

Investigation of factors affecting neck lymph node involvement and extracapsular spread in laryngeal cancers

Larenks kanserlerinde boyun lenf nodu tutulumunu ve ekstrakapsüler yayılımı etkileyen faktörlerin araştırılması

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ABSTRACT

Objectives: This study aims to investigate the clinical and pathological factors that may affect neck metastasis and extracapsular spread in laryngeal cancer patients.

Patients and Methods: Between January 2016 and December 2018, 56 patients (53 males, 3 females; mean age 60.8±9.5 years; range, 34 to 84 years) operated for laryngeal squamous cell carcinoma were included in this retrospective study. Patients were divided into two groups as those with and without neck metastasis. The neck metastasis group was divided into two groups as those with and without extracapsular spread. The effect of tumor localization, tumor volume measured from preoperative computed tomography or magnetic resonance images, vascular, thyroid cartilage, perineural and lymphatic invasion on neck lymph node involvement and extracapsular spread was investigated.

Results: In 30.4% of the cases (n=17), tumor (T)3-T4 glottic and in 60.6% (n=39) T1-T4 supraglottic tumors were detected. While only lymph node involvement was seen in 17.9% of the patients, 25% had extracapsular spread with lymph node involvement. The involvement of the supraglottic area increased the risk of neck metastasis by 6.756 fold and the risk of extracapsular spread by 9.258 fold statistically significantly (p=0.016).

Conclusion: Supraglottic tumors have a higher risk of lymph node involvement and extracapsular spread compared to advanced glottic tumors. Neck dissection is important for staging and locoregional control of the tumors in the supraglottic area.

Keywords: Extracapsular spread, laryngeal cancer, lymph node metastasis.

ÖZ

Amaç: Bu çalışmada larenks kanseri hastalarında boyun metastazını ve ekstrakapsüler yayılımı etkileyebilecek klinik ve patolojik etkenler araştırıldı.

Hastalar ve Yöntemler: Bu retrospektif çalışmaya Ocak 2016 - Aralık 2018 tarihleri arasında larenks skuamöz hücreli karsinomu nedeniyle ameliyat edilen 56 hasta (53 erkek, 3 kadın; ort. yaş 60.8±9.5 yıl; dağılım, 34-84 yıl) dahil edildi. Hastalar boyun metastazı olan ve olmayanlar olarak iki gruba ayrıldı. Boyun metastazı grubu ekstrakapsüler yayılımı olan ve olmayanlar olarak iki gruba ayrıldı. Tümörün yerleşim yerinin, ameliyat öncesi bilgisayarlı tomografi veya manyetik rezonans görüntülerinden ölçülen tümör volümünün, kan damarı, tiroid kıkırdak, perinöral ve lenfatik invazyonun boyun lenf nodu tutulumuna ve ekstrakapsüler yayılıma etkisi araştırıldı.

Bulgular: Olguların %30.4'ünde (n=17) tümör (T)3-T4 glottik, %60.6'sında (n=39) T1-T4 supraglottik tümör saptandı. Hastaların %17.9'unda sadece lenf nodu tutulumu, %25'inde ise lenf nodu tutulumuyla beraber ekstrakapsüler yayılım görüldü. Supraglottik alanın tutulumu istatistiksel olarak anlamlı şekilde boyun metastazı riskini 6.756 kat, ekstrakapsüler yayılım riskini 9.258 kat artırdı (p=0.016).

Sonuç: Supraglottik tümörlerde ileri glottik tümörlere kıyasla lenf nodu tutulumu ve ekstrakapsüler yayılım riski daha yüksektir. Supraglottik alandaki tümörlerin evrenmesi ve lokorejyonel kontrolü açısından boyun diseksiyonu önemlidir.

Anahtar sözcükler: Ekstrakapsüler yayılım, larenks kanseri, lenf nodu metastazı.

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Laryngeal carcinoma often occurs in the sixth and seventh decades and is significantly more common in males.^[1] Ninety-five percent of the laryngeal cancers are squamous cell carcinomas (SCCs). Despite all advances in surgical and radiotherapy (RT) protocols, the five-year survival rate has decreased from 66 to 63%.^[2] For this reason, it is important to investigate the factors affecting the prognosis and survival of patients in laryngeal cancer.

Lymph node metastasis is an important prognostic marker in patients with head and neck SCC.^[3] Two important pathological factors are the number of lymph nodes involved with tumor and extracapsular spread.^[4,5] In patients with extracapsular spread, survival is reduced by half compared to patients without spread.^[6,7]

In this study, we aimed to investigate the clinical and pathological factors that may affect neck metastasis and extracapsular spread in laryngeal cancer patients.

