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Original Article / *Özgün Makale*

Substantiality of surgical margins in laryngeal carcinoma surgery

Larenks karsinomu cerrahisinde cerrahi marjinlerin önemi

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ABSTRACT

Objectives: This study aims to investigate whether millimetric tumor distances to surgical margins have any association with recurrences in larynx cancers.

Patients and Methods: The study was conducted between January 2009 and December 2015 at Bağcılar Training and Research Hospital, Ear, Nose and Throat Clinic and included 159 patients (156 males, 3 females; mean age 60.1±9.5 years; range, 38 to 87 years) who were followed-up regularly after total or partial laryngectomy. Eighty-three patients, who underwent cordectomy or salvage laryngectomy, who did not undergo any surgical procedures, or who did not attend the follow-up visits were excluded.

Results: Mean duration of follow-up was 58±20.8 months (range, 36 to 85 months). Tumor involvement of surgical margins was identified in 14 patients (8.8%). Tumors were at a mean distance of 4.3±4.7 mm (range, 1 to 30 mm) to the surgical margins when those margins were reported to be clear. During follow-ups, 21 patients were diagnosed with recurrences. On comparison of the patient groups with or without recurrences, mean tumor distance to surgical margins in the recurrence group was 3.6±4.1 mm, whereas this value was 4.3±4.8 mm in the non-recurrence group. Surgical margins were positive in four patients in the recurrence group and in 10 patients in the non-recurrence group. There were no statistically significant differences between the two groups in terms of mean margins or surgical margins. Rates of recurrences were statistically significant in patients who underwent radiation therapy, who had invasion of thyroid and cricoid cartilages, who had extracapsular invasion in lymph nodes, who had perineural and lymphatic invasions, and in those with advanced stage tumor and node cancer. There were no statistically significant differences in terms of recurrence rates or tumor differentiation and metastasis stages in patients with epiglottis or vascular invasions.

Conclusion: Resection of tumor at millimetric distances to surgical margins or positive surgical margins in laryngeal cancer surgery were not detected to be associated with recurrences.

Keywords: Laryngectomy; larynx carcinoma; recurrence; surgical margins.

ÖZ

Amaç: Bu çalışmada cerrahi marjinlere milimetrik tümör mesafelerinin larenks kanserlerinde nüks ile ilişkili olup olmadığı araştırıldı.

Hastalar ve Yöntemler: Çalışma Ocak 2009 - Aralık 2015 tarihleri arasında Bağcılar Eğitim ve Araştırma Hastanesi, Kulak, Burun ve Boğaz Kliniğinde yapıldı ve total veya parsiyel larenjektomi sonrası düzenli takip edilen 159 hasta (156 erkek, 3 kadın; ort. yaş 60.1±9.5 yıl; dağılım, 38-87 yıl) dahil edildi. Kordektomi veya kurtarma larenjektomisi uygulanan, herhangi bir cerrahi işlem uygulanmayan veya takip muayenelerine gelmeyen 83 hasta çalışma dışı bırakıldı.

Bulgular: Ortalama takip süresi 58±20.8 ay (dağılım, 36-85 ay) idi. On dört hastada (8.8%) cerrahi marjinlerde tümör tutulumu saptandı. Cerrahi marjinler temiz olarak bildirildiğinde, tümörler söz konusu marjinlere ortalama 4.3±4.7 mm (dağılım, 1-30 mm) mesafede idi. Takiplerde, 21 hastaya nüks tanısı konuldu. Nüks olan ve olmayan hasta grupları karşılaştırıldığında, cerrahi marjinlere ortalama tümör mesafesi nüks grubunda 3.6±4.1 mm iken, bu değer nüks olmayan grupta 4.3±4.8 mm idi. Cerrahi marjinler nüks grubunda dört hastada, nüks olmayan grupta 10 hastada pozitif idi. İki grup arasında ortalama marjinler ve cerrahi marjinler açısından istatistiksel olarak anlamlı farklılık yoktu. Nüks oranları radyasyon terapisi gören, tiroit ve krikoid kıkırdağı invazyonu, lenf nodlarında ekstrakapsüler invazyon, perinöral ve lenfatik invazyon ve ileri evre tümör ve nodül kanseri olan hastalarda istatistiksel olarak daha anlamlı idi. Epiglot veya vasküler invazyonu olan hastalarda nüks oranları veya tümör diferansiyasyonu ve metastaz evreleri açısından istatistiksel olarak anlamlı farklılık yoktu.

Sonuç: Larenks kanseri cerrahisinde tümörün cerrahi marjinlere milimetrik mesafelerde rezeksiyonunun veya pozitif cerrahi marjinlerin nüks ile ilişkili olmadığı saptandı.

