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Neck recurrence in clinically node-negative oral cancer: 27-year experience at a single institution

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ABSTRACT

Objectives: Neck failure in patients with oral squamous cell carcinoma (OSCC) carries a poor outcome, yet the management of patients who initially present with clinically node-negative (cN0) neck is not clearly defined.
Patients and methods: Retrospective review of patients with cN0 OSCC treated at Memorial Sloan Kettering Cancer Center from 1985 to 2012, focusing on rate, pattern and predictors of neck failure, salvage treatment, and survival outcomes.
Results: Of 1,302 patients, 806 (62%) underwent elective neck dissection (END) and 496 (38%) had observation. 190 patients (15%) developed neck recurrence. Median follow-up was 58.5 months (range 1–343); 5-year neck recurrence-free survival (NRFS) was 85% and 80% for the END and observation group respectively ($p = .06$). Patients with neck failure had poorer outcomes than patients without neck failure (5-year overall survival, 37% vs. 74% [$p < .001$]; disease-specific survival [DSS], 41% vs. 91% [$p < .001$]). Independent predictors of neck failure were smoking, primary tumor subsite (hard palate and upper gum), and extranodal extension. 87% of patients underwent salvage treatment (END: 81.1%; observation: 94%). Salvage surgery with adjuvant (chemo) radiation had better DSS than surgery alone or nonsurgical salvage.
Conclusions: In our cohort of patients with initially cN0 OSCC triaged to END vs. observation using clinical parameters, 15% developed neck failure. Salvage treatment was feasible in most cases but survival was poorer compared to patients without neck failure. Surgery followed by adjuvant (chemo) radiation resulted in the best outcome.

Introduction

The incidence of oral squamous cell carcinoma (OSCC) has gradually increased during the last 4 decades [1]. Despite advances in surgical techniques, radiation therapy (RT), and systemic agents, 5-year overall survival (OS) has plateaued at 65% [2]. With the exception of prevention measures and early-detection educational initiatives, there have been no major changes in the management of patients with OSCC, which is primarily surgical [3,4]. Disease-specific survival (DSS) and OS, are, in large part, dependent on achieving local and regional control [5]. Regional recurrence in patients who present with clinically node-negative (cN0) neck is uncommon but carries a poor prognosis [6]. Several prognostic factors, including primary tumor (T) stage, tumor depth, perineural invasion (PNI), lymphovascular invasion (LVI), and aggressive tumor histological subtype, have been associated with an increased risk of neck recurrence [7,8]. Other factors, such as the subsite of the primary tumor within the oral cavity, have not been adequately addressed and may be significant [9].

Neck recurrences are typically treated with salvage surgery, with or without adjuvant therapy [10]. This salvage treatment must be individually tailored according to the extent of the neck recurrence, the feasibility of surgical resection, and the functional and aesthetic consequences of resection, in addition to host factors that may be relevant. In some cases, achieving regional control may be challenging,

Abbreviations: OSCC, oral squamous cell carcinoma; cN0, clinically node-negative; END, elective neck dissection; PORT, postoperative radiation therapy; NRFS, neck recurrence-free survival; RT, radiation therapy; DSS, disease-specific survival; OS, overall survival; CRT, chemoradiotherapy; AJCC, American Joint Committee on Cancer; HP, hard palate; UG, upper gum; PNI, perineural invasion; LVI, lymphovascular invasion; pT, pathological T stage; pN, pathological N stage; ECS, extracapsular spread

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especially in the setting of previous RT or chemoradiotherapy (CRT).

We reviewed our 27-year experience in neck management in patients with OSCC who initially presented with cN0 neck. Specifically, we sought to determine the incidence and pattern of neck recurrence in our cohort, the effect of neck recurrence on survival, the clinical and pathological factors predictive of neck recurrence, the rate and type of salvage treatment used, and lastly, the outcomes following salvage treatment.

Patients and methods

After approval was obtained from the Institutional Review Board at Memorial Sloan Kettering Cancer Center, 1302 patients with cN0 neck were identified from a cohort of 1866 patients who underwent surgical resection for OSCC from 1985 to 2012.

Clinical and pathological characteristics were recorded. Clinical factors consisted of sociodemographic characteristics (sex, age, smoking status, and alcohol consumption), tumor subsites, and American Joint Committee on Cancer (AJCC) clinical stage. The oral cavity subsites were categorized as buccal mucosa, floor of mouth, hard palate (HP), lower gum, retromolar trigone, tongue, and upper gum (UG). Pathological factors included histological grade, PNI, (LVI), margins, tumor thickness, AJCC pathological T (pT) stage, pathological N (pN) stage, and extra capsular spread (ECS). Salvage treatment was defined as any potentially curative treatment, surgical or nonsurgical, given to a patient following a recurrence in the neck. The salvage rate refers to the percentage of patients who received the salvage treatment.

