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Distribution of Metastatic Nodes in N0-1 Patients with Tonsillar Squamous Cell Carcinoma and Its Implications for Selective Neck Dissection

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Original Investigation

Abstract

Objective: We aimed to evaluate the pattern of neck metastasis in patients with primary tonsillar carcinoma treated by primary surgery and neck dissection. Impact of the extent of neck dissection and level of metastatic nodes on survival were also evaluated.

Methods: We evaluated 163 consecutive patients with tonsillar squamous cell carcinoma submitted for neck dissection and staged as cN0-1. Selective neck dissection was performed using a template encompassing levels I-III, whereas radical neck dissection led to the removal at levels I-V. For each patient, number of metastatic nodes, their distribution, and data regarding postoperative treatment and oncologic outcomes were analyzed.

Results: Occult neck metastasis at levels I, IV, and V were rare with two cases each. In the clinically negative (cN0) patients, there were no cases of metastasis at level V and two cases at level I or IV. The extent of neck dissection and level of metastatic nodes had no impact on disease-specific survival or neck recurrence.

Conclusion: We conclude that in cN0 patients, removal at levels II and III is mandatory but levels I, IV, and V may be spared.

Keywords: Oropharyngeal neoplasms, palatine tonsil, squamous cell carcinoma, metastasis, neck dissection

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Introduction

Incidence of tonsillar squamous cell carcinoma (SCC) has increased in the past 20 years, according to a population-based survey in England (1). The appropriate treatment for it is a matter of debate in the literature with evidence showing equally good results in surgery or radiation in early-stage tumors, whereas for late-stage tumors, exclusive chemoradiation and primary surgery followed by adjuvant have supporters (2-4). Presence of neck metastasis is a significant prognostic factor in patients with oropharyngeal carcinoma and is associated with a worsening in survival (5). Therefore, their treatment is an essential part of tonsillar SCC treatment, but the extent of treatment is open to discussion.

Initially, neck treatment was accomplished through radical neck dissection or its modifications, but the concept of predictability of metastatic spread (6) facilitated selective neck dissections (SND) in selected patients with lower morbidity but with equally effective oncologic results (7). The concept of SND was initially proposed for patients with clinically negative necks but was further extended to those with early-stage neck disease (8). However, the question remains at which levels removal should be performed. Previous reports suggested that a lateral neck dissection with removal at levels II–IV was the most adequate procedure for oropharyngeal carcinoma (6), but this finding was in disagreement with a previous report on our institution that favored the removal at levels I–III (9). A major limitation of both studies is the inclusion of multiple primary sites within the oropharynx, not only tonsillar SCC. In a report restricted to the tonsil as the primary site, occult neck metastases were found at levels II–IV in 23 clinically negative (cN0) patients (10).

Our aim was to review the pattern of neck metastasis in tonsillar SCC staged as cN0/cN1 treated by primary surgery and to evaluate the role and extent of SND.

Methods

We retrospectively reviewed patients treated for the primary tonsillar carcinoma between January 1985 and December 2005. Inclusion criteria were as follows: histologic diagnosis of SCC, primary surgical treatment, lack of extension of the oral cavity and/or hypopharynx, negative p16 expression, and clinical and radiological stage as cN0/cN1. Exclusion criteria were as follows: previous treatment, primary treatment by chemoradiation or exclusive radiotherapy, lack of neck dissection as part of surgical treatment, previous treatment for head and neck cancer, synchronous second primary tumor in the head and neck or esophagus, systemic metastasis at diagnosis, and extension beyond the oropharynx.

The tonsil was considered the primary site when no further subsides of the oropharynx were compromised. Otherwise, it should be center of the lesion and contain the major tumor burden. Neck staging was performed by physical examination and imaging methods (ultrasonography or computerized tomography). Clinical staging was updated based on physical and radiological findings to the 8th AJCC Cancer Staging Manual.

All patients were submitted for resection of the primary tumor and synchronous neck dissection. The extent of neck dissection was dictated by the institutional protocols during surgery. Patients operated prior to 1996 were always submitted to a radical neck dissection if the stage was cN1 or to modified radical neck dissection if it was cN0. Between 1996 and 1998, patients were prospectively randomized to SND or modified radical neck dissection (MRND) as part of a Brazilian multicentric protocol, and after 1998, SND was the most common procedure. The choice of selective neck dissection of levels I–III over a lateral neck dissection (levels II–IV) is based on a previous report on our institution (9).

Statistical analysis was performed using Stata 14.1 (Stata Corp, College Station, TX, USA). Categorical variables are presented as frequencies and continuous variables as mean and standard deviation (SD). The Cox model was used for survival analysis with disease-specific survival and neck recurrence as the outcome of interest. Initially, a univariate survival analysis was performed, and significant variables at this point were included in multivariate survival analysis. This project was approved by the institutional ethics committee (protocol 170412 – 06/15/2016) a statement for use of medical information in research was signed by all patients admitted to the institution.