Anahtar sözcükler: Larenjektomi; larenks karsinomu; nüks; cerrahi marjinler.

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The prevalence of larynx carcinoma is 72.7 per 100.000, and it is the most common cancer type of head and neck region.[1] Tumor, node, metastasis (TNM) staging[2] does not assist physicians in deciding on treatment modalities. Therefore, the selection of surgical method depends on the stage of tumor as well as other factors including the age and functional capacity of the patient, and comorbidities.[3] Among surgical techniques; cordectomy, vertical hemilaryngectomy, supraglottic laryngectomy, supracricoid laryngectomy, and total laryngectomy are the most commonly applied.[4] Given that larynx is a functional organ involved in production of voice and swallowing, the amount of intact tissue to be excised during tumor resection is of utmost importance.[5] A historical view demonstrating that the first tumor surgery of larynx was total laryngectomy, which had been performed for many years for the treatment of larynx cancers, shows that the aim was resection of tumor with excision of surrounding intact tissue broadly.[6] However, in following years, allowing closer tumor distances to surgical margins has helped protect functionality of the remaining organ, leading to more frequent applications of partial laryngectomy techniques. Today, the most significant concern of all surgeons dealing with tumor surgery is to try to protect the functionality of larynx while removing tumor tissue at sufficiently remote distances to surgical margins. Therefore, in laryngeal surgery, tumors are now resected at millimetric distances to surgical margins.[7] However, despite the several studies in the literature on tumor distance to surgical margins in laryngectomy, the issue has not been clarified, yet. Therefore, in this study, we aimed to investigate whether millimetric tumor distances to surgical margins have any association with recurrences in larynx cancers.

PATIENTS AND METHODS

Patients diagnosed with laryngeal cancer at Bağcılar Training and Research Hospital, Ear, Nose and Throat Clinic between January 2009 and December 2015 were screened retrospectively in the hospital electronic archiving system, and matched with the corresponding reports in the archives of the pathology clinic. Data of 252 patients were identified in the archive. Patients, who underwent total laryngectomy, supracricoid laryngectomy (cricohyoidopexy [CHP], cricohyoid epiglottopexy [CHEP]), supraglottic laryngectomy or vertical laryngectomy, depending on staging of tumor, were included. Patients were excluded if they were referred to chemoradiotherapy, if they did not adhere to treatment and did not attend follow-ups, if laryngofissures were performed, if they underwent endoscopic cordectomy or salvage total laryngectomy, or if they were diagnosed with distant metastases. Accordingly, 24 patients who were referred to chemoradiotherapy without surgery, 14 who were non-adherent to treatment and follow-ups, 45 who were applied laryngofissures or endoscopic cordectomy, six who underwent salvage total laryngectomy, and four who were diagnosed with distant metastases were excluded. Finally, 159 patients (156 males, 3 females; mean age 60.1±9.5 years; range, 38 to 87 years) who underwent surgery due to laryngeal carcinoma at our clinic were included. The study protocol was approved by the Istanbul Bağcılar Training and Research Hospital Ethics Committee (date: 16 June 2016, number: 476). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who were included in the study were further evaluated for the following factors including application of adjuvant radiotherapy, presence of tumor extending to surgical margins, distance of tumor to surgical margins in cases of no extension of tumor to surgical margins, invasion of the thyroid, epiglottic, and cricoid cartilages, extracapsular invasion of the lymph nodes in neck, tumor differentiation, and perineural, vascular, and lymphatic invasion of tumor. In addition to TNM staging, tumors were investigated on the staging of nodes and for presence of any metastases. The association of these factors to recurrences and survival were examined. New tumor formation in larynx or neck within the first five years of larynx surgery was concluded as recurrence.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 program (IBM Corp., Armonk, NY, USA). For descriptive statistics, means, standard deviations, medians, the lowest and highest values, frequencies and ratios were calculated. The distribution of the variables was assessed by Kolmogorov-Smirnov test. Mann-Whitney U test was used in the analysis of quantitative data. Chi-square test was used to analyze qualitative data. When chi-square test conditions were not met, Fischer's exact test was used. The degree of influence was evaluated by univariate and multivariate logistic regression.

RESULTS

Mean duration of follow-up was 58±20.8 months (range, 36 to 85 months). Of the patients, 75.5% (n=120) were still alive without tumor recurrence or metastases, while 11.3% (n=18) died due to tumor recurrence or metastases, and 13.2% (n=21) died due to other comorbid diseases (Table 1).