This study included three survival endpoints of interest: neck recurrence-free survival (NRFS), DSS, and OS, which were calculated from the date of initial curative surgery. Salvage DSS was calculated from the date of neck recurrence. NRFS, DSS, and salvage DSS were censored at the last recorded date of disease assessment. OS was censored at the last date a patient was known to be alive, regardless of disease status. A neck recurrence event was documented only if proven by biopsy. A death was considered an event for DSS if the patient was known to have active disease at the last disease assessment before death. Death from any cause was considered an event for OS.

Associations were identified by using the chi-square test. Univariate survival analysis was performed using the Kaplan-Meier method, and the log-rank test was used to determine significance. A p-value $< .05$ were considered statistically significant. Multivariable analysis was performed using Cox proportional hazard regression.

Results

Clinical and pathological characteristics and initial management

Table 1 shows the clinical and pathological characteristics of patients, stratified by modality of neck management. Of the 1302 patients with cN0 necks, (55%) were males, and the median age was 63 years (range, 15–96 years). The most common tumor subsite was the tongue (53%). Elective neck dissection (END) was carried out in 806 patients (62%). The remaining 496 patients (38%) were selected for observation based on the following criteria: (1) patients with small T1 tumors < 2 mm in thickness, according to preoperative clinical and radiological evaluation; (2) elderly patients with medical comorbidities who have substantially increased risk of severe postoperative complications from more extensive surgery; and (3) patients with tumors of the HP and UG, in whom the risk of occult neck metastases was traditionally thought to be low and who therefore underwent observation of the cN0 neck irrespective of T stage.

Clinical and pathological characteristics of patients, stratified by adjuvant treatment are shown in Supplementary Table 1. As expected, patients who underwent END were more likely to have adverse pathological factors, such as LVI, PNI, higher histological grade, and higher pT stage. In the END group, 282 patients (35.0%) received adjuvant RT or CRT after primary surgery. Thirty-five patients (7.1%) in the observation group received adjuvant RT or CRT after surgery of the primary site. In accordance with National Comprehensive Cancer Network guidelines, the RT field in patients with adverse factors included both the primary site and the neck [11].

Table 1
Clinical and pathological characteristics of patients with clinically negative neck nodes, stratified by neck management.

Variable	Observed (N = 496) N (%)	Elective neck dissection (N = 806) N (%)	*P*
Sex			.037
Female	243 (49)	347 (43)	
Male	253 (51)	459 (57)	
Age, years			< .001
< 60	169 (34)	382 (47)	
≥60	327 (66)	424 (53)	
Alcohol			.277
Never	154 (31)	227 (28)	
Ever	340 (69)	574 (71)	
Not known[a]	2 (0.4)	5 (0.6)	
Tobacco			.872
Never	175 (35)	280 (35)	
Ever	320 (65)	522 (65)	
Not known[a]	1 (0.2)	4 (0.4)	
cT stage			< .001
T1	300 (61)	264 (33)	
T2	129 (26)	380 (47)	
T3	18 (4)	70 (9)	
T4	30 (6)	85 (11)	
Not known[a]	19 (4)	7 (1)	
Site			< .001
Buccal Mucosa	29 (6)	51 (6)	
Floor of Mouth	65 (13)	108 (13)	
Hard Palate	34 (7)	2 (0.2)	
Lower Gum	39 (8)	127 (16)	
Retromolar Trigone	14 (3)	48 (6)	
Tongue	224 (45)	466 (21)	
Upper Gum	91 (18)	4 (0.4)	
LVI			< .001
No	294 (59)	517 (64)	
Yes	19 (4)	87 (11)	
Not known[a]	183 (37)	202 (25)	
PNI			< .001
No	283 (57)	406 (50)	
Yes	30 (6)	198 (25)	
Not known[a]	183 (37)	202 (25)	
Grade			< .001
Well	157 (32)	146 (18)	
Moderate	221 (45)	529 (66)	
Poor	26 (5)	102 (13)	
Not known[a]	92 (19)	29 (4)	
pT stage			< .001
T1	310 (63)	435 (54)	
T2	62 (13)	204 (25)	
T3	9 (2)	33 (4)	
T4	39 (8)	99 (12)	
Not known[a]	76 (15)	35 (4)	
Adjuvant RT	7%	35%	

cT: clinical T stage; LVI: lymphovascular invasion; PNI: perineural invasion; pT: pathological T stage; RT: radiation therapy.
[a] Not included in chi square analysis.

Incidence of neck recurrence

Fig. 1A shows the incidence of neck recurrence, stratified by management of the cN0 neck. 190 patients (15%) had neck recurrence. The overall 5-year NRFS was 83%. NRFS trended towards being better in the ED group compared to the observation group, but this was not statistically significant (85% vs. 80% [p = .063]; Fig. 1B). The median time to neck recurrence was 8.3 months. Among the patients in the END group, those who were pN+ had the highest rate of neck recurrence (50