Results

In total, we evaluated 163 consecutive patients. There were 146 males (89.57%) and 17 females (10.43%), and age ranged from 28 to 83 years (mean, 56 years; SD, 10.29 years). Based on the clinical and radiological examination, the primary tumor was staged as cT1 in 11 patients (6.75%), cT2 in 37 (22.70%), cT3 in 69 (42.33%), and cT4a in 46 (28.22%). The diagnosis of cT3 was made if the primary tumor size on either evaluation was considered >4 centimeters. Diagnosis of cT4a mainly relied on the clinical or radiological evidence of mandible invasion or trismus, inferring invasion of the pterygoid muscles. The neck was staged as cN0 in 105 patients (64.42%) and cN1 in 58 (35.58%). Selective neck dissections were performed in 34 patients (20.86%), whereas radical and modified radical neck dissections were performed in 129 patients (79.14%). The histological grade of the primary tumor was described as well-differentiated in 79 patients (48.47%), moderately differentiated in 56 (34.36%), poorly differentiated in 26 (15.95%), and unspecified in 2 (1.23%). Further, vascular invasion was diagnosed in 70 patients (43.75%), and perineural infiltration was present in 106 patients (65.03%).

The lymph node yield ranged from 1 to 95 (median, 42 lymph nodes). Three patients had <15 lymph nodes analyzed at pathological examination. The number of metastatic nodes ranged from 1 to 33 (median, 1 node). Sixty-four patients (39.26%) presented no neck metastasis at pathological examination. Pathological staging according to the clinical stage is demonstrated in Table 1. There was a significant difference among pN+ patients between those previously staged as cN0 and cN1 ($p<0.001$). Extranodal extension (ENE) was diagnosed in 30 patients (18.18%). The lymph node ratio (LNR) ranged from 0 to 0.623 (mean, 0.053; SD, 0.092). The distribution of metastatic nodes in the cervical levels according to the clinical status is demonstrated in Table 2. Notably, no patient had isolated neck metastasis at level IV or V. Additionally, among the cN0 patients, there were only three patients (6%) with metastasis at level IV or V and they were associated with metastasis in upper levels in all of them. Postoperative radiotherapy was performed in 127 patients (77.91%), and doses at the neck ranged from 4.000 to 6.500 centiGray.

Follow-up period ranged from 3.62 to 171.59 months. There were 12 recurrences in the neck and 61 deaths due to disease progression. In the univariate survival analysis, pT stage ($p=0.020$ for pT3 and $p=0.014$ for pT4a), presence of neck metastases ($p=0.015$), LNR ($p=0.006$), ENE ($p=0.001$), perineural infiltration ($p=0.007$), and vascular invasion ($p=0.014$) were statistically significant (Table 3). We used presence of neck metastases and not pN category because we intended to individually analyze the prognostic significance of ENE. Considering that pN category depends on ENE, it would cause collinearity of the variables in the model. The extent of neck dissection had no significance in disease-specific survival (HR: 1.207, 95% CI: 0.641–2.270, $p=0.559$) (Figure 1) or neck recurrence (HR: 3.35, 95% CI: 0.432–25.990, $p=0.247$) (Figure 2) on comparing radical and selective neck dissections. Due to the small number of patients with <15 retrieved lymph nodes and the lack of cancer-related deaths or recurrence in this group, no analysis was performed regarding this variable. The level of neck metastasis was not associated with neck recurrence (HR: 1.02, 95% CI: 0.012–2.341, $p=0.659$), but it was significant in the univariate analysis for disease-specific survival (HR: 3.749, 95% CI: 1.770–7.942, $p<0.001$). Alongside pT stage, ENE and vascular invasion remained significant in the multivariate analysis (Table 4).

Discussion

Theoretically, selective neck dissection should offer the same oncologic benefits as radical neck dissection but with a significant decrease in mortality. Its role and extension are well-established in patients with primary oral cavity SCC (11).

In a series of 333 previously untreated patients with oropharyngeal and hypopharyngeal SCCs of which 77 were cN0, nodal metastases were primarily diagnosed at levels II–IV, with metastatic nodes at levels I and V always associated with neoplastic spread to other levels in the pathological examination. Based on these findings, the authors proposed the removal at levels II–IV in patients submitted to END for oropharyngeal SCC. No attempt was made to define the pattern of nodal metastasis for each subset in the oropharynx (12). Another report on oropharyngeal carcinoma described the distribution of neck metastasis in 127 consecutive patients without differentiation of subsite. Among 33 ipsilateral END, there were no patients with isolated metastasis at levels I or IV (13). In a retrospective series of 58 patients with tonsillar carcinoma treated at a single institution,

