

Original Article

Which is The Best Strategy in Local Advanced Larynx Cancer? Total Laryngectomy Plus Radiotherapy or Larynx Preservation with Chemoradiotherapy: Single Center Experience

Lokal İleri Evre Larinks Kanserinde Hangi Strateji En İyisi? Total Larenjektomiye Radyoterapi Eklenmesi mi Organ Koruyucu Kemoradyoterapi mi? Tek Merkez Deneyimi

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ABSTRACT

Objectives: The treatment of locally advanced laryngeal cancer (LALC) is very challenging. In the last few decades there has been a shift from total laryngectomy towards organ-sparing approaches. The aim of the current study is to compare oncological outcomes between surgery (total laryngectomy) followed by radiotherapy and larynx preservation with chemoradiotherapy (CRT).

Materials and Methods: 114 patients with stage III-IV laryngeal cancer were included in the study, between 2009 and 2018. Thirty-six patients (31.6%) were performed total laryngectomy followed by radiotherapy and 78 (68.4%) underwent the larynx preservation approach. Survival differences between the groups were examined with the Kaplan-Meier test and cox-regression tests for factors affecting survival.

Results: 5-year overall survival (OS) was found 66.3 months and 74.1 months, in the larynx preservation and the surgical groups, respectively (p=0.29). There was no statistically difference between groups for OS in the patients with T3/N0-N1 (p=0.76), but surgical groups had longer OS in the patients with T3/N2-N3 (p=0.04). There was no statistically difference between groups for OS in the patients with T4/N0-N1 (p=0.47), however CRT groups had longer OS in the patients with T4/N2-N3 (p=0.02). The N2-N3 was the factor associated with poor progression-free survival and distant metastasis free survival in multivariate analysis (p<0.01). Age (≥65) was associated with a 2.1-fold increased risk of death (p=0.01). The trans-glottis tumors were associated with a 3.6-fold increased risk of tracheostomy (p<0.01).

Conclusion: The N0-N1 and N2-N3 should also be considered as well as advanced T-category for the treatment of LALC.

Keyword: larynx-preservation, chemoradiotherapy, cisplatin, cetuximab, survival

ÖZET

Amaç: Lokal ileri larinks kanserinin tedavisi çok zordur. Son birkaç on yılda total larenjektomiden organ koruyucu yaklaşımlara, yani kemoradyoterapiye doğru bir kayma olmuştur. Bu çalışmanın amacı, cerrahi (total larenjektomi) ardından radyoterapi ve kemoradyoterapi ile larinksin korunması arasındaki onkolojik sonuçları karşılaştırmaktır.

Gereç ve Yöntem: 2009-2018 yılları arasında evre III-IVa-b larinks kanserli 114 hasta çalışmaya dahil edildi. 36 hastaya (%31,6) radyoterapi ve 78 hastaya (%68,4) larinks koruyucu yaklaşım uygulandı. Larinks koruma yaklaşımları, indüksiyon kemoterapisi sonrası kemoradyoterapi veya eş zamanlı kemoradyoterapi idi. Gruplar arasındaki sağkalım farklılıkları Kaplan-Meier testi ve sağkalıma etki eden faktörler cox-regresyon testi ile değerlendirildi.

Bulgular: 5 yıllık genel sağkalım larinks koruma ve cerrahi gruplarda sırasıyla 66,3 ay ve 74,1 ay olarak bulundu (p=0.29). Evre III hastalarda 5 yıllık hastalık spesifik sağkalım (HSS) oranı cerrahi grupta

%63,3 iken kemoradyoterapi grubunda %66,2 idi ($p=0,83$). Evre IV hastalarda 5 yıllık HSS oranları cerrahide %68,6, kemoradyoterapi grubunda %46,2 bulundu ($p=0,22$). İleri N kategorisi (N2-N3), çok değişkenli analizde kötü progresyonsuz sağkalım ile ilişkili faktör olarak bulundu ($p<0,01$). Yaş (≥ 65) 2,1 kat ($p=0,01$), ileri T kategorisi (T4) 2 kat artmış ölüm riski ($p=0,03$) ile ilişkili bulundu. Trans-glottik tümörler 3.6 kat artmış trakeostomi riski ile ilişkili bulundu ($p<0,01$).

