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Neck metastasis in transglottic laryngeal carcinomas

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Abstract

In laryngeal cancers, the first metastasis occurs in the cervical lymph nodes This study aimed to determine the levels of cervical metastatic lymph nodes in patients with transglottic laryngeal carcinoma, the effect of tumor prognostic factors on cervical lymph node metastasis. The research retrospectively examined 32 patients who underwent total laryngectomy and neck dissection, with the diagnosis of transglottic squamous cell carcinoma (SCC). Age, gender, complaint, smoking status, and other prognostic factors were evaluated. All patients underwent total laryngectomy with 63 neck dissections. Seven patients had metastatic cervical lymph nodes. Among the prognostic factors, thyroid cartilage invasion, combined perineural–perivascular invasion, subglottic extension, extra laryngeal extension, and preoperative tracheotomy procedure had statistically significant effects on neck metastasis. In conclusion, dissection at level IIB should be reassessed to decrease morbidity due to the low prevalence of level IIB metastasis, both clinically and pathologically. In locally advanced laryngeal cancers, considering the prognostic factors, it is ideal to plan specific treatments for each patient.

Keywords: transglottic laryngeal carcinoma, level IIB, cervical metastasis, prognostic factors.

1. Introduction

Laryngeal squamous cell carcinoma (SCC) is the second most common malignancy in the head and neck region. It constitutes 20–25% of head and neck tumors and 2–5% of all body tumors (1). More than 90% of malignant laryngeal tumors are SCCs, and over 40% of cases are advanced (2). Tumors that originate from one part of the larynx, cross the ventricle, and cause vocal cord fixation are called transglottic cancers. Transglottic cancers make up less than 5% of all cases, and they cause paraglottic region involvement and neck metastasis at an early stage (3).

In laryngeal cancers, the first metastasis occurs in the cervical lymph nodes (CLN). Cervical lymph node metastasis (CLNM) is seen in 1–7% of early-stage glottic (T1–T2) cancers and 20–30% of advanced glottic (T3–T4) cancers (25-55%) (4). Occult or obvious metastases to the cervical region are the most important factor causing recurrence and a 50% reduction in survival time. In addition, if there is extracapsular extension (ECE) in the metastatic lymph node, survival is further reduced by 50% (5).

Radical neck dissection (RND), which Crile first implemented in 1906, has since evolved to be applied in the form of modified radical neck dissection (MRND) and selective neck dissection (SND) (6). It has been reported that SND does not negatively affect survival rates in patients without clinical lymphadenopathy (N0), and it is as effective as other comprehensive neck dissections and causes less morbidity (7). In patients undergoing SND, shoulder syndrome symptom scores were found to be better than those in patients who underwent RND (8). Surviving laryngeal carcinomas is associated with tumor, nodes, metastases (TNM) stage, subglottic extension, perineural–perivascular–thyroid cartilage invasion, extralaryngeal extension, and preoperative tracheotomy procedure (9,10).

This study examined the effects of age, gender, preoperative tracheotomy procedure, anterior commissure involvement, perineural invasion, perivascular invasion, thyroid cartilage invasion, subglottic and extralaryngeal extension, and pathology on CLNM to determine which lymph node levels exhibited cervical spreading and whether level IIB dissection was necessary in this context.

2. Materials and Methods

This research retrospectively compiled the files of 32 patients (three female, 29 male), who underwent total laryngectomy and neck dissection, with the diagnosis of transglottic laryngeal SCC, in University of Health Sciences-Samsun Education and Research Hospital, between January 2017 and December 2019. The study began by receiving numbered ethical approval (GOKA/2020/5/12) from the ethics

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committee of the University of Health Sciences-Samsun Education and Research Hospital Non-Interventional Clinical Researches Ethics Board. Patients who had undergone partial laryngeal surgery, as well as those with a history of radiotherapy, chemotherapy, or non-SCC laryngeal pathologies, were excluded.

