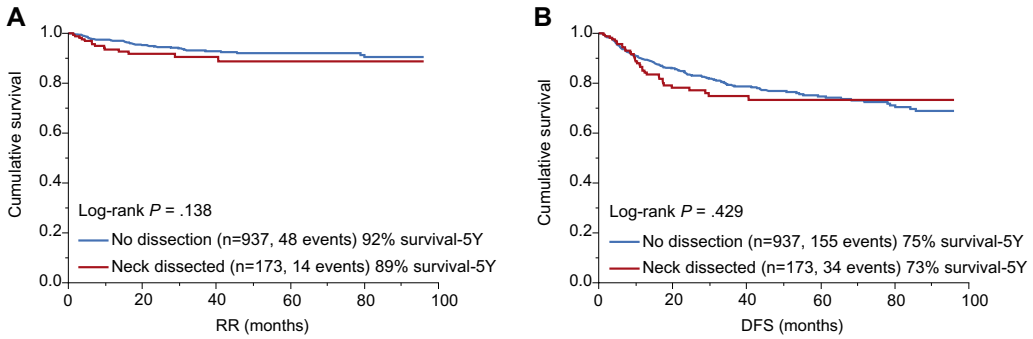

Figure 2. Kaplan-Meier analysis. (A) Five-year RR and (B) DFS calculated by the Kaplan-Meier method according to the neck management status. DFS indicates disease-free survival; RR, regional recurrence.

subgroup analysis of OS and DSS rates by nodal status in patients who underwent END revealed no differences between patients with and without occult metastases (Supporting Fig. 1). Because many more patients underwent observation (84%) rather than END, to control for a potential selection bias, we matched 298 patients (149 per group) for age, sex, ethnicity, recurrence status on presentation, immunosuppression status, and T classification. This internal validation method was chosen over others because matching techniques have been shown to produce stable and nearly unbiased estimates of predictive accuracy with increased power and decreased variability, regardless of the sample size. As shown in Supporting Figure 2, there were no differences in OS ($P = .754$ [log-rank]) or DSS ($P = .192$ [log-rank]) between the matched groups.

The 5-year OS rate was 44% for patients with locally advanced disease (T3-4) who underwent END and 54% for those who did not undergo END ($P = .070$ [log-rank]; Fig. 3); among patients with T1-2 tumors, the 5-year OS rate was 61% for those who had END and 66% for those who did not ($P = .431$ [log-rank]). Interestingly,