Sonuç: T3/N0-N1 ve T3/N2-N3 alt grupları ayrı ayrı değerlendirildiğinde, T3/N0-N1 hastalarda, kemoradyoterapi yüksek düzeyde larinks koruması sağlayan bir tedavi seçeneğidir.

Anahtar kelimeler: larinks koruma, kemoradyoterapi, sisplatin, setuksimab, sağkalım

Introduction

Larynx cancer causes 2% of all malignancies in the world. Also, it is the 2nd most common cancer in the head and neck region [1]. The standard treatment of locally advanced laryngeal cancer is unclear. In the last decades there, significant changes have evolved in locally advanced laryngeal cancer treatment. Until the 1980s, total laryngectomy (TL) was the main treatment modality and post-operative radiotherapy according to poor prognostic features was a possible treatment strategy. Besides the morbidity of the organ loss, the cosmetic discomfort of permanent stoma causes physiological and psychological problems in patients. The idea of organ protection treatment includes the possibility of treatment with a combination of radiotherapy and chemotherapy without compromising oncological outcomes. The studies that compare the outcomes between the TL plus postoperative radiotherapy with induction chemotherapy that consists of 5-fluorouracil and cisplatin followed by radiotherapy showed no different outcomes according to disease control or overall survival [2-4]. A subsequent study showed that concomitant chemoradiotherapy had good outcomes than induction chemotherapy followed by radiotherapy, in terms of local control and rate of larynx preserving and there were no differences in late adverse effects [5,6]. However, some studies in recent years have suggested that survival rates in locally advanced larynx cancer are reduced. They thought that the shift from surgical to organ-sparing approaches might cause these reduced

survival times. They claim that the reason for this reduced survival was a shift from surgery to organ-sparing approaches [1,7]. Therefore, in recent years, articles advocating the re-emergence of surgical approaches in locally advanced diseases have been published [8]. Currently, it is recognized that the best oncologic outcome in patients who has locally advanced tumors (T4a) been usually achieved by surgical treatment involving organ resection. But, deciding the method of treatment is quite challenging both for the physician, as well as the patient. In case of moderately extensive tumors suitable for TL (T3 and selected T4a), oncological outcomes of organ protection protocols should be kept in mind [9]. With this study, comparison of the treatment outcomes of surgical and non-surgical approaches are aimed.

Materials and Method

Patients

The trial was carried out by department of radiation oncology and Department of Otorhinolaryngology-Head and Neck Surgery together. 114 patients with locally advanced laryngeal cancer were included in this retrospective study, between March 2009 and December 2018. TNM staging was determined by clinical examination, endoscopy, computed tomography, and positron emission computed tomography, according to AJCC 7th staging [10]. All patients had been evaluated by the tumor board which consisted of head and neck surgeons, pathologists, radiation oncologists, medical oncologists, radiologists, and nuclear medicine specialists.

After the evaluation for each case, the appropriate treatment modalities are presented to the patient by describing meticulously the pros and cons of each treatment both in terms of oncological outcomes as well as potential effects. For this study group with T3-4 laryngeal cancers, the suggested treatment options were either surgery or organ-preserving approach. Groups were then created according to the patient's treatment choice for this cohort. The patients who underwent partial laryngectomy, the ones with previous treatment to the head and neck area, the ones with poor Karnofsky Performance Scales (<70) and patients with surgically unresectable tumors were excluded from the study. Both induction chemotherapy followed by chemoradiotherapy and concomitant chemoradiotherapy was accepted as larynx preservation approaches. The written informed consent was obtained from all participants. The trial was approved by the local ethics committee (Number 2020/395).

Surgical Approach

The surgical approach was resection of the primary tumor plus bilateral modified radical neck dissection. Thirty-six patients (31.6%) underwent total laryngectomy plus adjuvant radiotherapy. Post-operative adjuvant radiotherapy was started four weeks after surgery and it was applied 2.0 Gy per fraction per day with five fractions per week. 60 Gy dose was applied to the tumor bed for patients with R0 resection. Uninvolved lymph nodes and supraclavicular nodes were applied 50-60 Gy.