Patients who were admitted with hoarseness and dyspnea and were diagnosed with laryngeal carcinoma after endoscopic examination were hospitalized. Neck and thorax contrast tomography was conducted. Then, direct laryngoscopy was performed; biopsies were taken; and the laryngeal lesions were mapped. Tracheotomies were opened in the same session for patients with breathing difficulties. Total laryngectomy and radical and/or functional neck dissections were performed in patients with advanced (T3–T4) transglottic tumors whose pathology results reported SCC. As a result of clinical, radiological, and preoperative evaluation, RND was performed on the side with suspected lymphadenopathy, and functional neck dissection (FND) was performed on the opposite side. Bilateral FND was applied to N0 patients. Neck dissection specimens were also reviewed with the relevant pathologist and ordered separately as levels I, IIA, IIB, III, IV, and V. According to the pathology specimen report, patients with more than one metastatic lymph node, with ECE, subglottic extension (1cm anteriorly and 0.5cm posteriorly), and perineural cartilage invasion were treated based on the decision of the tumor council. Local–regional recurrences and overall survival were recorded by following the patients for between six and 29 months (average: 12.8 months).

Information concerning age, gender, complaint, smoking status, tumor placement, tumor histopathology in the pathology specimen report, anterior commissure involvement, subglottic extension, extralaryngeal spread, perineural–perivascular–thyroid cartilage invasion, metastatic–reactive lymph nodes, and ECE (especially level IIB) was compiled. Pathological TNM staging was also determined according to the American Joint Committee on Cancer (AJCC) (2017). The data obtained from the study were analyzed via the Statistical Package for the Social Sciences (SPSS) program (version 22.0, SPSS Inc.). During this evaluation, qualitative data were expressed as numbers (n) and percentages (%); the measurement data were expressed as means and standard deviations. In the statistical analyses, the consistency of continuous variables with the normal distribution was evaluated via the Kolmogorov–Smirnov Test. Pearson's Chi-squared test was used to compare categorical data. P = 0.05 was accepted as the statistical significance limit.

3. Results

The study included 32 patients with transglottic laryngeal cell carcinoma, who were aged 44 to 75 years (mean: 58.4 years). Three patients were female (average age: 46), and 29 were male (average age: 58.8). There was no statistically significant difference in CLNM between male and female patients (p = 0.536) or between smokers and non-smokers (p = 0.591). When the relationship between smoking and lymph node metastasis by gender was examined, again no statistically significant difference was found (p = 0.541). Although the complaints of patients with transglottic tumors varied, hoarseness was observed in 19 patients and respiratory distress in 13. Tracheotomy was performed in seven patients (21.8%) due to breathing difficulties (Table 1).

Table 1. Demographic features, habits and laryngeal location of the tumor

		Patient number	CLNM	p*
Age	58.8 (44-75) years			
Gender	Female	3	1	p=0,536
	Male	29	6	
Smoking	Female	2	1	p=0,541
	Male	29	6	
Complaint	Hoarseness	19		
	Respiratory distress	13		-

*p Pearson Chi-square test.

Patients underwent bilateral neck dissection along with total laryngectomy. Of the 63 neck dissections, five were RND and 58 were FND. In the clinical examination, 18 patients (56.25%) had palpable lymphadenopathy in the neck (56.25%). Six of these (18.75%) presented metastatic cervical lymph nodes, confirmed by pathology; these were bilateral in four patients (12.5%) and unilateral in two (6.25%). In 12 (37.5%) patients with clinical lymphadenopathy (N+), there were no metastatic lymph nodes in the neck. In one N+ patient (right, level IV), a metastatic lymph node was reportedly caused by prostate adenocarcinoma. As a result, of pathological evaluation in one N0 patient (3.1%), metastasis was detected at level IIA. 13 patients (40.6%) without clinical adenopathy presented metastatic adenopathy in the neck. One of these had two lymphadenopathies at level IV, which is reported as thyroid papillary carcinoma metastasis, and a total thyroidectomy was performed.

