Retrospective Analysis of Laryngeal Cancer Patients in a Tertiary Referral Center

Original Investigation

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Abstract

Objective: In this study, we aimed to evaluate the effects of demographic data and comorbid diseases on the prognosis and treatment diagnosed with laryngeal squamous cell cancer (LSCC).

Methods: Medical records of LSCC patients treated and followed up in a single referral center between 2008 and 2019 were retrospectively reviewed. In addition to the demographic data, the results of overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), locoregional-free survival (LRFS), and factors affecting recurrence were analyzed.

Results: We included 573 patients with a mean age of 60.1±9.8 years. Of the 573 patients, 94.2% (540) were men, 93.7% (537) were smokers, 40.1% had at least one comorbid disease, and 69.8% (400) presented with glottic LSCC. The five-year OS, DSS, DFS, and LRFS rates for all cases were 65.7%, 79.9%, 67%, and 74.7%, respectively. In early-stage LSCC treatment, the rates of OS (p=0.008), DFS (p=0.024) and LRFS (p=0.01) were statistically significantly higher in the endolaryngeal laser surgery (ELS) group compared with the radiotherapy (RT) group. In advanced-stage LSCC treatment, total laryngectomy had statistically significantly higher five-year DFS (p=0.003) and LRFS (p=0.002) rates compared to chemoradiotherapy.

Conclusion: Our study showed that ELS provided higher rates of OS, DFS, and LRFS compared to RT in the treatment of early-stage LSCC. Recurrence was significantly higher in supraglottic tumors, advanced-stage tumors, and in patients with clinical N positivity.

Keywords: Clinical oncology, laryngeal cancer, squamous cell carcinoma, laryngectomy, organ preservation, survival

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Introduction

Laryngeal squamous cell cancer (LSCC) is the most common head and neck squamous cell carcinoma (HNSCC) in Türkiye, and the second and third most common HNSCC in Europe and the United States, respectively. Every year seven out of 100,000 people, approximately 3,500 new cases, are diagnosed with LSCC in Türkiye (1-3). Globally, nearly 180,000 patients are diagnosed with laryngeal cancer every year, and 95,000 people die with this diagnosis (4). The well-known major etiological factors are smoking and consuming tobacco products. Alcohol, genetic predisposition, gastroesophageal reflux, and viral infections may also play a role. Smoking is thought to be responsible for 30% of cancer-related deaths worldwide, and smokers are ten times more likely to develop laryngeal cancer than non-smokers (5). The combination of alcohol and cigarette abuse synergistically increases the likelihood of cancer development (6).

There are several treatment modalities, both surgical and non-surgical for laryngeal cancer, and the treatment plans are mostly designed based on the stage of the disease. The main purpose is to eradicate cancer as well as to preserve most of the structure and functions of the larynx. Applied treatments to patients are based on patients' choices as well as the physicians' and institutional preferences. Radiotherapy (RT) is used as a non-surgical treatment in the early stages of LSCC, whereas surgical options include transoral endolaryngeal or open partial surgeries, whereas the main treatment modality in advanced-stage disease has been total laryngectomy (TL) for many years. In 1991, the well-known study of Veteran Affairs of Laryngeal Cancer Study Group (VALCSG) (7) reported that survival outcomes were similar for both non-surgical organ preservation treatment and TL plus adjuvant treatments. In the three decades following this study, advances in chemotherapy (CT) and RT regimens have made organ preservation protocols more popular. However, controversies continue in the literature on whether the TL or the organ preservation regimen is best oncologically and functionally in advanced-stage patients, or at least which of the two is the best choice for which patients.

Survival rates in LSCC did not improve in the last four decades despite improved diagnosis and treatment modalities, but apparently, the rate of laryngeal preservation has increased (8).

The purpose of the presented study was to evaluate the prognostic factors along with demographic data, comorbid diseases, and treatment outcomes in LSCC patients who were treated in a single referral head and neck center.

Methods

This retrospective study was conducted following the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 76/10, date: 25.11.2019).

Patients and Treatment Strategy

The charts of the laryngeal cancer patients that were treated in a single referral head and neck center between January 2008 and May 2019 were retrospectively analyzed. Patients with mild to severe dysplasia, non-epithelial cancers, and salivary gland cancers, and those who were lost to follow-up were excluded from the study, and those who were followed-up for at least five years, either alive or dead, were included in the study. Carcinoma *in situ* (Cis), stage 1, and stage 2 were considered early stages, and stages 3 and 4 were considered advanced stages. Data of the patients included in the study were retrieved from the medical records. The pack-year (PY) definition used in the history of smoking was calculated by multiplying the number of packs smoked per day by the number of years of smoking. Details of staging and treatment plans were based on the decisions of the multidisciplinary tumor board. The patients were staged according to the American Joint Committee on Cancer (AJCC) 7th edition (2010).