Non-surgical approach

We considered the treatment of organ protection as induction chemotherapy followed by chemoradiotherapy, concurrent radiotherapy combined with cisplatin, or concurrent radiotherapy combined with cetuximab (bio-radiotherapy). For these patients, it was accepted as an organ loss that

total laryngectomy performed after recurrence or tracheostomy performed for any reason. 78 of 114 patients (68.4%) were treated with the intent of larynx preservation. 71 (92%) of 78 patients had cisplatin as concurrent chemotherapy (100 mg/m² every 3 weeks or 50mg/m² a week). Cetuximab was administered to seven patients (8%) according to published protocols [11]. Induction chemotherapy was administered to 16 of 78 patients (20.5%) and 62 of 78 patients (79.5%) received concurrent chemotherapy for the organ-preserving protocol. High-risk planning target volume (PTV) (primary tumor volume and associated nodes), intermediated-risk PTV, and low-risk PTV received the prescribed dose as 70Gy, 60Gy, and 54Gy respectively.

Statistical analysis

IBM SPSS Statistics software (Version, 21, Armonk;NY: IBM Corp) was used to analyze the data of the study. Evaluation of normality was performed by using the Shapiro-Wilk test. To compare categorical variables Chi-square or Fisher's exact tests were used. The survival time between groups was compared with Kaplan-Meier analysis and log-rank tests. The effective factors on survival such as gender, T category, N category, treatment modalities were determined with the in the univariate test. $p < 0.05$ was accepted as statistically significant. Variables with p values $< .05$ were entered into a backward stepwise regression in multivariate analysis.

Results

The median age was 60 (range: 31-79). 12 (10.5%) of the patients were female and 102 (89.5%) were male. In the non-surgical group, 63 patients (79.5%) had a complete response, while 11 patients (14.1%) had a partial response. There was a stable response for 2 patients (2.6%) and progression for 3 patients (3.8%). In the non-surgical group, 17 of 78 patients (21.8%) underwent salvage surgery.

Table 1. The general characteristics of the patients

		Total	Total laryngectomy plus radiotherapy n	(%)	Larynx preservation n	(%)	p
Gender	Female	12	0	0	12	15.4	0,01
	male	102	36	100	66	84.6	
Age	<65	72	22	61.1	50	64.1	0.83
	>65	42	14	38.9	28	35.9	
Tumor site	Glottis	21	1	2.8	20	25,6	<0,01
	Supra-glottis	59	14	38.9	45	57.7	0,05
	Sub-glottis	7	6	16.7	1	1.3	<0,01
	Trans-glottis	27	15	41.7	12	15.4	<0,01
T category	T3	85	21	58.3	65	82.3	0,01
	T4	29	15	41.7	14	17.7	
N category	N0-1	89	27	75.0	63	79.7	0,62
	N2-3	25	9	25.0	16	20.3	
Stage	III	66	12	33.3	53	67.1	<0,01
	IVA	48	24	66.7	26	32.9	
Tracheostomy		56	36	100	20	25.3	<0,01
Local recurrence	-	91	32	88.9	62	78.5	0,20
	+	23	4	11.1	17	21.5	
Death	alive	66	25	69.4	42	53.2	0.10
	ex	48	11	30.6	37	46.8	

p: Fisher's Exact Test value

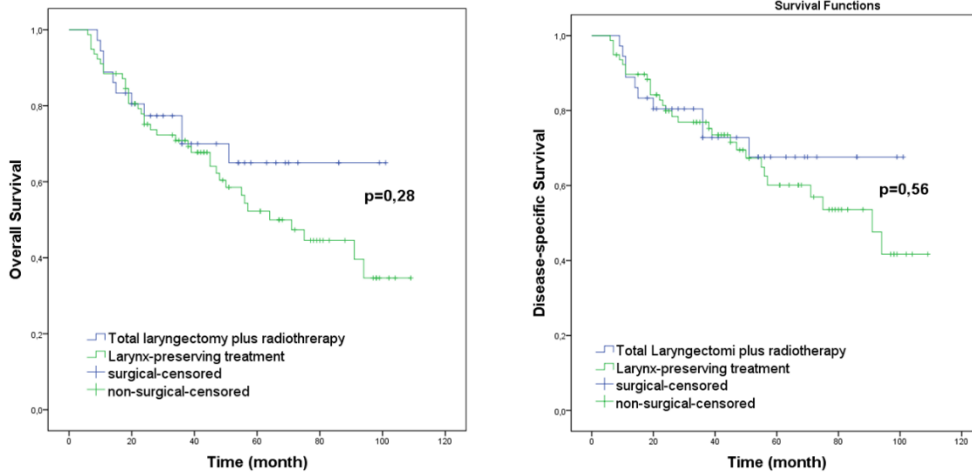


Figure 1: Kaplan-Meier survival curves between total laryngectomy plus radiotherapy and larynx preserving.