In seven patients, 19 metastatic lymph nodes were identified as pathological: 42.1% at level IIA, 26.3% at level III, 21% at level IV, 5.2% at level V, 5.2% at level IIB, and 0.0% at level I. Level IIB metastasis was seen in only one patient. This patient had bilateral level IIA, level III, and level IV metastasis. In the same patient, ECE was seen at level IIA and on the opposite side at level IV. While the level IIB metastasis rate was 3.12% among all patients, the rate among patients with metastatic lymphadenopathy was 14.2%. Six of the 32 patients included in the study were T4aN+M0; one was T3N+M0; 14 were T4aN-M0; and 11 were T3N-M0 (Table 2).

Table 2. Tumor location, histopathology, clinical and histopathological cervical lymphadenopathy and TNM classification

Patient no	Tumor location	Histopathology	CLN	Clinical		Histopathological		Level IIB	TNM
				Right	Left	Right	Left		
1	Transglottic	SCC	cN+/pN+ (n=6) %18.75	IIA,III,IV	IIA,III,IV	IIA,III,IV (ece*)	IIA (ece), III,IV	+	pT4N3bM0
2	Transglottic	SCC		III,IV	V	III(ece), IV	V(ece)	-	pT4N3bM0
3	Transglottic	SCC		IIA,III,IV	IIA, III	IIA, III(ece)	-	-	pT4N2aM0
4	Transglottic	SCC		IIA,III,IV,V	IIA	III,V	IIA	-	pT4N2cM0
5	Transglottic	SCC		IIA,III	-	IIA	-	-	pT4N1M0
6	Transglottic	SCC		IIA,III,IV	IIA	IIA, IV	IIA	-	pT4N2cM0
7	Transglottic	SCC	cN+/pN0 (n=12) %37.5	IIA,III	-	-	-	-	pT4N0M0
8	Transglottic	SCC		III	-	-	-	-	pT4N0M0
9	Transglottic	SCC		IIA	-	-	-	-	pT4N0M0
10	Transglottic	SCC		IIA,III,IV	IIA	-	-	-	pT4N0M0
11	Transglottic	SCC		IIA	-	-	-	-	pT4N0M0
12	Transglottic	SCC		IV	-	Prostate met (IV)	-	-	pT4N0M0
13	Transglottic	SCC		IIA, III	-	-	-	-	pT4N0M0
14	Transglottic	SCC		IIA	IIA	-	-	-	pT4N0M0
15	Transglottic	SCC		III	-	-	-	-	pT4N0M0
16	Transglottic	SCC		III	-	-	-	-	pT4N0M0
17	Transglottic	SCC		IIA,II,IV	III	-	-	-	pT4N0M0
18	Transglottic	SCC		IIA	-	-	-	-	pT4N0M0
19	Transglottic	SCC	cN0/pN+ (n=1)%3.1	-	-	IIA	-	-	pT3N1M0
20	Transglottic	SCC	cN0/pN0 (n=13) %40.6	-	-	Papillary ca met (IV)	-	-	pT4N0M0
21	Transglottic	SCC		-	-	-	-	-	pT4N1M0
22	Transglottic	SCC		-	-	-	-	-	pT3N0M0
23	Transglottic	SCC		-	-	-	-	-	pT3N0M0
24	Transglottic	SCC		-	-	-	-	-	pT3N0M0
25	Transglottic	SCC		-	-	-	-	-	pT3N0M0
26	Transglottic	SCC		-	-	-	-	-	pT3N0M0
27	Transglottic	SCC		-	-	-	-	-	pT3N0M0
28	Transglottic	SCC		-	-	-	-	-	pT3N0M0
29	Transglottic	SCC		-	-	-	-	-	pT3N0M0
30	Transglottic	SCC		-	-	-	-	-	pT3N0M0
31	Transglottic	SCC		-	-	-	-	-	pT3N0M0
32	Transglottic	SCC		-	-	-	-	-	pT3N0M0

*ece=extracapsular extension

In this study, thyroid cartilage invasion, combined perineural–perivascular invasion, subglottic extension, and extralaryngeal spread were found to be statistically significant in the occurrence of CLNM (p = 0.020, p = 0.006, p = 0.000, p = 0.000, respectively). The difference between CLNM incidence was also significant in patients with and without preoperative tracheotomy (p = 0.006) (Table 3).

