The Relationship Between Local Properties and Neck Metastasis

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ABSTRACT

Objective: To observe the association between local properties of larynx cancer and neck metastasis.

Methods: In total, 119 patients who underwent total or partial laryngectomy and neck dissection for laryngeal carcinoma at the Otolaryngology Head and Neck Surgery Clinic of Health Sciences University Gaziosmanpaşa Taksim Training and Research Hospital between 2003 and 2016 were enrolled in this study. Postoperative pathological examinations included tumor histopathology, tumor differentiation; perineural, cartilage, and lymphovascular invasion; laryngeal primary tumor localization; anterior commissure; piriform sinus apex; tongue root; pre-epiglottic region; thyroid cartilage; band; aryepiglottic plateau; laryngeal ventricle; arytenoid vocal processes; arytenoid involvement; vocal cord movements; and metastatic lymph node status in neck dissection. Tumor histopathology and the association between invasion and neck dissection in the anatomical regions that determine local spread were investigated.

Results: Patient age, opening of preoperative tracheotomy, and status of vocal cord movements did not affect neck metastasis. Piriform sinus, tongue base retention, band involvement, aryepiglottic plica involvement, involvement of laryngeal face epiglottis, and involvement of arytenoid significantly affected local spread.

Conclusion: Although similar findings have been reported in the literature, multidisciplinary studies involving more patients, especially those with neck metastasis, are warranted to arrive at a definite conclusion.

Keywords: Larynx cancer, laryngectomy, neck metastasis

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INTRODUCTION

Laryngeal cancers are the most common head-neck tumors (in case skin tumors are excluded from the classification). Approximately 2%-5% of cancers diagnosed worldwide within 1 year are laryngeal cancers. It is seen five times more in males than in females (1). Surgical, radiotherapy, and chemoradiotherapy methods are used in the treatment. If radiotherapy is preferred as the primary treatment and the result is unsuccessful, surgery is applied as rescue treatment (1). In early stage tumors, surgery (stage 1 or 2) or radiotherapy treatment can be applied alone, or combined therapy is required in advanced stages (2).

The rate of neck metastasis is approximately 20%–30% in laryngeal tumors. Although factors, such as tumor histology, T stage, and local spread of primary tumor, are related to the spread to cervical lymph nodes, the results are generally variable (3). Unfortunately, cervical metastasis reduces the chance of treatment by 50%; hence, the status of cervical lymph nodes

is the most important prognostic factor (4-6). Therefore, the approach to neck lymph nodes is extremely important when planning treatment (7). When deciding on the dissection of the neck, it is not only decided by whether the lymph node is palpable or not, the localization, size, and character of the tumor should also be taken into consideration, as these properties may increase the incidence of latent tumor metastasis. The whole treatment scheme should be considered when deciding the neck dissection.

Radical neck dissection (RND), which was first described by Crile in 1906 and later evolved by Martin, was the first choice of treatment for cervical metastases for many years. However, subsequent developments in the approach to the neck led to the popularization of conservative methods. Selective or modified neck dissections yielded results that are successful and close to the results of RNDs, resulting in less morbidity at the same time (7, 8). However, there is no conclusive treatment consensus in cases where lymph node positivity cannot

be detected (N0) by conventional examination methods. It is known that latent metastasis in N0 neck ranges between 20% and 50%. It is indicated that latent metastasis may be present up to 10% even if fine needle aspiration biopsy is used in addition to imaging methods, such as ultrasonography, computed tomography, and magnetic resonance imaging. It is recommended that elective neck dissection should be added to the treatment in tumors with high latent metastasis as in the supraglottic region (7). Especially after selective neck dissections for N0 necks become more popular, the importance of cervical lymph node classification and lymph node levels to which malignant regions metastasized has increased.

For hypopharyngeal and laryngeal malignancies, elective surgical treatment of lymph nodes in levels II, III, and IV was considered appropriate, whereas surgery of lymph nodes was recommended for level VI when the postcricoid region, subglottic area, and apical apex of the primal sinus were involved (9-12). While deciding the treatment plan of the latent metastasis rate and since in the high-risk groups elective neck dissection is recommended, factors affecting regional lymph node metastasis are attempted to be determined. As a result, the localization of the tumor and the degree of the histological differentiation of the tumor were reported as the two most related factors with regard to metastasis (13).