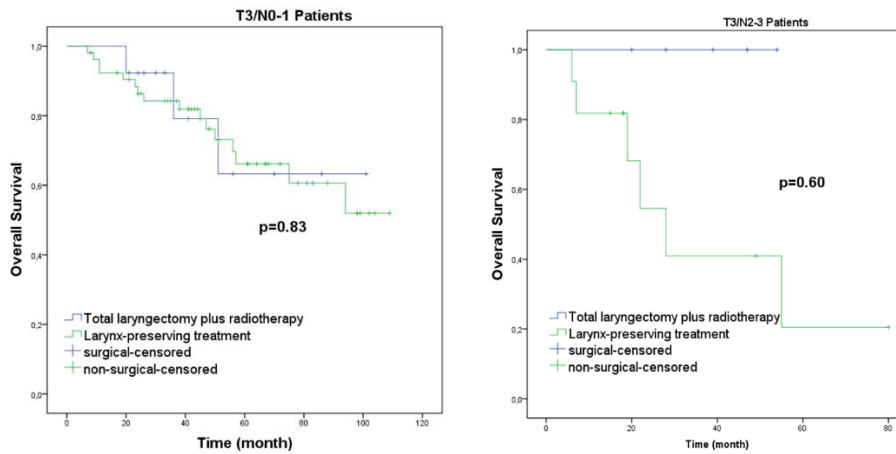


Figure 2: Intergroup survival curves according to N stage in T3 patients

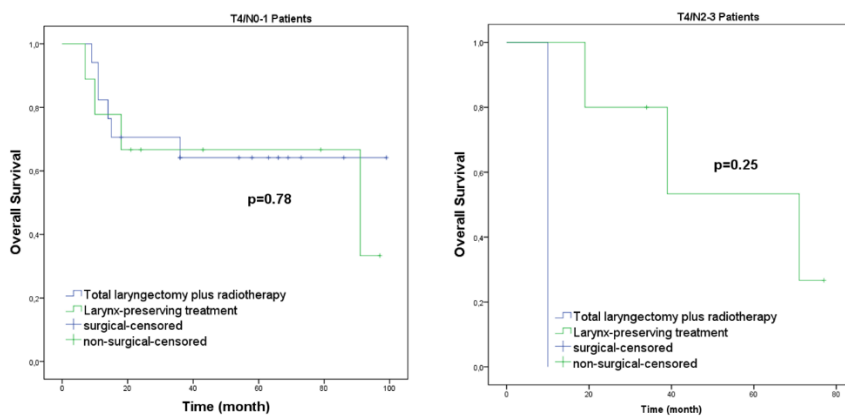


Figure 3: Intergroup survival curves according to N stage in T4 patients.

In the last visit, 66 patients (57.9%) were alive at last examination. 39 patients (34.2%) died from cancer and nine patients (7.9%) died from non-cancer related causes. The patient's characteristics are summarized in Table 1.