Table 3. Effect of prognostic factors on CLNM

Prognostic factors	n=32	CLNM	p
Ant. commissure involvement	24	7	0.084
Thyroid cartilage invasion	20	7	0.020
Perineural invasion	3	1	0.614
Perivascular invasion	2	1	0.320
Perineural-perivascular invasion	2	2	0.006
Subglottic extension	9	6	0.000
Extralaryngeal spread	9	7	0.000
Preop tracheotomy	7	2	0.006

Adjuvant radiotherapy was applied to 20 patients, who presented thyroid cartilage invasion, extralaryngeal spread, subglottic extension, and multiple and/or ECE metastatic lymphadenopathy. The patients were followed from six to 29 months (average: 12.8 months). Three patients with ECE lymphadenopathy and one patient with peristomal recurrence died within six months. One patient who underwent total laryngectomy and right RND refused opposite-neck surgery and radiotherapy. This patient was admitted with a mass in the opposite neck 1.5 months later. Only 12 patients who underwent surgery and 16 patients who underwent adjuvant radiotherapy (total: 28 patients) were examined at regular intervals.

4. Discussion

There is no ideal treatment protocol for advanced laryngeal carcinomas. Treatment plans are devised according to the extent of each tumor and the presence of cervical lymphadenopathy. CLNM is the most important prognostic factor affecting survival (11). It is difficult to detect the primary site in the examination because patients with transglottic tumors of the larynx usually go to the doctor late. Clinically or radiologically, lymphadenopathy has been reported to cause poor prognosis in patients with laryngeal carcinomas. In neck surgical treatment, which began with RND, shoulder atrophy and loss of function may be caused by cutting the spinal accessory nerve, and morbidities—such as increased intracranial pressure and, thus, increased mortality—have made MRND, and, later, SND, more commonly applied treatments (12). Muzaffer applied RND to 61 patients, MRND to 54 patients, and SND to 61 patients, and reported no difference between the three groups in terms

of regional relapse and overall survival over a two-year follow-up period (13). Chepeha et al. compared MRND and SND patients in terms of shoulder function and found shoulder function to be more limited in patients who underwent MRND (12). In the present study, 63 neck dissections were performed in 32 patients with transglottic laryngeal carcinoma. RND was applied to five necks and FND to the remaining 58 necks, according to the clinical, radiological, and preoperative findings. Metastatic lymphadenopathies with ECE were reported in three of the RND necks and in one of the FND necks. Three patients who underwent RND died within six months due to regional recurrence and one due to peristomal recurrence. One patient with RND rejected opposite-neck surgery and radiotherapy. This patient was admitted with a mass in the opposite neck 1.5 months later.