Tumor extension beyond surgical margins was identified in 8.8% (n=14) of the patients. None of these patients were reoperated. No tumor tissue was detected at surgical margins in 91.2% (n=145) of the patients. In these 145 patients, the mean distance of tumor to surgical margins was 4.3±4.7 mm (range, 1 to 30 mm, median value, 3) (Table 1).

Of the 90 patients who underwent total laryngectomy, seven patients (7.7%) were detected with tumor continuity at surgical margins. In 83 patients (92.3%), no tumor extension beyond surgical margins was demonstrated, and their mean distance of tumor to surgical margins was 4.6±5.2 mm (range, 1 to 30 mm).

Table 1
Demographic and histopathological characteristics of patients

	n	%	Mean±SD	Median	Min-Max
Age (year)			60.1±9.5	60	38-87
Gender					
Female	3	1.9			
Male	156	98.1			
Duration of follow-up (month)			58.0±20.8	56	36-85
Survival					
Alive	120	75.5			
Death due to tumor recurrence	18	11.3			
Death due to other comorbid diseases	21	13.2			
The nearest surgical margin (mm)			4.3±4.7	3	1-30
Positive surgical margin					
-	145	91.2			
+	14	8.8			
Postoperative adjuvant radiotherapy					
-	93	58.5			
+	65	40.9			
Thyroid cartilage invasion					
-	114	71.7			
+	45	28.3			
Epiglottic cartilage invasion					
-	111	69.8			
+	48	30.2			
Cricoid cartilage invasion					
-	148	93.1			
+	11	6.9			
Extracapsular invasion					
-	131	82.4			
+	28	17.6			
Vascular invasion					
-	126	79.2			
+	33	20.8			
Perineural invasion					
-	144	90.6			
+	15	9.4			
Lymphatic invasion					
-	118	74.2			
+	41	25.8			

SD: Standard deviation; Min: Minimum; Max: Maximum.

In one of nine patients (11.1%) with supraglottic laryngectomy, there was tumor existence at surgical margins. In eight patients (88.9%) who had no tumor existence at surgical margins, the mean distance of tumor to surgical margins was 3.2±4.5 mm (range, 1 to 15 mm). In six (46.1%) of 13 patients who underwent CHEP, there was tumor existence at surgical margins. In seven patients (53.9%) with no tumor extension at surgical margins, the mean distance of tumor to surgical margins was 3.7±2.8 mm (range, 1 to 10 mm).

None of the 14 patients who underwent CHP were reported with tumor presence at surgical margins. The mean distance of tumor to surgical margins was 3±2.1 mm (range, 1 to 8 mm). There was no tumor existence at surgical margins in none of the four patients who underwent vertical, frontolateral, and frontoanterior laryngectomies. Their mean distance of tumor to surgical margins was 4.7±3.6 mm (range, 2 to 10 mm).

A total of 65 patients (40.9%) received postoperative adjuvant radiotherapy. Of these, 14 had positive surgical margins. The remaining 94 patients (59.1%) did not receive radiotherapy (Table 1).

Histologically demonstrated thyroid cartilage invasion was present in 45 patients (28.3%). Thyroid cartilage invasion was not demonstrated in 114 patients (71.7%). Epiglottic cartilage invasion was present in 48 patients (30.2%) but absent in 111 patients (69.8%). Cricoid cartilage invasion was present in 11 patients (6.9%), whereas no cricoid cartilage invasion was seen in 148 patients (93.1%) (Table 1).

According to the histopathological results of all patients, 33 patients (20.8%) had vascular invasions compared to 126 patients (79.2%) who had no vascular invasions. Perineural invasion was present in 15 patients (9.4%); however, no perineural invasion was detected in 144 patients (90.6%). Forty-one patients (25.8%) had lymphatic invasions, while 118 patients (74.2%) had no lymphatic invasions (Table 1).

As regards to tumor metastases at neck, 102 patients (64.1%) were identified as N_0. Neck metastases (N^+) were detected in a total of 57 patients (35.9%). Twenty-eight patients with neck metastases had extracapsular invasions. Of patients with N^+, 49.1% were identified with extracapsular invasions (Table 2).

Reviewing histopathological results of the patients in terms of tumor differentiation revealed well-differentiated (Grade 1) tumors in 40 patients (25.2%), moderately-differentiated ones (Grade 2) in 80 patients (50.3%), and poorly-differentiated ones (Grade 3) in 39 patients (24.5%) (Table 2).

Table 2
Patient's tumor differentiation according to tumor, node, and metastasis

	n	%
Tumor differentiation		
Grade 1	40	25.2
Grade 2	80	50.3
Grade 3	39	24.5
T Stage		
1	14	8.8
2	54	34.0
3	54	34.0
4	37	23.3
N Stage		
0	102	64.2
1	14	8.8
2	41	25.8
3	2	1.3
M Stage		
-	150	94.3
+	9	5.7

T: Tumor; N: Node; M: Metastasis.