The aim of the present study was to retrospectively evaluate the postoperative pathology specimens of our patients who had undergone surgery for laryngeal tumors in our clinic between 2003 and 2016 for purpose of verifying the relationship between the local dissemination, tumor site, histological grade and size of the tumor, and cervical lymph node (LN) involvement in neck dissection materials.

METHODS

This was a retrospective study. A total of 119 patients who underwent neck dissection in addition to total or partial laryngectomy due to laryngeal cancer in Gaziosmanpaşa Taksim Training and Research Hospital, Otorhinolaryngology Clinic between 2003 and 2016 were included in the study. Approval for the study was obtained from the local ethics committee of Gaziosmanpaşa Taksim Training and Research Hospital (Consent no.: 70-11, 07, 2018).

For each case, gender, age, and TNM classification (American Joint Committee on Cancer-Cancer Staging Manual 2010) were specified individually. Preoperative tracheostomy and movement of vocal cords of the cases were investigated. The laryngeal surgery of the cases was total laryngectomy, and supracricoid laryngectomy (cricohyoidopexy and cricohyoidoepiglottopexy), near total laryngectomy, and neck surgeries were type 3 modified RND (functional).

In the postoperative pathology of specimens, histopathology of the tumor; tumor differentiation; subglottic extension; localization of the primary tumor in the larynx; lymphovascular spread; perineural invasion; involvement of the apex of the piriform sinus, anterior commissure, tongue root, thyroid car-

tilage, pre-epiglottic region, and non-laryngeal soft tissue; and the properties of the metastasis positive LNs in neck dissection were examined. The effects of tumor histopathology and invasion to anatomical regions that determines the local dissemination and the tumor histopathology on the decision of neck dissection are examined. Patients who had T4 tumor, bone or cartilage invasion, perineural invasion, invasion of soft tissues of the neck, vascular invasion, multiple metastatic LN, extracapsular extension in the LN, and subglottic extension of >5 mm in the front and 10 mm at the back were referred to the appropriate radiotherapy centers for postoperative radiotherapy treatment.

Statistical Analysis

Data were analyzed by using the Statistical Package for Social Sciences version 22.0 program (IBM Corp., Armonk, NY, USA). Data were expressed as mean±standard deviation, median (minimum-maximum), frequency, and ratio for descriptive statistics. Kolmogorov-Smirnov test was used to determine the distribution of the parameters. Independent sample t-test and Mann-Whitney U test were used for quantitative data analysis. Chi-square test and when the conditions of this test were not met Fisher's exact test were used for qualitative data analysis. The effect level was investigated by multivariate logistic regression.

RESULTS

The study was performed on a total of 119 patients between 2003 and 2016. The ages of the cases were between 37 and 82 years. The average age is 58 years. There was no significant difference for age and age distribution of patients with or without LN involvement ($p>0.05$) (Table 1). There was no significant difference in vocal cord motion distribution ($p>0.05$) in the group with or without LN involvement. As the histological grade decreased from well-differentiated to less, the rate of LN involvement increased significantly ($p<0.05$) (Table 2). The LN involvement rate in the supraglottic region was significantly higher than that in the transglottic and glottic-subglottic regions ($p<0.05$). The LN involvement rate in the transglottic region was significantly higher than that in the glottic-subglottic region ($p<0.05$) (Table 3). When the extracapsular dissemination, perineural invasion, lymphovascular dissemination, piriform sinus involvement, tongue root involvement, band involvement, aryepiglottic fold involvement, involvement of the laryngeal face of the epiglottis, arytenoid vocal process involvement, arytenoid cartilage involvement parameters are analyzed, it is found that the rate of LN involvement in the group with cartilage invasion and extracapsular dissemination statistically significantly increases LN involvement ($p<0.01$) (Table 4). It was observed that LN involvement was an independent and significant ($p<0.05$) risk factor of perineural invasion, histology, and involved region in multivariate reduced model ($p<0.05$) (Table 5).