PATIENTS AND METHODS

This retrospective study included 56 patients (53 males, 3 females; mean age 60.8±9.5 years; range, 34 to 84 years) who underwent partial or total laryngectomy and bilateral or unilateral neck dissection for laryngeal SCC at Istanbul University, Cerrahpaşa Faculty of Medicine between January 2016 and December 2018. Tumor (T)3-T4 stage patients with glottic tumors and T1-T4 stage patients with supraglottic tumors were included. Bilateral neck dissection was performed in all patients who had supraglottic tumors. According to the pathology reports, the patients were divided into two groups as those with and without neck metastasis. The neck metastasis group was divided into two groups as those with and without extracapsular spread. The medical and pathological records of the patients were evaluated and the factors affecting neck metastasis and extracapsular spread were examined. These include tumor localization, blood vessel, cartilage, perineural and lymphatic invasion, and tumor volume measured from preoperative computed tomography or magnetic resonance images. Patients with a history of preoperative RT and a second primary tumor were excluded. Both macroscopic and microscopic extracapsular spreads were recorded as positive. The study protocol was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval date: 12 February 2019, No: 38/05). Because the design of the study was retrospective and the medical records of the patients were examined, patient consent forms could not be obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The data were analyzed using the IBM SPSS version 22.0 (IBM Corp.; Armonk, NY, USA). In the descriptive findings section, categorical variables were presented as number and percentage, and continuous variables as mean±standard deviation and median (minimum, maximum). Pearson's chi-square test or Fisher's exact chi-square test were used to compare categorical variables. The suitability of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (if $n \geq 50$, Kolmogorov-Smirnov test and if $n < 50$, Shapiro-Wilk test). T-test in independent groups was used for paired group comparisons for the numerical data which were found to have normal distribution. In multivariate analysis, the effect of different variables on the presence of extracapsular invasion was evaluated by logistic regression analysis.

RESULTS

Glottic tumors were detected in 30.4% (n=17) and supraglottic tumors in 60.6% (n=39) of the patients. Vertical or horizontal partial laryngectomy was performed in 33 patients (58.9%). Twenty-three patients (41.1%) were treated with total laryngectomy. All patients underwent unilateral or bilateral neck dissection considering the localization of the tumor and the stage of the disease.

While 57.1% of the patients had no neck involvement, 17.9% had only neck lymph node involvement and 25% had neck lymph node involvement and extracapsular spread (Table 1).

Histopathological examination of tumor materials revealed vascular invasion in 48.2% (n=27), lymphatic invasion in 78.6% (n=44), perineural invasion in 39.3% (n=22). Cartilage invasion was detected in 39.3% (n=22) of the patients.

Fifteen (38.4%) of the 39 patients who had tumors involving the supraglottic area were in the T1 and T2 stages: Two patients were T1 and 13 patients were

	n	%
- Neck involvement, - extracapsular spread	32	57.1
+ Neck involvement, - extracapsular spread	10	17.9
+ Neck involvement, + extracapsular spread	14	25.0
Total	56	100.0

	Negative		Positive		<i>p</i> *
	n	%	n	%	
Vascular invasion (n=56)					
Positive	14	51.9	13	48.1	0.440
Negative	18	62.1	11	37.9	
Lymphatic invasion (n=56)					
Positive	22	50.0	22	50.0	0.039
Negative	10	83.3	2	16.7	
Perineural invasion (n=56)					
Positive	9	40.9	13	59.1	0.048
Negative	23	67.6	11	32.4	
Cartilage invasion (n=56)					
Positive	12	54.5	10	45.5	0.752
Negative	20	58.8	14	41.2	
Tumor localization (n=56)					
Supraglottic	18	46.2	21	53.8	0.012
Glottic	14	82.4	3	17.6	

* Pearson's chi-square test was applied.

T2. Neck metastasis was present in seven (46%) of these 15 early stage patients. Extracapsular spread was detected in six of these patients.

There was no statistically significant relationship between vascular and cartilage invasion and lymph node metastasis ($p>0.05$). There was a significant relationship between tumor localization and lymph node metastasis ($p=0.042$) (Table 2).

There was no significant difference between vascular, lymphatic, perineural and cartilage invasion and extracapsular spread ($p>0.05$). Extracapsular spread was significantly higher in supraglottic tumors than glottic tumors (Table 3).

No significant difference was found between tumor volume and lymph node involvement and extracapsular spread ($p=0.169$, $p=0.504$, respectively) (Table 4).

	Negative		Positive		<i>p</i> *
	n	%	n	%	
Vascular invasion (n=56)					
Positive	19	70.4	8	29.6	0.440
Negative	23	79.3	6	20.7	
Lymphatic invasion (n=56)					
Positive	31	70.5	13	29.5	0.258†
Negative	11	91.7	1	8.3	
Perineural invasion (n=56)					
Positive	15	68.2	7	31.8	0.343
Negative	27	79.4	7	20.6	
Cartilage invasion (n=56)					
Positive	17	77.3	5	22.7	0.752
Negative	25	73.5	9	26.5	
Tumor localization (n=56)					
Supraglottic	26	66.7	13	33.3	0.043†
Glottic	16	94.1	1	5.9	

* Pearson's chi square test was applied; † Fisher's Exact test was applied.