Table 3
Comparison of age and gender distribution, surgical margins and adjuvant radiotherapy in patients with or without recurrence

	Recurrence (-)				Recurrence (+)				
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	*p*
Age (year)			59.8±9.2	60			61.8±11.5	58	0.714*
Gender									0.299**
Female	2	1.4			1	4.8			
Male	136	98.6			20	95.2			
The nearest surgical margin (mm)			4.3±4.8	3			3.6±4.1	2	0.567*
Positive surgical margin									0.075**
-	128	92.8			17	81.0			
+	10	7.2			4	19.0			
Postoperative adjuvant radiotherapy									0.000**
-	88	63.8			5	23.8			
+	49	35.5			16	76.2			

SD: Standard deviation; * Mann-Whitney U test; ** Chi-square test.

According to the criteria of 2010 American Joint Committee on Cancer, staging of laryngeal cancer in terms of T and N stages as reported by pathological examination revealed that 14 patients (8.8%) were with T_1, 54 patients (34%) were with T_2, 54 patients (34%) were with T_3, and 37 patients (23.3%) were with T_4

Table 4
Comparison of histopathologic evaluation in patients with or without recurrence

	Recurrence (-)		Recurrence (+)		
	n	%	n	%	*p**
Thyroid cartilage invasion					0.009
-	104	75.4	10	47.6	
+	34	24.6	11	52.4	
Epiglottic cartilage invasion					0.397
-	98	71.0	13	61.9	
+	40	29.0	8	38.1	
Cricoid cartilage invasion					0.019
-	131	94.9	17	81.0	
+	7	5.1	4	19.0	
Extracapsular invasion					0.000
-	120	87.0	11	52.4	
+	18	13.0	10	47.6	
Vascular invasion					0.071
-	110	79.7	16	76.2	
+	28	20.3	5	23.8	
Perineural invasion					0.016
-	128	92.8	16	76.2	
+	10	7.2	5	23.8	
Lymphatic invasion					0.003
-	108	78.3	10	47.6	
+	30	21.7	11	52.4	

* Chi-square test.

Table 5
Comparison of recurrence and non-recurrence groups in terms of tumor differentiation and tumor, node, and metastasis staging

	Recurrence (-)		Recurrence (+)		
	n	%	n	%	*p**
Tumor differentiation					0.467
Grade 1	37	26.8	3	14.3	
Grade 2	68	49.3	12	57.1	
Grade 3	33	23.9	6	28.6	
T Stage					0.000
1	14	10.1	0	0.0	
2	54	39.1	0	0.0	
3	46	33.3	8	38.1	
4	24	17.4	13	61.9	
N Stage					0.000
0	97	70.3	5	23.8	
1	10	7.2	4	19.0	
2	30	21.7	11	52.4	
3	1	0.7	1	4.8	
M Stage					0.411
-	131	94.9	19	90.5	
+	7	5.1	2	9.5	

T: Tumor; N: Node; M: Metastasis; * Chi-square test.

tumors, while 102 patients (64.2%) were with N_0, 14 patients (8.8%) were with N_1, 41 patients (25.8%) were with N_2, and two patients (1.3%) were with N_3 tumors (Table 2).

During the follow-up period, nine patients (5.7%) were identified with distant metastases. Eight of these patients were diagnosed with lung metastasis, and one was identified with lung and bone metastases (Table 2).

The patients were divided into two groups as patients with or without recurrences. In the recurrence group, there were 21 patients (20 males, 1 female). There were no significant differences between the two groups in terms of gender (p>0.05). The mean ages of the patients in the recurrence and non-recurrence groups were 61.8±11.5 years and 59.8±9.2 years, respectively. There were no significant differences between the groups in terms of mean age (p>0.05) (Table 3).

In terms of surgical margins, the closest distance of tumor to surgical margins was 4.3±4.8 mm in the non-recurrence group, whereas it was 3.6±4.1 mm in the recurrence group. The comparison of these two groups for the closest distance to surgical margins revealed no significant differences (p>0.05). As regards to positive surgical margins, negative surgical margins were detected in 128 patients (92.8%) in the non-recurrence group; however, 10 patients (7.2%) without recurrences were identified with positive surgical margins. Among the patients with recurrences, 17 patients (81%) were with negative surgical margins, and four patients (19%) were with positive surgical margins. In terms of positive surgical margins, there were no significant differences between the two groups (p>0.05) (Table 3).