According to the predictable cervical metastasis model for head and neck SCCs, dissection of the most affected areas and elective dissection of other regions, if there is no metastasis in these nodes, is controversial (2). Among 164 patients with laryngeal carcinoma, Mnejja et al. found 7% of the metastases at level IIA, 4.3% at level III, 2.7% at level IV, and 2.4% at level IIB (14). Gross et al. reported the results of elective and therapeutic neck dissections performed on patients with laryngeal and hypopharyngeal carcinoma and found level IIB metastasis to be 4% and 17%, respectively (15). In these patients, Gross et al. did not find a significant relationship between primary tumor stage, metastasis at levels IIA and III, clinical nodal stage, or ECE and level IIB metastasis. Sezen et al. dissected 673 lymph nodes from level IIA and 340 lymph nodes from level IIB because of 98 neck dissections performed in 67 patients with supraglottic, glottic, and subglottic laryngeal carcinomas. They reported that 11 (3.23%) of 340 lymph nodes dissected from level IIB were metastatic. They did not detect level IIB metastasis in any N0 patients. The distribution of cervical lymph node metastases in the patients who underwent neck dissection was as follows: eight (42.1%) at level IIA, five (26.3%) at level III, four (21%) at level IV, one at level V (5.2%), and one at level IIB (5.2%) (16). In the present study, level IIB metastasis was observed in only one patient, who had clinical and pathological bilateral metastases at levels IIA, III, and IV. In the same patient, ECE was detected at level IIA on one side, and metastases were detected on the opposite side at level IV. While the level IIB metastasis rate was 3.12% among all patients, the rate among patients with metastatic lymphadenopathy was 14.2%. In this study, the total number of reactive lymph nodes detected at levels I, IIA, III, IV, and V in the cervical region was 17.5 on the side where the tumor in the larynx was predominant, 14.3 on the opposite side of the neck, 4.3 at level IIB on the same side as the tumor, and 3.2 on the opposite side of the neck at level IIB.

It has been reported that the most important prognostic factor affecting survival in laryngeal carcinoma is N stage. The other prognostic factors determine survival rate as they increase cervical metastasis. Yilmaz et al. reported that perivascular and perineural spread affect survival and recurrence by causing an increase in CLNM (17). Aydin et al. found a significant relationship between thyroid cartilage invasion and CLNM, and Bai et al. determined that extralaryngeal involvement was associated with CLNM (18,19). Lucioni et al. reported a correlation between paratracheal lymph node and laterocervical node involvement in patients with posterior subglottic extension (20). Özağaç et al. found no significant correlation between preoperative tracheotomy and neck metastasis in patients with laryngeal carcinoma (21). In the present study, combined perineural–perivascular invasion, thyroid cartilage invasion, extralaryngeal spread, and subglottic extension were found to significantly affect CLNM ($p=0.020$, $p=0.006$, $p= 0.000$, $p=0.000$, respectively). However, anterior commissure involvement and solely perineural or perivascular invasion did not significantly affect CLNM ($p=0.084$, $p=0.614$, $p=0.320$, respectively). The authors also found a significant difference between the incidence of CLNM in patients with and without preoperative tracheotomy ($p = 0.006$).

Approximately 60% of locally advanced laryngeal SCC patients require adjuvant radiotherapy. Skora et al. reported that adjuvant radiotherapy was given to 138 patients in the T3-4N0M0 stage, who underwent total laryngectomy and neck dissection; 34 patients experienced recurrence, and the five-year survival rate was 76% (22). Kennedy et al. found a five-year local and regional control rate of 92% after adjuvant radiotherapy in their study consisting of 36 patients in the T3-T4aN0 stage (23). In the present research, adjuvant radiotherapy was applied to 20 patients with postoperative thyroid cartilage invasion, subglottic extension, and multiple or ECE metastatic lymphadenopathy. The patients were followed between six and 29 months (average: 12.8 months). Local and regional recurrence occurred in five of the patients receiving adjuvant radiotherapy, and four of them died. Disease-free follow-up of 27 (84.3%) patients continues. Limitations of the present study included its retrospective design, the low number of patients, the short follow-up period, and the examination of only transglottic tumors.

In conclusion, transglottic laryngeal carcinomas, latent or overt neck metastases can be seen due to the locally advanced stage of the tumor. Dissection at level IIB should be reassessed to decrease morbidity, especially in N0 necks, due to the low incidence of level IIB metastasis, both clinically and pathologically. In treating advanced laryngeal cancers, considering the prognostic factors, the ideal approach would be to create an appropriate treatment plan for each patient.

Conflict of interest

The authors declare no conflict of interest.

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