Table 1. Correlation between pathological and clinical stage in patients with tonsillar squamous cell carcinoma

	Pathological staging		
Clinical staging	pN0	pN+	Total
cN0	55	50	105
cN+	9	49	58
	64	99	163

Table 2. Distribution of metastatic lymph nodes according to level

Neck levels	All patients	cN0 patients	cN1 patients
I	2	2	0
II	63	34	29
III	2	1	1
I+II	8	4	4
I+V	1	0	1
II+III	12	6	6
II+IV	2	0	2
II+V	1	1	0
III+IV	1	0	1
I+II+IV	2	0	2
II+III+IV	2	1	1
II+III+V	2	0	2
I+II+III+IV	1	1	0
Total	99	50	49

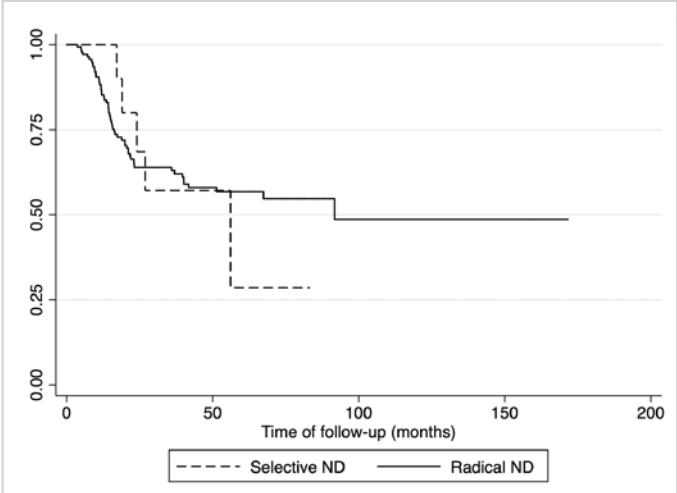

Figure 1. Kaplan–Meier curve for disease-specific survival according to the extent of neck dissection extension

Table 3. Univariate survival analysis using disease-specific survival as the outcome of interest

Variable	Values	HR	95% CI	p
Tobacco consumption	No	1		
	Yes	2.963	0.585–14.997	0.189
Alcohol consumption	No	1		
	Yes	1.351	0.511–3.569	0.544
Age		1.003	0.967–1.040	0.849
Sex	Male	1		
	Female	0.332	0.045–2.452	0.280
pT stage	1	1		
	2	3.351	0.394–8.042	0.230
	3	7.662	2.470–9.500	0.020
	4a	12.824	4.679–17.955	0.014
Vascular invasion	No	1		
	Yes	2.542	1.209–5.343	0.014
Perineural infiltration	No	1		
	Yes	2.801	1.326–5.917	0.007
Neck staging	pN0	1		
	pN+	1.944	1.387–4.806	0.015
Metastasis in levels IV/V	No	1		
	Yes	3.739	2.094–7.679	0.009
Lymph node ratio		5.709	3.102–16.890	0.006
Extranodal extension	No	1		
	Yes	3.924	1.836–8.022	0.001
PO radiotherapy	No	1		
	Yes	0.480	0.139–1.654	0.245

PO: post-operative

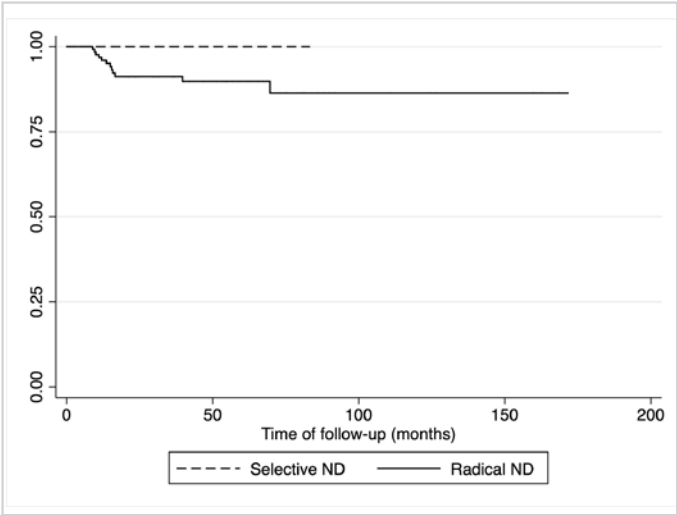

Figure 2. Kaplan–Meier curve for cervical recurrence according to the extent of neck dissection. Selective neck dissection encompasses removal at levels I-III

Table 4. Multivariate survival analysis using disease-specific survival as outcome of interest