In terms of receiving adjuvant radiotherapy, in the non-recurrence group, there were 88 patients (63.8%) who did not receive radiotherapy, while there were 49 patients (35.5%) who did. In the recurrence group, there were five patients (23.8%) who did not receive radiotherapy, while there were 16 patients (76.2%) who did. The recurrence rate was found to be significantly higher in the group of patients who received radiotherapy (p<0.05) (Table 3).

As regards to thyroid cartilage invasion, 104 patients (75.4%) in the non-recurrence group did not have any invasions, whereas 34 patients (24.6%) did. In the recurrence group, 10 patients (47.6%) did not have thyroid cartilage invasion; however, 11 patients (52.4%) did. The rate of thyroid cartilage invasion in the recurrence group was significantly higher compared to the non-recurrence group (p<0.05) (Table 4).

Invasion of the epiglottic cartilage was also examined in the non-recurrence and recurrence groups. In the non-recurrence group, 98 patients (71%) were without any epiglottic cartilage invasion, while 40 patients (29%) had invasions. In the recurrence group, 13 patients (61.9%) did not have any epiglottic cartilage invasions, while eight patients (38.1%) did. When the non-recurrence and recurrence groups were compared, there were no significant differences between the two groups in terms of epiglottic cartilage invasion ($p>0.05$) (Table 4).

When the non-recurrence and recurrence groups were evaluated for the presence of cricoid cartilage invasion, it was observed that in the non-recurrence group, 131 patients (94.9%) did not have any cricoid cartilage invasion, while seven patients (5.1%) did. In the recurrence group, 17 patients (81%) did not have any cricoid cartilage invasion, while four patients (19%) did. The rate of cricoid cartilage invasion was significantly higher in the recurrence group compared to the non-recurrence group ($p<0.05$) (Table 4).

In terms of extracapsular invasion, in the non-recurrence group, 120 patients (87%) had no extracapsular invasions, while 18 patients (13%) did. In the recurrence group, 11 patients (52.4%) did not have any extracapsular invasion, whereas 10 patients (47.6%) did. The rate of extracapsular invasions was significantly higher in the recurrence group compared to the non-recurrence group ($p<0.05$) (Table 4).

Vascular invasion rates were examined as well in both groups. In the non-recurrence group, 110 patients (79.7%) did not have any vascular invasions, while 28 patients (20.3%) did. In the recurrence group, 16 patients (76.2%) had no vascular invasions, in contrast to five patients (23.8%) with vascular invasions. When the two groups were compared in terms of the presence of vascular invasions, there were no significant differences between the recurrence and non-recurrence groups ($p>0.05$) (Table 4).

When perineural invasions were examined in the two groups, 128 patients (92.8%) in the non-recurrence group did not have any perineural invasions, but 10 patients (7.2%) did. In the recurrence group, 16 patients (76.2%) did not have any perineural invasions, while five patients (23.8%) did. In the recurrence group, the perineural invasion rate was significantly higher compared to that of the non-recurrence group ($p<0.05$) (Table 4).

Table 6
Univariate and multivariate models

	Univariate model			Multivariate reduced model		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.02	0.97-1.07	0.371			
Gender	0.29	0.03-3.39	0.327			
Postoperative adjuvant radiotherapy	5.75	1.98-16.64	0.001			
Thyroid cartilage invasion	3.36	1.31-8.61	0.011			
Epiglottic cartilage invasion	1.51	0.58-3.92	0.399			
Extracapsular invasion	6.06	2.25-16.30	0.000			
Cricoid cartilage invasion	4.40	1.17-16.62	0.029			
Vascular invasion	1.23	0.41-3.64	0.711			
Perineural invasion	4.00	1.21-13.18	0.023			
Lymphatic invasion	3.96	1.54-10.21	0.004			
The nearest surgical margin (mm)	0.96	0.84-1.10	0.565			
Positive surgical margin	3.01	0.85-10.67	0.088			
Tumor differentiation	1.42	0.73-2.74	0.300			
T Stage	5.42	2.48-11.86	0.000	4.80	1.96-11.79	0.001
N Stage	2.56	1.55-4.23	0.000	2.45	1.33-4.52	0.004
M Stage	1.970	0.381-10.191	0.419			

OR: Odds ratio; CI: Confidence interval; T: Tumor; N: Node; M: Metastasis.

In terms of lymphatic invasions, in the non-recurrence group, 108 patients (78.3%) did not have any lymphatic invasions, while 30 patients (21.7%) did. In the recurrence group, 10 patients (47.6%) did not have any lymphatic invasions, while 11 patients (52.4%) did. The rate of lymphatic invasion was significantly higher in the recurrence group compared to the non-recurrence group ($p<0.05$) (Table 4).