In general, endolaryngeal laser surgery (ELS), open partial surgery (OPS), or RT options were used as a single treatment modality in patients with Cis, T1, and T2 glottic or supraglottic cancers. Alternatively, chemoradiotherapy (CRT) or TL options were considered in T3 cancers, and the TL option was used in T4-stage tumors.

Follow-up

The patients were followed up and examined twice a month in the first six months, monthly in the second six months, bi-monthly in the second year, quarterly in the third year, and biannually in the fourth and fifth years, and annually after five years. On every visit, a fiberoptic laryngoscope, videolaryngostroboscope, or 70° rigid laryngoscope was used in laryngeal examinations. Microlaryngoscopic examination was done under general anesthesia if a suspicious lesion was defined during the follow-up period. Neck and chest CTs were taken annually for the first five years, and then chest P/A X-ray annually. In our clinical practice, we do not routinely screen patients with a positron emission tomography scan for early laryngeal tumors.

Statistical Analysis

SPSS for Windows version 23.0 software was used for statistical analysis. Numerical variables were expressed as mean ± standard deviation or median along with the attribute variables as numbers and percentages. The Shapiro–Wilk test was used to determine the normality of numerical variables. The chi-square test or Fisher's exact test was used to investigate whether there was an intergroup difference in terms of attribute variables. The Kaplan–Meier product limit

estimation method was used to predict survival probabilities. The Mantel–Cox log-rank test was used to compare the survival curves of different groups. The Cox proportional regression analysis was used to determine the factors that affected survival. The level of significance was determined as $p<0.05$.

Results

Demographic data and tumor characteristics of the 573 patients LSCC are shown in Table 1. Mean patient age was 60.1±9.8 years and 540 (94.2%) of the cases were men. In total, 537 of the patients (93.7%) had a history of smoking with an average rate of 41.5 PY cigarettes, and 83 (14.5%) had a regular alcohol consumption history. At least one comorbid disease was found in 230 (40.1%) of the cases, and the most prevalent one was hypertension (141 cases, 24.6%). The most frequent localization of the tumor was the glottis (400 patients, 69.8%), followed by the supraglottis (169 patients, 29.5%). Four patients (0.69%) had subglottic tumors (one patient stage 2, and three patients stage 4 LSCC). According to TNM staging, 321 (56%) were staged as early, and 252 (44%) were as advanced. Most of the patients (480 cases, 83.76%) had N0 neck at presentation. Overall anterior commissure (AC) involvement was found in 247 cases (43.1%); and in 112 (39.4%) of 284 cases with early-stage glottic LSCC. The most common treatment type was ELS in 182 cases (31.8%). Other treatments used at the early stages were RT in 75 cases (13.1%) and OPS in 69 cases (12%). In the advanced stages, CRT was used as the first treatment option in 166 cases (29%) and TL was used in 81 cases (14.1%) (Table 1).

The five-year overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), locoregional-free survival (LRFS) rates of the 573 cases were 65.7%, 79.9%, 67%, and 74.7%, respectively. The survival rates of the variables are summarized in Table 2.

The OS (p=0.005), DSS (p=0.046), and LRFS (p=0.035) rates of the patients without comorbid diseases were significantly higher than that of the patients with at least one of the comorbid diseases (Table 3). The presence of hypertension did not appear to statistically affect OS (p=0.067), but there was a statistically significant decrease in the rates of DSS (p=0.005), DFS (p=0.02), and LRFS (p=0.001) in patients with HT.

Patients with supraglottic tumors appeared to show a significant decrease in five-year OS ($p<0.001$), DSS ($p<0.001$), and DFS ($p<0.001$) rates, compared to those with glottic tumors, but there was no difference in LFRS rates (p=0.059) (Table 3).