Variable	Values	HR	95% CI	p
pT stage	1	1		
	2	4.011	0.501–32.132	0.191
	3	8.253	1.124–60.613	0.038
	4a	9.542	1.280–71.149	0.028
Vascular invasion	No	1		
	Yes	1.833	1.013–3.317	0.045
Presence of neck metastasis	No	1		
	Yes	2.247	1.268–3.979	0.006
Metastasis in levels IV/V	No	1		
	Yes	2.274	1.059–5.392	0.042
Extranodal extension	No	1		
	Yes	2.802	1.956–5.219	0.021

presence of metastatic nodes at level IV was diagnosed in 4.6% of cN0 patients, and no patient presented occult metastasis at level I or V. The proposed template for END and therapeutic neck dissection in cN1 and cN2a patients is the removal at levels II–IV (10). In a report on 80 patients with primary oropharyngeal SCC, the rate of neck metastasis was 62% for all T stages, with a predominance of level II spread (67% of pN+ patients). The prevalence of the metastasis at level I was 3% and level IV was 10% (14). Although the distribution of neck metastasis is not reported, a retrospective series analyzing the results of SND in oropharyngeal SCC described their template as encompassing levels I–III (15).

In a previous series from our department, no isolated neck metastasis at level IV was demonstrated. This series included all primary oropharyngeal sites and had a limited number of primary tonsil SCC patients who were analyzed irrespective of clinical stage. But despite these differences, the results are strikingly similar (9).

A prospective series of patients with oropharyngeal SCC demonstrated a predominance of metastasis at levels II–IV. In 24 ipsilateral cN0 neck dissections, there were eight with metastatic lymph nodes at pathological examination. Metastases at level I were found in two patients, but no patient presented metastases at level IV, but in 46 ipsilateral cN+ neck dissections, metastases at level IV were more frequent than at level I. The authors support a SND removal at levels I–IV in patients with primary oropharyngeal SCC (16).

The impact of the extent of neck dissection on survival has been analyzed by prospective studies in the primary oral cavity (11) and laryngeal SCC (17), but no prospective trials comparing the extent of neck dissection are available for patients with oropharyngeal carcinoma. Although the series by Lim et al. (13) and Mosto et al. (10) report on survival outcomes, no attempt was made to compare results among different neck dissection templates.

In our series, selective neck dissection was performed using a template encompassing levels I–III in all patients, whereas radical neck dissection led to the removal at levels I–V. The rate of occult neck metastasis at levels I and IV was identical, with two cases each in cN0 patients. When we compared the results of SND and MRND, no difference was found in terms of disease-specific survival and neck recurrences. In our series, the level of neck metastasis did not have any prognostic significance. The impact of the level of neck metastasis as a prognostic factor has been previously demonstrated in oral SCC (18). In this series, the low incidence of metastasis at levels IV and V may respond to this lack of effect. In a series including patients with multiple primary sites, the rate of neck recurrence was similar between SND and MRND. Remarkably, they did not show any improvement with the addition of adjuvant radiotherapy for neck recurrence while comparing pN+ patients (19).

The prognostic variables we identified with survival analysis are in accordance with previously described series. The presence of lymphovascular invasion increases the relative risk of cancer-related death in a series of oral cancer patients by 2.99 (20). Moreover, the rate of distant metastasis in these patients is higher (21). The impact of the level harboring metastatic lymph nodes was initially recognized for nasopharyngeal carcinoma with lower levels carrying a significantly worse prognosis (22). The presence of metastatic lymph nodes at level IV was significant for disease-specific survival in patients with oropharyngeal SCC but not for neck recurrence. In a previous report concerning oral cancer, we have shown a similar prognostic impact on disease-specific survival at level IV metastatic lymph nodes (18). The presence of ENE is associated with poorer prognosis and a significant association with distant metastatic progression (OR: 2.18, 95% CI: 1.23–3.87) in a recent meta-analysis of patients

with head and neck cancer (21). In the oropharyngeal carcinoma, however, two distinct situations arise. In p16+ patients, its prognostic role is limited with only patients with soft tissue deposits being significantly affected. In other situations, ENE carries no negative prognostic impact (23, 24).

Conclusion

We conclude that in cN0 patients, removal at levels II and III is mandatory but levels I, IV, and V may be spared, possibly lead to a significant decrease in surgical morbidity because lesions of the phrenic nerve, a mandibular branch of the facial nerve, and chylous fistula are associated with removal at levels I and IV. The choice of elective neck dissection should be a selective neck dissection. In our results, radical neck dissections presented no disease-free or disease-specific survival advantages over selective neck dissections. In our series, disease-specific survival depended on the T category of the primary tumor, vascular invasion, and several neck dissection-related factors such as presence of metastatic nodes, ENE, and, in pN+ patients, the level of neck metastasis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of A. C. Camargo Cancer Center (CEP170412 – 06/15/2016)

Informed Consent: Informed consent was obtained from all participants who participated in this study.

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