Tumor differentiation rates were assessed across groups as well. In the non-recurrence group, 37 patients (26.8%) had Grade 1 tumors, 68 patients (49.3%) had Grade 2 tumors, and 33 patients (23.9%) had Grade 3 tumors. In the recurrence group, three patients (14.3%) had Grade 1, 12 patients (57.1%) had Grade 2, and six patients (28.6%) had Grade 3 tumors. When compared in terms of tumor differentiation, the distribution of patients into these three tumor-grading subgroups did not result in any significant findings for recurrences ($p>0.05$) (Table 5).

In terms of T staging of the disease, in the non-recurrence group, 14 patients (10.1%) had T_1 tumors, 54 patients (39.1%) had T_2 tumors, 46 patients (33.3%) had T_3 tumors, and 24 patients (17.4%) had T_4 tumors. Tumor stages were significantly more advanced in the recurrence group compared to those of the non-recurrence group ($p<0.05$) (Table 5).

As regards to N staging, in the non-recurrence group, 97 patients (70.3%) had N_0 tumors, 10 patients (7.2%) had N_1 tumors, 30 patients (21.7%) had N_2 tumors, and one patient had N_3 tumors. In the recurrence group, the N stages of tumors were significantly more advanced when compared to the non-recurrence group ($p<0.05$) (Table 5).

The univariate model analysis revealed significant influences of radiation therapy, thyroid cartilage invasion, extracapsular invasion, cricoid cartilage invasion, perineural invasion, lymphatic invasion, and T and N staging of cancers on the prognosis of patients in both non-recurrence and recurrence groups ($p<0.05$) (Table 6).

The multivariate reduced model demonstrated that the influence of T and N staging of cancers on prognosis were significant and independent for both the non-recurrence and recurrence groups ($p<0.05$) (Table 6).

DISCUSSION

According to Surveillance Epidemiology and End Results' 2015 data, laryngeal cancers constitute 0.8% of newly diagnosed malignancies each year.[8] They are the most common malignancies of the head and neck region when skin malignancies are excluded. They account for 25% of all head and neck cancers.[6] The rates increase at the ages of 55-65 and larynx cancers are more common in males.[8,9] In our study, the mean ages and gender ratios were similar to other studies in the literature: the mean age was calculated as 60±9.5 years and the rates of larynx cancers were much higher in males.

Surgical approaches in the treatment of laryngeal cancers consist of resection of tumors if tumor is resectable, and the addition of either only radiotherapy or of radiochemotherapy to the treatment regimen if it is indicated. Indications for adjuvant radiotherapy include presence of tumors at surgical margins, presence of perineural invasion, bone and cartilage involvement, extralaryngeal involvement, and advanced Stage diseases, namely T_3, T_4 and N_2, N_3 Stage tumors.[10] Two large studies of locally advanced, resectable tumors have shown significant effects of combined or single fractional radiotherapy on survival.[11,12] In a multicenter study conducted by the European Organisation for Research and Treatment of Cancer; patients with high-risk cancers of larynx, oral cavity, oropharynx and hypopharynx, and patients with squamous cell carcinoma were randomized into two groups of treatment comprised of either radiotherapy solely or radiochemotherapy, where in the latter group, patients received cisplatin combined with radiotherapy given at the same dose with the former group.[13] High risk was defined to be T_3 and T_4 disease regardless of lymph node staging (excluding T_3N_0), presence of tumor at surgical margins, extracapsular dissemination, and vascular invasion; or presence of lymph nodes at level 4 or 5 for oral cavity and oropharyngeal tumors. Concomitant chemoradiotherapy during the mean duration of follow-up of 60 months in that study was reported to lead to better results significantly in terms of five-year disease-free survival (47-36%), survival (53-40%), and locoregional relapses (18-31%) compared to the rates obtained by administration of postoperative radiotherapy.[13] In our study, tumor staging was found to be a significant parameter for recurrence. No recurrences were experienced neither by 14 patients in Stage T_1 nor by 54 patients in Stage T_2. There were 14 N^+ patients identified in the early stages (T_1 and T_2). Even in the presence of lymph node metastases, early Stage tumors have lower risk of recurrences than advanced Stage tumors (T_3 and T_4). Eight (14.8%) of the 54 patients with T_3 Stage tumors and 13 (35.1%) of the 37 patients with T_4 Stage tumors had recurrences. In advanced Stage tumors, the rate of N^+ was higher with a rate of 42% (43/105) than in early Stage tumors. The rate of recurrences increases as tumor dissemination advances.