Early-stage patients had significantly better survival rates than the advanced stages in all survival analyses (OS, DSS,

Table 1. Patient demographics and clinical data

Characteristics	**Overall cohort, n=573**
Clinical history	
Age, mean ± SD	60.1±9.8
Gender, male, n (%)	540 (94.2)
Comorbid disease, n (%)	230 (40.1)
Smoking history, n (%)	537 (93.7)
Alcohol use, n (%)	83 (14.5)
Tumor site n (%)	
Glottis	400 (69.8)
Supraglottis	169 (29.5)
AC involvement	247 (43.1)
Stage, n (%)	
Early-stage	**321 (56)**
Carcinoma *in situ*	53 (9.2)
I	166 (29)
II	102 (17.8)
Advanced-stage	**252 (44)**
III	151 (26.4)
IV	101 (17.6)
Clinical T, n (%)	
T *in situ*	53 (9.2)
T1	166 (29)
T2	102 (17.8)
T3	151 (26.4)
T4	101 (17.6)
Clinical N, n (%)	
N0	480 (83.8)
N1	36 (6.3)
N2a	5 (0.9)
N2b	18 (3.1)
N2c	29 (5.1)
N3	5 (0.9)
Histological type, n (%)	
Carcinoma *in situ*	53 (9.2)
Well-differentiated	222 (38.7)
Moderately differentiated	225 (39.2)
Poorly differentiated	73 (12.9)
Type of treatment, n (%)	
ELS	182 (31.8)
RT	75 (13.1)
OPS	69 (12)
TL	81 (14.1)
CRT	166 (29)
Recurrence, n (%)	**176 (30.7)**
Death, n (%)	**182 (31.8)**

AC: Anterior commissure, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, RT: Radiotherapy, SD: Standard deviation, TL: Total laryngectomy

Table 2. Five-year survival rates in all parameters

Characteristics	OS 5-yr (%)	DSS 5-yr (%)	DFS 5-yr (%)	LRFS 5-yr (%)
Overall	65.7	79.9	67	74.7
Age (yrs)				
<65	69.9	80.9	66.9	74
≥65	54.9	78.3	67.4	76.5
Gender				
Male	64.5	79.2	67	74.8
Female	78	90.9	66	72.2
Smoking				
<30 PY	73	84.3	72.8	76.6
>30 PY	60.3	76.7	64.3	74.5
Comorbid disease				
No	69.6	83.1	69.9	79.1
Yes	58.8	75.1	62.3	68
Localization				
Supraglottic	52.8	69.8	55.5	68.9
Glottic	71.4	84.4	72.2	77.7
Histopathologic type				
Carcinoma *in situ*	85.1	94.5	81	82.2
Well-differentiated	73.2	85.5	73.3	78.1
Moderately differentiated	58	74.9	62.7	71.7
Poorly differentiated	44.4	62.9	44.8	64.6
Stage				
Early	78.9	91.8	77.6	85.5
Advanced	48.3	64.6	52.8	65.1
Stage				
Carcinoma *in situ*	87.1	95.2	79.1	80.6
I	82.6	96	78.4	82.8
II	70.7	84.8	74.6	80.2
III	52.2	71.2	56.1	66.2
IV	42.4	54.2	47	63.2
T stage				
T *in situ*	87.1	95.2	79.1	80.6
T1	82.6	96	78.4	82.2
T2	67.3	82.7	69	77.4
T3	49.4	66.4	54.6	63.6
T4	45.6	59.2	53.8	72.1
N stage				
N0	70.3	85.6	72.1	78.7
N+	38.4	50.2	39.1	51.4
N stage				
N0	70.3	85.6	72.1	78.7
N1+N2a	45.9	57.2	40.3	52.2
N2b and above	31.1	43.3	37.5	51.6
AC involvement				
No	65.6	80.8	70.6	77.4
Yes	64.6	78.8	62	71
Early stage glottic AC involvement				
No	84	97.1	85.8	88.1
Yes	75.2	85.7	65.2	68
Type of treatment				
ELS	85	94.4	78.5	82.5
OPS	74.2	92.7	81.5	89.2
RT	71.5	87.3	67.4	70.8
TL	48.8	69.5	64.4	75.9
CRT	48.1	61.2	47.9	58.9

AC: Anterior commissure, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, PY: Package-year, RT: Radiotherapy, SD: Standard deviation, TL: Total laryngectomy, DSS: Disease-specific survival, DFS: Disease-free survival, LRFS: Locoregional-free survival, OS: Overall survival

LRFS, DFS; p<0.001). N+ patients had significantly worse survival rates in all survival analyses compared to N0 patients (p<0.001). Upon comparison of the N+ cases, when grouped as N1+N2a and N2b+N3, among themselves, no significant difference was observed in any survival analysis (OS p=0.23, DSS p=0.34, DFS p=0.82, LRFS p=0.62). AC involvement did not significantly affect survival (OS p=0.65, DSS p=0.87, DFS p=0.3, LRFS p=0.53). However, when AC involvement was taken into consideration in early-stage glottic cancers, a statistically significant decrease was seen in DSS, LRFS, and DFS (DSS p=0.04, DFS p=0.01, LRFS p=0.01) (Table 3).