Survival

The median overall survival (OS) was 75 months for all the patients, with a median follow-up of 41 months. The 5-year OS rates were found 60% in the surgical group and 52.3% in the non-surgical group. The differences between groups were not found statically significant ($p=0.28$). Disease-specific survival (DSS) was 76.2 months in the surgical group, while it was 73.1 months in the non-surgical group ($p=0.56$)(Figure 1). Additionally, progression-free survival (PFS) was 75.2 months in the surgical group and it was 71.0 months in the non-surgical group ($p=0.27$). In patients with stage III, 5-year OS rate was 57,5% in the surgical group, while that's the rate was 57,4% in the non-surgical group. However, there was no significant statistical difference between the groups ($p=0.76$). Also, in patients with stage IV, 5-year OS rates were found 68.6% in the surgical group and 40,4% in the non-surgical group, respectively. The difference didn't achieve to statistically significant value ($p=0.11$). When the outcomes were evaluated in terms of T-category, 5-year OS rate was 73,8% in the surgical group in patients with T3, while that's the rate was 51,7% in the non-surgical group ($p=0.08$). When the subgroups of T3 cases were examined; 5-year OS rate was 57,5% in total laryngectomy + RT arm and 57,4% in chemoradiotherapy arm in the T3N0-1 cases ($p = 0.76$). However, in T3N2-N3 cases, this ratio was 100% in the total laryngectomy + RT arm and 17,9% in the chemoradiotherapy arm ($p=0.04$) (Figure 2). Also, in patients with the T4 category, the 5-year OS rates were found 52.5% and 54,4% for surgical and non-surgical groups, respectively ($p=0.83$). No difference in survival was found between groups in terms

of T4-category. When the subgroups were examined in terms of T4, in the T4N0-1 patients the 5-year OS rate was 64,2% in the surgical group while this rate was 53,3% in the non-surgical group ($p:0,47$). But, in the T4N2-3 patients the 5-year OS rate was 26,7% in the non-surgical group while this rate was 0% in the surgical group (There was one patient and he died at the tenth month) ($p:0,02$) (Figure 3).

In 58 of the 78 patients (74.4%), the larynx was preserved. Larynx preservation rates were found 76.8% and 71.8% at the 2nd and 5th years, respectively. While the 5-year larynx preservation rate of patients treated with induction chemotherapy and sequential radiotherapy was 71.8%, it was 72.9% in patients receiving only chemoradiotherapy. There were no statistically significant differences between groups ($p=0.97$). Also, 5-year larynx preservation rates were found 74.3% in patients with T3 and 60.6% in patients with T4 ($p=0.17$). In patients receiving cetuximab during radiotherapy, 5-year larynx-preservation rates were found as 51.4%, while in patients receiving cisplatin this rate was found 73.9%, but differences between groups were not found statistically significant ($p=0.13$). However, in terms of OS, between patients receiving cetuximab and patients receiving cisplatin, the difference was statistically significant (33 months versus 77.2 months, respectively, $p<0.01$).

Univariate and multivariate analyses

In univariate and multivariate analysis, the advanced age (>65) was found as factor affecting OS (HR:2.17, 95%CI: 1.154-4.100, $p<0.01$) and advanced T status (T4) was found as factor affecting OS (HR:2.05, 95%CI: 1.061-3.964, $p=0.03$). The treatment approach (surgical versus non-surgical) was not detected as a factor affecting OS (HR: 1.43, 95%CI: 0.732-2.820, $p=0.29$) (Table 2). The advanced stage (stage-IVA-B) and N-category (N2-N3) were the factors associated with poor progression-free survival, in univa-

Table 2. Univariate and multivariate analysis

		Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p
Overall Survival							
Gender	Female	1.04	0.376-2.919	0.93			
	Male						
Age	≤65						
	>65	2.18	1.234-3.851	<0.01	2.17	1.154-4.100	0.01
T category	T-3						
	T-4	1.96	1.021-3.798	0.04	2.05	1.061-3.964	0.03
N category	N0-N1						
	N2-N3	1.26	0.643-2.481	0.49			
TNM Stage	III						
	IVA-B	1,55	0.881-2.747	0.12			
Treatment	Surgery plus radiotherapy						
	Larynx-preserving	1.43	0.730-2.812	0.29			
Tumor sub-site	Glottis						
	Supra-glottis	0.38	0.137-1.064	0.26			
	Sub-glottis	0.86	0.451-1.643				
	Trans-glottis	0.57	0.131-2.552				
Progression-free Survival							
Gender	Female	0.95	0.337-2.674	0.92			
	Male						
Age	≤65						
	>65	1.18	0.619-2.254	0.61			
T category	T3	1,57	0.795-3.104	0.19			
	T4						
N category	N0-N1						
	N2-N3	2.65	1.379-5.127	<0.01	2.65	1.379-5.124	<0.01
TNM Stage	III						
	IVA-B	2.24	1.193-4.242	0.01			
Treatment	Surgery plus radiotherapy						
	Larynx-preserving	1,21	0.576-1.182	0.29			
Tumor sub-site	Glottis						
	Supra-glottis	2.44	0.846-7.079	0.22			
	Sub-glottis	0.81	0.091-7.253				
	Trans-glottis	2.61	0.834-8.227				