DISCUSSION

The planning of neck dissection treatment is controversial in cases with laryngeal cancer. The general principle is that the

Table 1. Comparison of neck metastases according to age ranges

		Without LN involvement				With LN involvement				p
		Mean±SD	/	n-%	Med (Min-Max)	Mean±SD	/	n-%	Med (Min-Max)	
Age		57.1	±	9.0	57.0 35.0 - 78.0	58.3	±	11.5	59.0 35.0-83.0	0.532
Age	35-50	18		23.4		10		23.8		0.569
	51-65	46		59.7		22		52.4		
	>65	13		16.9		10		23.8		

Chi-square test/Mann-Whitney U test

Table 2. Comparison of neck metastases according to preoperative tracheotomy, vocal cord movements, and histology

		Without LN involvement		With LN involvement		p
		n	%	n	%	
Preoperative tracheotomy	Yes	12	70.6	5	29.4	0.584
	No	65	63.7	37	36.3	
Vocal cord movement	Decreased	13	75.0	3	25.0	0.886
	Fixed	12	63.2	7	36.8	
	Mobile	52	63.4	30	36.6	
Histology	Poor	0	0.0	11	100.0	0.000
	Medium	44	61.1	28	38.9	
	Well	32	94.1	2	5.9	

Chi-square test

Table 3. Comparison of neck metastases in glottic, subglottic, transglottic, and supraglottic tumors

	Without LN involvement		With LN involvement		p
	n	%	n	%	
Involved region					
Glottic	30	100.0	0	0.0	0.0000
Subglottic	3	100.0	0	0.0	
Transglottic	28	66.7	14	33.3	
Supraglottic	16	36.4	28	63.6	

Chi-square test

neck should be treated in the same way as the primary tumor. However, clinically, the role of surgery in N0 neck is unclear. Kowalski (14) reported that a positive LN metastasis in the neck is associated with a significant reduction in local control and surveillance. To decide neck treatment especially in N0 cases, it is extremely important to determine the region of the tumor, T stage, the degree of histopathological differentiation, and local spread.

In the present study, we examined 119 patients who underwent unilateral or bilateral neck dissection in addition to partial/total laryngectomy due to laryngeal squamous cell carcinoma. In our study, the histological differentiation of the tumor and the rate of metastasis in neck dissection material were compared. When we examine the distribution according to histopathological grades, of the 119 cases, 9.4% (n=11) were poorly differentiated, 61.5% (n=72) were moderately differentiated, and 29.1% (n=34) were well-differentiated. According to the histological differentiation, LN positivity in neck dissection specimen materials showed a statistically significant difference (p<0.05). Kowalski et al. (13) suggested that the degree of histological differentiation of the tumor is among the two most striking factors in neck metastasis in a study they conducted with 103 patients. Similarly, Korolkowa and Osuch-Wojcikiewicz (15) showed that in addition to tumor localization and spread, histological differentiation is also significant with regard to LN metastasis. Moreover, in our study, a statistically significant relationship was found between histological grade and LN metastasis. In a multivariate reduced model, LN involvement was found to be an independent and significant (p<0.05) risk factor of perineural invasion, histology, and affected region.

When the distribution according to tumor localizations was analyzed, of the 119 cases, 25.2% (n=30) were glottic, 2.5% (n=3)

Table 4. Comparison of the groups with and without LN involvement with regard to statistical significance