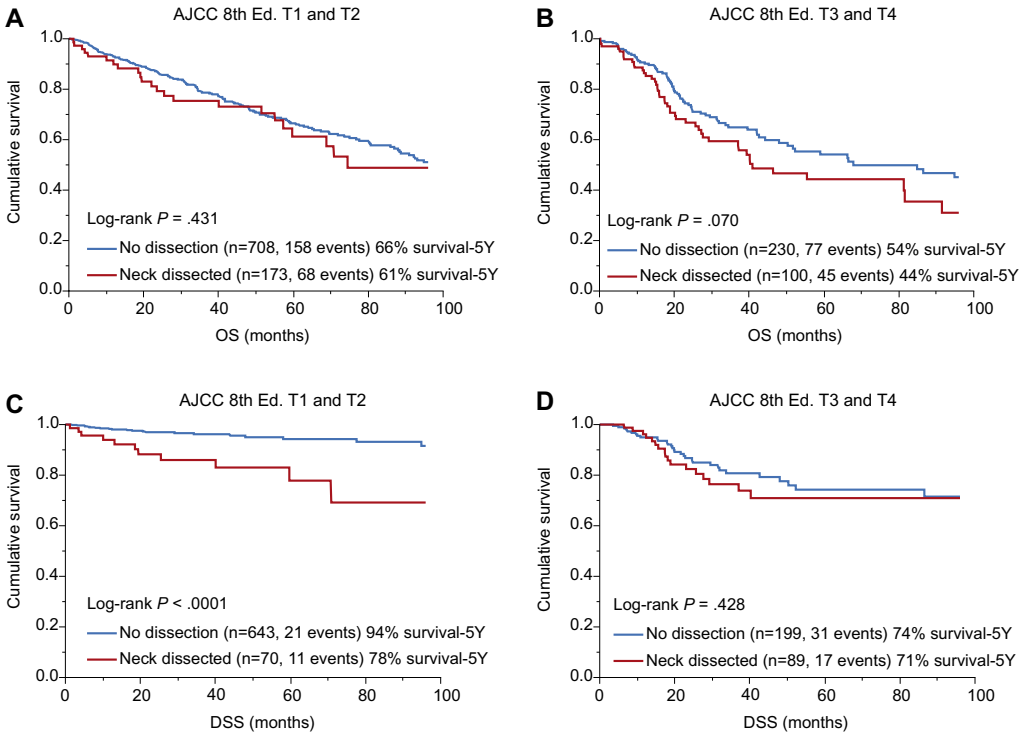

Figure 3. Kaplan-Meier analysis. Five-year OS of patients with (A) early (T1-2) and (C) advanced (T3-4) head and neck cutaneous squamous cell carcinoma and 5-year DSS of patients with (B) early (T1-2) and (D) advanced (T3-4) head and neck cutaneous squamous cell carcinoma calculated by the Kaplan-Meier method according to the neck management status. AJCC indicates American Joint Committee on Cancer; DSS, disease-specific survival; OS, overall survival.

patients with early disease (T1-2) who did not have END had better 5-year DSS rates than those who had END (94% vs 78%; $P < .001$ [log-rank]). Among patients with locally advanced disease (T3-4), we found no difference in DSS ($P = .428$).

The variables that were introduced into the Cox regression model (n = 1111) were age, sex, immunosuppression status, recurrence status at presentation, margin status, T and N classification, presence/absence of neural invasion, treatment group (surgery, surgery and radiotherapy, or surgery and chemoradiation), and neck management (END vs observation). In the multivariate analysis, age, immunosuppression status, and presence/absence of neural invasion, but not neck management, were independently associated with both OS and DSS (Table 2).

DISCUSSION

Most cSCCs present at an early stage, and data on the impact of nodal metastases on cSCC outcomes are scarce and insufficient to determine the optimal role of elective neck treatment. In mucosal head and neck squamous cell carcinoma (SCC), an END is generally indicated if the probability of occult cervical metastases is greater than 15% to 20%.[17] Our finding of a 20% rate of occult neck metastases in patients with cSCC would seem to support the performance of END in patients with cSCC as practiced in those with mucosal SCC. However, our data indicate a lack of a survival advantage in patients who had END compared with those who were observed. The low rate of regional recurrence in patients who were observed (49 of 938 [5%]) makes the overall occult incidence rate for this study much lower than the conventional threshold for END. This might explain the favorable neck control rates in our study and should be taken into consideration when one is contemplating management of the neck in cSCC. Furthermore, our subgroup analyses suggest that END did not improve survival rates, even for patients with advanced disease (T3-4). Interestingly, the regional recurrence rate in the observation group was lower than the rate of occult nodal metastasis in the END group. This patient population is generally older, and it is possible that patients with occult nodal metastasis are lost

TABLE 2. Cox Regression Analysis of Prognostic Factors for Overall and Disease-Specific Survival