In our study, lymph node involvement of the disease was found to be significantly associated with recurrences. Of N_0 patients, 4.9% (5/102) were recurrent; while the rates were 28.5% (4/14) with N_1, 26.8% (11/41) with N_2, and 50% (1/2) with N_3. The recurrence rate was significantly higher as 28% (16/57) for patients with N^+. Although having a N_1 Stage tumor is a significant factor for recurrences, it does not fulfill the indication criteria for radiotherapy as described in the literature.

The concept of surgical margins is referred to in indications for postoperative treatment; however, three distinct definitions for this concept exist in the literature. Tumor existence at surgical margins is defined as "invasion of surgical margins", a tumor at a distance microscopically at <5 mm to surgical margins is defined as "close surgical margins", and a tumor at a distance microscopically at >5 mm to surgical margins is defined as "clean surgical margins".[14] A study conducted by Sessions et al.,[14] examining the treatment outcomes of $T_3N_0M_0$ glottic carcinomas, tumor existence at a distance <5 mm to surgical margins was defined as "close surgical margins". Five-year survival rates in this study was 71% in the group with clean surgical margins, 60% in the group with close surgical margins, and 47.1% in the presence of tumor at surgical margins. In our study, the distance of tumor to surgical margins was found to be at a mean of 3.6±4.1 mm, with a median value of 3 in the recurrence group; whereas the values were 4.3±4.8 mm and 2 for the non-recurrence group, respectively. Four patients (19%) out of 21 who experienced recurrences and 10 patients (7.2%) out of 138 patients without recurrences were identified with tumor existence at surgical margins. Statistically, rate of having tumors at surgical margins was not significantly different between the recurrence and non-recurrence groups ($p>0.05$). When the mean distance of tumors to surgical margins was assessed, no statistically significant differences were detected between the recurrence and non-recurrence groups, although a mean of 4.3 mm distance to surgical margins was observed in the non-recurrence group compared to that of 3.6 mm in the recurrence group. A 56-patient study conducted by Wenig and Barry[15] reported a follow-up of hemilaryngectomy patients with positive surgical margins, without adjuvant radiotherapy, and concluded that as surgical margins need to be defined by tumor localization in malignancies of head and neck region, millimetric values were adequate for larynx. Particularly for tumors of glottic region, millimetric surgical margins are adequate due to the characteristics of lymph drainage in this region.[15] Barry reports some issues regarding commenting on surgical margins in pathological reports. Islands of tumors tend to be reported as positive surgical margins. Therefore, it is suggested to examine the tissue excised from the resection margin.[15] A study by Bauer et al.[16] demonstrated significant association of positive surgical margins with recurrences.

In our study, there were no significant differences between the two groups of patients with or without tumor existence at surgical margins in terms of recurrences ($p>0.05$). Of the patients, 19.04% in the recurrence group and 7.24% in the non-recurrence group had tumor existence at surgical margins; however, this difference was not statistically significant ($p>0.05$). No recurrences were detected during a follow-up period of 38 months in 10 of the 14 patients with positive surgical margins (71.4%). One of the probable reasons for this condition is increased efficacy of adjuvant radiotherapy and chemotherapy applied postoperatively by evolving technology. Microscopic residual disease control can be achieved effectively by radiation therapy. Another reason can be false positives in the pathological evaluation results due to lack of anatomical integrity. It is warranted that further detailed analysis is needed with patient series of higher numbers using other variables in groups with common characteristics. In laryngeal surgery, the amount of excised material influences the functional capacity postoperatively. Therefore, it is warranted to assess the millimetric distances of areas of excisions while adhering to the oncological surgical procedures.

In terms of obtaining local control, radiation therapy provides benefits when given either alone or with chemotherapy as a postoperative adjuvant therapy.[13] Of the patients, 76.2% with recurrences and 35.8% without recurrences received radiotherapy. Receiving radiation therapy was found to be statistically significant in terms of recurrences. Radiotherapy indications applied at our clinic is in compliance with the literature, where they are defined as the presence of tumor at surgical margins, three or more lymph node metastases, and perineural or cartilage invasions. As the patients fulfilling these criteria comply with the criteria for poor prognosis, the patients receiving radiotherapy are observed with higher rates of recurrences. A 96-patient study of Spector et al.[17] demonstrated that postoperative radiotherapy did not improve survival rates of patients with positive surgical margins, while it improved the survival rates of patients in all groups and decreased the rate of recurrences.