		Without LN involvement		With LN involvement		p
		n	%	n	%	
Cartilage invasion	No	63	79.7	16	20.3	0.000
	Yes	14	35.0	26	65.0	
Extracapsular dissemination	No	77	72.0	30	28.0	0.000
	Yes	0	0.0	12	100.0	
Subglottic extension	No	62	62.6	37	37.4	0.291
	Yes	15	75.0	5	25.0	
Perineural invasion	No	76	75.2	25	24.8	0.000
	Yes	1	5.6	17	94.4	
Lymphovascular dissemination	No	73	76.8	22	23.2	0.000
	Yes	4	16.7	20	83.3	
Anterior commissure	No	36	59.0	25	41.0	0.183
	Yes	41	70.7	17	29.3	
Apex of piriform sinus	No	72	74.2	25	25.8	0.000
	Yes	5	22.7	17	77.3	
Tongue root	No	76	68.5	35	31.5	0.001
	Yes	1	12.5	7	87.5	
Pre-epiglottic region	No	75	66.4	38	33.6	0.099
	Yes	2	33.3	4	66.7	
Band	No	41	87.2	6	12.8	0.000
	Yes	36	50.0	36	50.0	
Thyroid cartilage	No	65	64.4	36	35.6	0.850
	Yes	12	66.7	6	33.3	
Fold	No	55	82.1	12	17.9	0.000
	Yes	22	42.3	30	57.7	
Ventricle	No	35	63.6	20	36.4	0.821
	Yes	42	65.6	22	34.4	
Laryngeal face of the epiglottis	No	59	80.8	14	19.2	0.000
	Yes	18	39.1	28	60.9	
Vocal process of arytenoid	No	40	57.1	30	42.9	0.039
	Yes	37	75.5	12	24.5	
Arytenoid cartilage	No	63	70.8	26	29.2	0.017
	Yes	14	46.7	16	53.3	
Chi-square test (Fisher's test)						

subglottic, 37% (n=44) supraglottic, and 35.3% (n=42) transglottic. The highest rates of positivity are seen in supraglottic and transglottic cases, followed by glottic involvement. When the distribution of neck metastases by regions was examined, the highest metastasis rate was determined as the supraglot-

tic area in 28 (63%) out of 44 patients. Of the 42 patients with transglottic tumors, 14 had metastatic metastases. There were significant differences between regions. The LN involvement rate in the supraglottic region was significantly higher than that in the transglottic and glottic-subglottic regions ($p<0.05$). LN

Table 5. Comparison of perineural invasion, histology, and detection of neck metastases according to the site of logistic regression model in laryngeal tumors

	p	OR	95% CI	
			Lower limit	Upper limit
Perineural invasion	0.001	54.516	4.05-	600.6
Histology	0.001	0.060	0.01-	0.30
Involved region	0.014	2.187	1.17-	4.07
	Model accuracy	Total	%82.9	
		LN (-)	%98.7	
		LN (+)	%53.7	
Logistic regression reduced model				

involvement in the transglottic region was significantly higher than that in the glottic–subglottic regions ($p<0.05$). In addition, LN involvement was found to be an independent and significant ($p<0.05$) risk factor in the multivariate reduced model. In the literature, Tomik et al. (16) reported in their study of 1400 patients that tumors localized to the supraglottic and glottic regions have a high probability of metastasis, and accordingly, these are the regions affecting the prognosis (17). Similarly, Kowalski (14), Nguyen-Tan et al. (18), and Osuch-Wojcikiewicz and Korolkowa (15) also suggested in their studies that the primary tumor region is important in determining neck metastasis (17). In addition, Marks et al. (19), in their study of 540 patients, found the occult metastasis rate in supraglottic and transglottic cancers to be lower than that in the glossoepiglottic and the marginal supraglottic region. In our study and in studies where the rate of neck metastasis of the supraglottic region involvement is high (15-18), subunits of the supraglottic region (central and marginal) are not specified. With this, the central or marginal localization of the supraglottic tumor is a factor that changes the rate of metastasis. In addition, the main difference may be related to the size of the tumor since tumors at higher levels, such as the glossoepiglottic region and the marginal supraglottic dissemination, indicate that local dissemination may be wide.

In the present study, we compared LN involvement with respect to different regions of the larynx. These regions were classified as anterior commissure, false cords, aryepiglottic fold, apex of the piriform sinus, tongue root, pre-epiglottic region, thyroid cartilage, arytenoid cartilage, ventricle, laryngeal face of the epiglottis, and arytenoid vocal process. The incidence of anterior commissure involvement was not significant in the group with and without LN involvement ($p>0.05$). Kowalski et al. (20) reported that the presence of tumor in the anterior commissure, one of the prognostic factors, does not have an effect on prognosis. In our study, we evaluated the relationship between the presence of tumor in the regions causing the change of the T phase, such as the