	Tumor volume (cm ³)		<i>p</i> *
	Mean±SD		
Lymph node involvement			
Negative	7.5±10.7		0.169
Positive	7.3±4.5		
Extracapsular spread			
Negative	7.6±9.7		0.504
Positive	6.8±3.3		

SD: Standard deviation; * T test was applied in independent groups.

In supraglottic tumors, the risk of lymph node involvement increased 6.756 fold, while the risk of extracapsular spread increased 9.258 fold compared to glottic tumors ($p=0.016$) (Tables 5 and 6).

DISCUSSION

Lymph node involvement, positive surgical margin, T stage, locoregional metastasis, and extracapsular spread of tumor cells in patients with neck lymph node involvement are the most important prognostic factors in head and neck SCC.^[8,9] In the recently published tumor-

node-metastasis (TNM) classification, extracapsular spread is one of the main factors that increase the N stage of the tumor.^[10] Therefore, we aimed to evaluate the clinical and histopathological factors that may affect lymph node involvement and extracapsular spread in laryngeal SCC patients.

Surgery, radiotherapy, and chemotherapy can be used in the treatment of laryngeal cancers. These treatment methods can be used alone or in combination according to the patient's condition, stage, and localization of the disease.^[8] Unlike supraglottic tumors, early stage glottic tumors are those with low risk of lateral neck metastasis. These tumors are currently being treated with transoral laser surgery or primary RT. In our study, only patients with T3-T4 stage glottic tumor who underwent laryngectomy and neck dissection were included. Only 17.6% of these patients had neck metastasis. In a study performed by Erdağ et al.^[11] on 24 T2N0 glottic laryngeal SCC patients, lateral functional neck dissection was performed in all patients. None of the patients had lymph node metastasis.^[11]

Supraglottic tumors have a higher risk of lymphatic metastasis than glottic tumors. This is because the supraglottic region has a large lymphatic network and lymphatic drainage is bilaterally to the neck. Therefore, a more aggressive approach to neck is required in supraglottic tumors.^[12] Even in clinical N0 tumors,

	OR	95% CI	<i>p</i> *
Age†	0.992	0.927-1.062	0.817
Lymphatic invasion‡	4.380	0.750-25.582	0.101
Perineural invasion§	3.342	0.853-13.094	0.083
Tumor localization¶	6.756	1.424-32.066	0.016

OR: Odds ratio; CI: Confidence interval; † According to low age; ‡ According lymphatic invasion; § According to perineural invasion; ¶ According tumor localization.

	OR	95% CI (Upper-lower limit)	<i>p</i> *
Age†	0.952	0.887-1.022	0.176
Lymphatic invasion‡	4.673	0.491-44.454	0.180
Tumor localization§	9.258	1.004-85.375	0.050

OR: Odds ratio; CI: Confidence interval; † According to low age; ‡ According lymphatic invasion; § According to tumor localization.

bilateral neck dissection is recommended because occult metastasis rate is more than 20%. Lateral neck dissection including levels 2-4 in supraglottic laryngeal SCC patients has a high surgical control rate and low mortality.^[3] Redaelli de Zinis et al.^[3] found an occult metastasis rate of 26% in their study of 402 patients with supraglottic tumors. They recommended elective level 2-4 neck dissection in T2-T4 supraglottic tumors. In our study, all supraglottic tumors were treated with bilateral neck dissection. Ten patients had bilateral lymph node metastasis. In supraglottic tumors, the risk of lymph node involvement and extracapsular spread was higher than T3-T4 glottic tumors.

In a study, it was reported that disease-related mortality and the risk of recurrence are higher in the presence of macroscopic extracapsular spread. No increased risk of recurrence and mortality has been demonstrated in cases of limited or encapsulated microscopic invasion of the lymph node of the tumor. In addition, tumor localization and T stage were not related to extracapsular spread.^[13] In our study, in contrast, neck lymph node involvement and extracapsular spread risks were higher in supraglottic tumors compared to T3-T4 glottic tumors. In a study of laryngeal and hypopharyngeal cancers, Barroso Ribeiro et al.^[14] found lymph node metastasis in 47.6% of clinical N0 patients. They stated that patients with multinodal extracapsular spread had lower survival and higher locoregional involvement and distant metastasis rates than patients with extracapsular spread at a single node.

In a study of 121 locoregional advanced laryngeal cancer patients, extracapsular spread and infiltrative growth pattern were reported as the main prognostic factors. Presence of nodal stage 2-3 disease and presence of lymphovascular and perineural invasion have been shown to have a negative impact on prognosis of the disease.^[15]

The limitations of this study were the small number of patients and the absence of statistics on survival rates. Since the patients were operated on in the last two years, the survival time of three or five years and the relationship between survival rates and pathological factors could not be specified.

In conclusion, supraglottic tumors have high risk of metastasis and extracapsular spread to neck lymph nodes. In supraglottic tumors, neck should be treated during the initial treatment period even in the early stages. In our study, although there was no relationship between cartilage and lymphovascular invasion and neck involvement, studies with larger sample sizes are needed for better evaluation of this condition.

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