		Overall Survival			Disease-Specific Survival			Regional Recurrence–Free Survival		
Variable		*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI
Age	y	<.001	1.049	3.60-6.26	<.001	1.042	1.024-1.060	.093	1.026	0.996-1.058
Sex	Male	.039	1		.415	1		.488	1	
	Female		0.647	0.428-0.977		0.805	0.471-1.374		0.704	0.262-1.893
Recurrence on presentation	No	.238	1		.654	1		.848	1	
	Yes		1.179	0.896-1.551		1.090	0.748-1.588		1.071	0.528-2.174
Chronic immunodeficiency	No	<.001	1		.003	1		.182	1	
	Yes		1.802	1.332-2.442		1.879	1.266-2.788		1.638	0.793-3.382
Pathologic T classification	T1	.024	1		.311	1		.013	1	
	T2		1.492	1.014-2.196		1.298	0.706-2.387		1.057	0.374-2.987
	T3		1.240	0.737-2.088		1.537	0.748-3.157		0.051	0.008-0.350
	T4		1.995	1.142-3.484		1.184	0.527-2.660		0.022	0.002-0.256
Pathologic N classification	N0	.3773	1		.778	1		.119	1	
	N1		0.661	0.276-1.581		1.298	0.706-2.388		2.134	0.407-11.202
	N2		1.018	0.354-2.931		1.537	0.748-3.157		5.976	1.381-25.848
	N3		1.787	0.801-3.985		1.183	0.527-2.660		4.278	N/A
Margin status	Negative	.162	1		.917	0.977	0.636-1.502	.419	1.412	0.611-3.267
	Positive		0.783	0.557-1.103						
Neural invasion	No	.033	1		.028	1.951	1.037-3.673	<.001	1	
	Yes		1.770	1.043-2.674					37.392	5.059-276.399
Radiotherapy	No	.004	1		.084	0.668	0.424-1.053	.180	1	
	Yes		0.593	0.145-0.846					0.549	0.228-1.317
Chemotherapy	No	.597	1		.522	1		.024	1	
	Yes		1.155	0.676-1.974		1.238	0.652-2.351		3.244	1.166-9.032
Elective neck dissection	No	.080	1		.527	1		.995	1	
	Yes		1.364	0.963-1.931		1.169	0.724-1.888		0.997	0.380-2.615

Abbreviations: CI, confidence interval; HR, hazard ratio; N/A, not applicable.

to follow-up because of a non–cancer-related death before the clinical presentation of regional recurrence. Although this might suggest a selection bias associated with the decision of whether to perform END, it also highlights the potentially modest impact that END has in this patient population. This should be further evaluated prospectively. Still, regardless of the patient characteristics or clinical reasons that led to the performance of END, regional recurrence was not different between the END and observation groups, and most patients in the observation group who had a regional recurrence were successfully treated with salvage therapeutic neck dissection.

The less prominent survival advantage of END in cSCC versus mucosal SCC may be due to the older age of cSCC patients (median age, 70 vs 55 years) and the higher rates of immunosuppressive comorbidities (eg, insulin-dependent diabetes mellitus and hematologic malignancies). This is further demonstrated by the relatively low rate of cancer-related death after 5 years among patients who did not have END (11%) in comparison with the overall death rate (37%). Also, our multivariate regression analysis identified only age, immunosuppression status, and the presence/absence of neural invasion, rather than the systemic treatment regimen (ie, adjuvant chemotherapy), as independent determinants of both OS and DSS. This is consistent with our hypothesis that patient factors, rather that tumor pathologic features (especially nodal metastasis), are associated with survival, and it is supported by previous data also showing that immunosuppression is a predictor of both outcomes and rates of nodal metastasis in cSCC.[18,19]

This study has several limitations. Treatment was not assigned in a randomized fashion; this might suggest underlying issues that resulted in worse prognoses for patients who had END. That said, our multivariate analysis revealed that adjuvant radiotherapy was associated with a significantly lower risk of death of any cause ($P = .004$) and a marginally significantly lower risk of cancer-specific death ($P = .08$). These findings, together with previous reports with a higher rate of occult regional metastasis and the potential survival benefit with neck radiation in patients with cSCC, suggest that adjuvant radiation might be beneficial and should be considered in these patients.[20,21]