anterior commissure, considering the neck metastasis that is one of the most important prognostic factors. From this point of view, although Kowalski et al. (20) did not evaluate neck dissection in their study, the results we obtained with regard to anterior commissure are close to each other. LN involvement was significantly higher in patients with piriform sinus involvement than in those without piriform sinus involvement ($p<0.05$). Bien et al. (21), in their study of 12,888 cases who were operated between 1991 and 2001, reported that tumors with piriform sinus involvement have a high rate of metastasis. Similarly, Marks et al. (19), in their study of 540 patients, reported that the marginal region of the supraglottis, as well as the piriform sinus, has a high rate of neck metastases. In our study, 17 (77.3%) out of 22 specimens with diffuse piriform sinus dissemination had metastasis in neck dissection material. Piriform sinus tumors are also found in the group with high metastasis rate. Metastasis was also detected in 77.3% in our study, so neck dissection is important in patients with piriform sinus involvement. LN involvement was found to be significantly higher in patients with tongue root involvement than in those without tongue root involvement ($p<0.05$), which correlated with previous studies with large patient groups.

In the present study, the rate of pre-epiglottic involvement was not significantly different in the group with and without LN involvement ($p>0.05$). When the rate of pre-epiglottic involvement and the rate of metastases to the neck in the involvement of this region were evaluated, four (66.7%) out of six specimens had metastasis to the neck. The involvement of the pre-epiglottic region was not statistically significant with regard to metastasis. Bai et al. (22) found that pre-epiglottic involvement is present in 55.5% (10/18) of the supraglottic tumors that are metastasized to the neck, whereas those without neck metastases were 29.1% (14/48). The results were found to be statistically significant and showed that the presence of tumor in the pre-epiglottic region was an important prognostic factor for development of metastasis. However, Suoglu et al. (23), in their study of 52 patients with tumor limited to the supraglottic and glottic–supraglottic areas, suggested that tumor spread to the pre-epiglottic region does not affect survival. In this study, there are only six patients with pre-epiglottic involvement, and owing to this, the presence of no statistical difference is a natural result; however, owing to the presence of high involvement of 66.7% and the literature, considering the pre-epiglottic region as a high-risk region with regard to neck LN dissemination would be more accurate.

In our study, the rate of involvement of the thyroid cartilage was not significant in the group with and without LN involvement ($p>0.05$). Tumor metastasis was detected in 6 (33.3%) out of 18 neck dissection specimens in this group, and it was found to be statistically significant. Thyroid cartilage invasion is determined as T4a in all three regions as supraglottic, glottic, and subglottic. Shah et al. (24) suggested extended neck dissection for T4 supraglottic tumors as a result of their studies. In our study, we did not find the presence of thyroid cartilage involvement as significant with regard to neck metastasis; however,

owing to the small number of patients, it is of course more appropriate to consider the findings of more multicenter studies. Considering the literature, it is important to perform operation with neck dissection in patients with preoperative thyroid cartilage invasion.

LN involvement was significantly higher in groups with the involvement of aryepiglottic fold, arytenoid, band, and laryngeal face of the epiglottis than in groups without involvement ($p < 0.05$). These results are compatible with the studies related to supraglottic tumors in the literature and are important for planning neck dissection. LN involvement was significantly higher in the group with cartilage invasion than in the group without cartilage invasion ($p < 0.05$). LN involvement was significantly higher in the group with perineural invasion than in the group without ($p < 0.05$). LN involvement was significantly higher in patients with lymphovascular dissemination than in those without lymphovascular dissemination ($p < 0.05$). Although these three criteria are statistically significant with regard to LN involvement, they cannot point us the way regarding preoperative neck dissection since these are histopathological findings, but they are important for adjuvant radiotherapy treatment.

CONCLUSION

Laryngeal cancer is a disease that can be complicated because of both it can be locally aggressive and its neck metastases. In these patients, surgical treatment of the neck should be performed, especially when the tumor is locally advanced. In this way, patient survival increases.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziosmanpaşa Taksim Training and Research Hospital. (Approval Date: 11.07.2018; Approval No.:70)

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