A comparison of the treatment types in early stages showed five-year OS rates to be 85%, 71.5%, and 74.2% for ELS, RT, and OPS, respectively. ELS had a statistically significant advantage over RT in terms of OS rates in early-stage treatments (p=0.008). However, ELS and OPS (p=0.07), and OPS and RT (p=0.4) were not significantly different in terms of OS. Assessment of DSS in terms of the treatment types -ELS, RT, and OPS-showed no significant superiority to each other in early-stage treatments (RT + ELS p=0.06, APC + RT, p=0.39, APC + ELS p=0.41). It was seen that LRFS rates of RT were significantly lower compared to the other two treatment types (OPS/RT p=0.009, RT/ELS p=0.01) (Table 3).

In the analysis of the survival outcomes according to the type of treatment in the advanced stage, no statistically significant differences were found between CRT and TL in terms of five-year OS and DSS rates (OS p=0.4, DSS 0.12). In the five-year DFS and LRFS rates, TL had a significant advantage over CRT (DFS p=0.003, LRFS p=0.002) (Table 3).

Recurrence was observed in 30.7% of the cases. Analysis of the factors affecting recurrence revealed that recurrence was observed in 39.1% of supraglottic tumors and 26.7% of glottic tumors at all stages (p=0.004). Recurrence was observed in 41.7% of advanced-stage tumors and 22.1% of early-stage tumors (p<0.001). Recurrence was observed in 53.8% of N+ cases and 26.3% of N0 cases (p<0.001). Further, sex, age, the amount of smoking, and AC involvement in all cases did not significantly appear to affect recurrence (gender p=0.52, age p=0.57, smoking p=0.17, AC p=0.34). When considering the type of treatment, the highest recurrence rates were seen in patients who received RT (36%) in early cases and CRT (45.8%) in advanced cases, respectively. The lowest recurrence rate was observed in ELS with 17.6% (Table 4), which was applied in early cases.

Discussion

A well-known etiological factor of LSCC is smoking. Smoking plus alcohol abuse may act synergistically in cancer development (6). In this study, 93.7% of the patients were cigarette addicts, but only 83 cases (14.5%) had both alcohol and smoking history.

Table 3. Univariate cox regression for survival groups

	Overall survival		Disease-specific survival		Disease-free survival		Locoregional-free survival	
Variable	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**
Age >65	**0.001**	1.79 (1.33–2.41)	0.13	1.36 (0.9–2.06)	0.96	1 (0.73–1.39)	0.61	0.9 (0.61–1.33)
Female gender	0.4	0.74 (0.36–1.5)	0.23	0.5 (0.16–1.6)	0.45	0.76 (0.37–1.55)	0.57	0.79 (0.34–1.8)
Smoking (>30 PY vs. <30 PY)	**0.002**	1.66 (1.2–2.29)	**0.039**	1.58(1.02–2.44)	**0.04**	1.39 (1.01–1.92)	0.56	1.11 (0.77–1.6)
Comorbid disease	**0.005**	1.51 (1.13–2.02)	**0.04**	1.49 (1–2.21)	0.31	1.16 (0.86–1.57)	**0.03**	1.45 (1.02–2.05)
Supraglottic localization	**0.001**	2 (1.48–2.69)	**0.001**	2.25 (1.5–3.36)	**0.001**	1.68 (1.24–2.29)	0.059	1.42 (0.98–2.06)
AC involvement	0.65	1.07 (0.79–1.43)	0.87	1.03 (0.69–1.53)	0.3	1.16 (0.86–1.57)	0.53	1.11 (0.78–1.57)
Advanced stage	**0.001**	3.69 (2.69–5.06)	**0.001**	7.4 (4.39–12.5)	**0.001**	2.47 (1.83–3.34)	**0.001**	2.18 (1.54–3.1)
Clinical N+ vs. N0	**0.001**	3.5 (2.55–4.83)	**0.001**	5.3 (3.56–7.97)	**0.001**	3.22 (2.31–4.49)	**0.001**	3.26 (2.21–4.8)
N2b and above vs. N1+N2a	0.23	1.37 (0.8–2.35)	0.34	1.34 (0.72–2.48)	0.82	1.06 (0.61–1.86)	0.62	1.17 (0.61–2.26)
Early stage glottic SCC AC involvement	0.27	1.38 (0.76–2.5)	**0.04**	2.97 (1.01–8.7)	**0.01**	1.82 (1.1–3)	**0.01**	1.93 (1.12–3.32)
Type of treatment (RT vs. ELS)	**0.008**	2.3 (1.24–4.3)	0.068	2.6 (0.92–7.74)	**0.024**	1.81 (1.08–3.03)	**0.01**	2.08 (1.18–3.65)
Type of treatment (OPS vs. RT)	0.4	0.77 (0.42–1.42)	0.39	0.61 (0.2–1.87)	0.066	0.56 (0.3–1.03)	**0.009**	0.36 (0.17–0.77)
Type of treatment (OPS vs. ELS)	0.079	1.79 (0.93–3.43)	0.41	1.64 (0.49–5.41)	0.95	1.01 (0.55–1.86)	0.47	0.75 (0.35–1.61)
Type of treatment (TL vs. CRT)	0.4	0.85 (0.57–1.24)	0.12	0.67 (0.41–1.11)	0.003	0.49 (0.31–0.79)	**0.002**	0.39 (0.21–0.7)