a value of $p < 0.05$ was considered statistically significant

Table 3. Univariate and multivariate analysis for larynx-preserving survival

		Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p
Gender	Female						
	Male	3.19	0.427-23.865	0.23			
Age	<65						
	≥65	1.52	0.421-1.024	0.06			
T category	T3						
	T4	1.84	0.721-5.499	0.18			
N category	N negative						
	N positive	1,29	0.498-1.199	0.24			
TNM Stage	III						
	IVA-B	2,75	1.142-6.660	0.02	1.97	0.753-5.157	0.16
Tumor sub-site	Glottis						
	Supra-glottis	0.197	0.068-0.574				
	Sub-glottis	0.309	0.134-0.716				
	Trans-glottis	15.160	2.482-92.598	<0.01	3.66	1.461-9.205	<0.01
Treatment	ICT followed by CRT						
	Concurrent bio/chemo-radiotherapy	0.98	0.592-1.651	0.96			
Concomitant drug	Cisplatin (chemo-therapy)						
	Cetuximab (bio-therapy)	2.49	0.724-8.560	0.14			

ICT; Induction chemotherapy, CRT; concurrent chemoradiotherapy, a value of $p < 0.05$ was considered statistically significant

riate analysis (HR:2.24, 95%CI:1.193-4.242, $p=0.01$ and HR:2.65, 95%CI:1.379-5.127, $p < 0.01$, respectively) (Table 2). N-category (N2-N3) was associated with an approximately 2.6-fold increased risk of progression (HR:2.65, 95%CI:1.379-5.127, $p < 0.01$) (Table 2). In univariate analysis, N-category (N0-N1 v N2-N3), and stage (stage III v IVA-B) were associated with distant metastasis. (HR:3.76, 95%CI:1.623-8.731, $p < 0.01$ and HR:2.51, 95%CI:1.073-5.898, $p=0.02$). In multivariate analysis, only N-category (N2-N3) was associated with distant metastasis (HR:3.76, 95%CI: 1.623-8.731, $p < 0.01$) (Table 2).

When the patients were evaluated in terms of larynx preservation; in univariate analysis, trans-glottic tumor and stage were found as factors affecting larynx-preservation survival

(HR:3.667, 95%CI: 1.461-9.205, $p < 0.01$ and HR:2.75, 95%CI:1.142-6.660, $p=0.02$, respectively). Multivariate analysis showed that trans-glottis tumors were associated with a 3.6-fold increased risk of tracheostomy (HR: 3.66, 95%CI: 1.461-9.205, $p < 0.01$) (Table 3).

Discussion

Organ preservative approaches for advanced laryngeal cancer have been well established in the literature in terms of effectiveness and safety [2,5,6]. According to the results of the Veterans Affairs Laryngeal Cancer Study Group and RTOG91-11 study, there has been a shift from surgical approaches to chemo-radiotherapy in the last few decades, in locally advanced larynx cancer treatment. In the cohort of this study, approximately 70% of patients have organ-protective approaches. This current study confirmed that there has

been a shift from surgical treatments to larynx protection treatments. Especially, all of the female patients preferred the organ-protective approaches. In this respect, it is compatible with literature. However, in recent years, the authors have begun to advocate surgical priority over chemoradiotherapy. In the study based on SEER data, Carvalho et al., first announced a reduction in survival times in patients with larynx cancer. They suggested that organ protection protocols increased from 37.4% to 50.6%, which led to a decrease in survival [12]. Similarly, Chen et al., argued that the risk of death for 4-year overall survival increased by 13% in patients treated with CRT, due to the increased use of CRT in the treatment of locally advanced diseases [13]. This relationship has been replicated in subsequent studies [14-16]. However, the oncological results of treatment selection are still debated in studies in the literature. Rades et al., found that tumor size and histologic grade were affecting OS. They did not find any differences between surgery plus adjuvant treatment and larynx-preserving treatment in terms of survivals [17]. Similarly, Timme et al., found that the 5-year overall survival rate was 45% and %46 in patients receiving chemoradiotherapy and in patients undergoing surgery, respectively, and it was not statistically significant [18]. In this current study, we didn't find a significant statistical difference between the laryngeal-preservation and non-preservation approaches, both overall survival and disease-specific survival. Additionally, when patients were evaluated for T-category, we found that there was a tendency towards larynx-protection protocol in patients with T3 tumors, whereas there was a tendency towards surgery in patients with T4a tumors. This situation coincides with studies in the literature [7]. Many authors agree that oncological outcomes are similar in patients with T3 tumors, whether total laryngectomy or larynx protection therapy is selected [7,19]. However, some studies have shown that total laryngectomy plus