Thyroid cartilage is a barrier for tumors, and invasion of it implies poor prognosis.[18] In case of its involvement at the preoperative period, aggressive surgical treatment is warranted. A retrospective 89-patient study by Choi et al.[19] reported that thyroid cartilage involvement was one of the most influencing factors on survival and that total laryngectomy should be performed instead

of chemotherapy if it was found to be present. The same study demonstrated that occult involvement of the thyroid cartilage worsened prognosis in T_{1b} and T_2 tumors and that there was a 25 to 50% possibility of thyroid cartilage involvement in patients with no such finding detected by magnetic resonance imaging or computed tomography. Caution should be exercised to detect thyroid cartilage involvement as it would worsen prognosis in patients with early Stage tumors accompanied by decreased vocal cord movements. It was suggested that partial laryngectomies should be discussed to be performed in these patients even at earlier stages of tumor. Our study, too, demonstrated thyroid cartilage invasion, which was observed at a significantly higher rate in the group of patients with recurrences, as a poor prognostic sign compatible with other study results in the literature ($p<0.05$).

A 161-patient study evaluating cartilage involvement in larynx cancers by Gómez Serrano et al.[20] reported that the most common invasion was observed in thyroid cartilage (15.5%) and it was followed by epiglottic cartilage invasion (13%). In this study, thyroid cartilage involvement was found to be associated with survival at a greater extent while epiglottic cartilage involvement was not found to be associated with survival rates. In our study, 28% and 30% of patients were identified with thyroid and epiglottic cartilage invasions, respectively. Epiglottic cartilage involvement was not found to be associated with recurrences ($p>0.05$), which is a finding compatible with the reports in the literature.

Another cartilage is the cricoid with lower rates of involvement but with greater extent of association with prognosis.[20] A study examining cricoid cartilage in 335 patients with Stage T_2 and T_3 tumors by Fiorella et al.[21] demonstrated cricoid cartilage microinvasions in 12% of the patients. None of patients with Stage T_2 tumors, and 8% of patients with Stage T_3 tumors were identified with microinvasions of cricoid cartilage, which were also detected in lesions extending to subglottic area at rates around 20%. Cricoid cartilage invasion is important for peristomal recurrences as well. In our study, it was observed that 11 patients (6.9%) were identified with cricoid cartilage involvement, and this phenomenon was demonstrated to be associated with recurrences significantly ($p<0.05$).

A study conducted by Oosterkamp et al.[22] including follow-up of 65 patients demonstrated that lymph node metastases without extracapsular dissemination were significant indicators for predicting survival without distant metastases. Presence of metastatic lymph nodes were demonstrated to present at a three times higher risk for distant metastases. Furthermore, lymph node metastases with extracapsular dissemination were observed at nine times higher risk for distant metastases compared to the risk in patients without lymph node metastases. In our study, extracapsular dissemination was observed in 47.6% of the patients with recurrences, and was found to be an important factor signifying tumor aggression and recurrences. Recurrence rates were found to be significantly higher in this group of patients compared to the rates observed in patients without extracapsular invasion.

A 94-patient study by Yılmaz et al.[23] demonstrated vascular and perineural invasions as significant prognostic factors in both disease free survival and local recurrences, and determined that vascular invasions significantly increase regional recurrences. Both vascular and perineural invasions have been shown to influence development of distant metastases significantly.

Moreover, Fagan et al.[24] demonstrated by their study that perineural invasion is associated with poor prognosis and decreased rates of survival. A study by Rubin et al.[25] reported the importance of perineural invasion on the grounds that stomal recurrences may originate from residual tumor cells remained in the proximal nerve roots after total laryngectomy. A study of 256 patients by Chirilă et al.[26] reported that minor neural involvement increased local recurrences. Another study with 396 patients by Chirila et al.,[27] too, determined that lymphatic and vascular invasions were significant prognostic factors for disease free survival, regional, and distant metastases . In our study, lymphatic ($p<0.05$) and perineural ($p<0.05$) invasions were found to be significant prognostic factors for recurrences, whereas no association between vascular invasion and recurrences was demonstrated ($p>0.05$).

One of the advantages of this study is the sufficient follow-up duration of patients. Furthermore, the pathological records of our patients were satisfactory and in good order.

A disadvantage and limitation of this study could be the small sample size. However, a review of the literature demonstrated that our number of patients and follow-up period are in alignment with other reports.

In conclusion, larynx surgery usually warrants tumor resection with millimetric surgical margins in order to spare the organ. The results of our study indicates that very close surgical margins or even positive surgical margins are not of primary importance for the risk of recurrences. For larynx cancers, the parameters found to be associated with recurrences were thyroid or cricoid cartilage invasion, extracapsular invasion, perineural invasion, lymphatic invasion, or T and N stages of cancer. Studies with larger series of patients are needed to determine the association of surgical margins with recurrences.

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