Although it is not possible to disentangle these patient factors from the "direct" effect of END, our propensity score–based matching validation showed no survival benefit for patients who had END, even among patients with advanced disease. Although our finding of

significantly higher DSS rates in patients with early disease (T1-2) who did not have END in comparison with those who had END suggests that deaths in this patient population might be related to preexisting or procedure-associated morbidities, the study design precluded us from concluding that. We found higher rates of advanced and recurrent disease in the END group, yet our multivariate regression analysis did not identify these factors as potential causes of the difference in survival rates. The study spans over 25 years, and although treatment trends have changed during this period of time, we present a standardized approach practiced by our multidisciplinary team. Furthermore, no evidence of heterogeneity between time periods (1995-2009 and 2010-2019) was noted. It is important to note that most patients were closely monitored for regional recurrence by physical examination and ultrasonography or computed tomography in the first 2 years after their surgery. Hence, the feasibility of neck surveillance and salvage surgery in case of recurrence should be considered when one is deciding whether or not to perform an END. Taken together, these findings support further evaluation of less extensive surgical approaches (eg, sentinel lymph node biopsy for high-risk T1 patients or any T2 patient) or observation of the regional lymphatics in patients who are clinically node negative, even those with advanced or recurrent disease at the primary site. Although this was a large study and there was internal validation by matching, a prospective clinical trial is needed to fully assess the role of END in cSCC. Until then, the regional treatment of patients with cSCC should be based on risk stratification and multidisciplinary input.

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CONFLICT OF INTEREST DISCLOSURES

David I. Rosenthal reports participation on an advisory board for Merck. Renata Ferrarotto reports consulting fees from Bicara Therapeutics and payments or honoraria from Medscape and Intellisphere as well as participation on a data safety monitoring board or advisory board for Regeneron-Sanofi and Prelude Therapeutics. Kenneth Tsai reports consulting fees from Sanofi/Regeneron, Merck, Pfizer, Sun Pharma, and NFlection Therapeutics and stock or stock options in NFlection Therapeutics. Michael K. Wong reports participation on a data safety monitoring board or advisory board for Pfizer, EMD-Serono, Bristol-Myers Squibb, Regeneron, Adagene, Castle Biosciences, and Exicure and on an editorial board for CURE Magazine. Priyadharsini Nagarajan reports a leadership role in the American Society of Dermatopathology. Neil D. Gross reports clinical trial support from Regeneron; consulting fees from Sanofi-Genzyme; participation on advisory boards for Regeneron, PDS Biotechnology, and Shattuck Labs; and stock options in PDS Biotechnology. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Moran Amit: Concept; acquisition and performance of the analysis; drafting of the manuscript, tables, and figures; responsibility for the overall content; and review of the final document and approval for publication. **Chuan Liu:** Data acquisition and review of the final document and approval for publication. **Jobran Mansour:** Data acquisition and review of the final document and approval for publication. **Frederico O. Gleber-Netto:** Substantial contributions to the acquisition and performance of the analysis and review of the final document and approval for publication. **Samantha Tam:** Substantial contributions to the acquisition and performance of the analysis and review of the final document and approval for publication. **Erez N. Baruch:** Substantial contributions to the acquisition and performance of the analysis and review of the final document and approval for publication. **Mohamed Aashiq:** Concept and review of the final document and approval for publication. **Adel K. El-Naggar:** Concept and review of the final document and approval for publication. **Amy C. Moreno:** Concept and review of the final document and approval for publication. **David I. Rosenthal:** Concept and review of the final document and approval for publication. **Bonnie S. Glisson:** Concept and review of the final document and approval for publication. **Renata Ferrarotto:** Concept and review of the final document and approval for publication. **Michael K. Wong:** Concept and review of the final document and approval for publication. **Michael R. Migden:** Concept and review of the final document and approval for publication. **Goujun Li:** Concept and review of the final document and approval for publication. **Anshu Khanna:** Data acquisition and review of the final document and approval for publication. **Ryan P. Goepfert:** Concept and review of the final document and approval for publication. **Priyadharsini Nagarajan:** Data acquisition and review of the final document and approval for publication. **Randal S. Weber:** Concept and review of the final document and approval for publication. **Jeffrey N. Myers:** Concept and review of the final document and approval for publication. **Neil D. Gross:** Concept; drafting of the manuscript, tables, and figures; responsibility for the overall content; and review of the final document and approval for publication.

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