radiotherapy is superior to non-surgical approaches in patients with T4A tumors [20-23]. In this study, T3 patients who underwent total laryngectomy tended to have longer OS than non-surgical patients, although this did not reach statistical significance. It can be thought that the association of N2-3 lymph node metastasis is more effective in this trend than the effect of the T category alone. The results of patients with T4 tumors were also very close between the non-surgical approach and surgical approach. In this current study; T4/N2-3 patients who were initially treated with the organ preservation protocol had longer OS than patients who underwent surgery. Whether with chemoradiotherapy or induction chemotherapy, the initial effect of systemic chemotherapy might have led to this result. While local control could be achieved with radiotherapy in this group of patients, distant metastasis might be reduced with systemic chemotherapy. Because in multivariate analysis, N2-3 status was associated with distant metastasis. In the GORTEC trial, 3-year OS rates were found as 60% and larynx preservation rates were found %66 [24]. Also, in the TAX-324 study, the 3-year OS rate was 60% and the larynx preservation rate was 70.3% [25]. In the study of EORTC, the 3-year OS rate was found 48.5% for laryngeal cancer, and the 3-year larynx-free survival rate was 52% [3]. In the long-term results of RTOG 91-11 study, they upgraded their results that 10-year OS rate was found 38.8% for patients treated with induction chemotherapy plus radiotherapy (ICT+RT), while it was 27.5% for patients treated with concurrent chemoradiotherapy (CRT) [6]. Additionally, they showed that the 10-year laryngectomy-free survival rate was found as 28.9% in patients with treated ICT+RT and 23.5% in patients with treated CRT. We found in this current work that 5-year OS rate was 55% for patients treated with ICT+RT and was 52% for patients treated with CRT. In this current study, the 5-year larynx protection rates were found as 71.8% in patients

receiving ICT+RT and 73.1% in patients receiving CRT. These results are comparable to the results of the RTOG 91-11 study which a cornerstone of larynx protection strategies.

Bonner et al., had demonstrated the efficacy of cetuximab in patients with head and neck cancer and then the TREMPLIN study was designed [11,26]. This study investigated that after three cycles of induction chemotherapy (consist of taxan, cisplatin, and 5-fluorouracil), compare between concurrent radiotherapy with cisplatin and concurrent radiotherapy with cetuximab. They reported that larynx preservation rates were 87% in the cisplatin arm and 82% in the cetuximab arm, at 18 months. And also, the 3-year OS rate did not differ between groups. In this current study, the larynx-preservation rate did not differ between patients receiving cetuximab and receiving cisplatin, but the OS of patients with cisplatin had better than those receiving cetuximab. However, it should not be ignored that cetuximab treatment was used in patients with comorbid diseases who were not suitable for chemotherapy in this study. The limitations of this study are as follows: there

is a limited number of patients and the follow-up time is also short. It is a non-randomized study, so data were obtained from different sources (partly from patient cards, partly from electronic files and national database). In this study, acute and late side effects related to treatment and quality of life analysis were not evaluated.

Conclusion

Our results show that chemoradiotherapy remains a successful method in patients who want laryngeal protection. However, T3/N0-N1 and T3/N2-N3 subgroups should be evaluated differently and different treatment strategies should be considered. Excellent results are obtained with chemoradiotherapy for T3/N0-N1 patients. However, especially in T3/N2-N3 patients, total laryngectomy should also be kept in mind, despite the patient's desire to protect the larynx. In very advanced disease such as T4/N2-3, it may be necessary to consider the control of systemic disease rather than the treatment of local disease.

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