AC: Anterior commissure, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, PY: Package-year, RT: Radiotherapy, SCC: Squamous cell carcinoma, TL: Total laryngectomy, CI: Confidence interval, HR: Hazard ratio

The types of treatments for laryngeal cancers evolved in the last three decades and the rate of laryngeal preservation increased, however, the survival rates did not. Transoral laser and robotic surgeries have replaced most of the open partial surgeries with similar oncological but better functional results. Non-surgical treatments have also replaced most of the total laryngectomies with reasonable functional results. In this case series, the leading treatment type was laser surgery (31.8%) and chemoradiation (29%) followed by radiation (13.1%), OPS (12%), and the TL rate was noticeably low (14.1%). A survival analysis of all cases showed five-year DSS and DFS rates to be 79.9% and 67%, respectively. Survival results in our institution are compatible with the current literature along with significantly low rates of TL (14.1%).

Since most of the patients are in their 60s and have a smoking history, one or more comorbid diseases were present at the time of diagnosis in most patients. In their review of the publications, Alho et al. (9) found that the prognosis for laryngeal cancer was the worst in patients with larynx, pharynx, or tongue cancers with the same comorbidity score. These study results revealed that 40% of the cases (230 patients) had at least one of the accompanying diseases, namely, hypertension, diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease. The most common comorbidity was hypertension (n=141, 25%). It was determined that the rates of OS (69.6% vs. 58.8%), DSS (83.1% vs. 75.1%), and LRFS (79.1% vs. 68%) were statistically higher in patients without comorbid diseases. It was also noted that DSS, DFS, and LRFS rates were significantly higher in patients without hypertension than in those diagnosed with hypertension.

Regional lymph node metastases are one of the most important factors affecting the prognosis of laryngeal cancers. It is known that as the tumor stage (T) advances, the clinical and occult lymph node metastasis rate increases (10). Clinically, N+ lymph node reduces the overall survival of patients by 50% (11). Clinical lymph node positivity was found in 93 cases (16.2%) in our study, therefore the number of clinical N0 stages at presentation was predominantly higher than the N+ stages. We do not know the actual rate of occult metastasis as only those undergoing total or open partial laryngectomy had neck dissection. In another study conducted in our institution, patients undergoing total or partial laryngectomy plus elective neck dissection for N0 neck, the occult metastasis rate was found that 17.4% (12). Based on our clinical data, we believe that current high-

resolution imaging techniques reveal neck metastasis more accurately than in previous decades. In the present study, the five-year OS rates in clinical N0 and N+ cases were 70.3% and 38.4%, respectively. It was observed that the LRFS, DSS, and DFS rates in N+ patients decreased significantly. Knowing the fact that neck metastasis is an absolute dismal factor along with our low rates of both clinical (16.2%) and occult neck metastasis (17.4%), correct decisions for the neck treatment should be given in each case. In other words, only necks with clinically positive nodes or N0 necks with a high potential of occult metastasis should be treated. In another study on N+ patients with hypopharynx and larynx cancer, Ho et al. (13) determined that classical N staging had less prognostic value than the number of metastatic lymph nodes, and suggested the limitations of an N classification based only on laterality and lymph node size. In our study, clinical N+ patients were divided into two groups, N1+2a or N2b and above, and in all survival analyses, no significant difference was found between N1+2a or N2b patients, which is also consistent with the findings of Ho et al. (13).

Table 4. Recurrence characteristics and p-values in 176 LSCC patients

Characteristic		Recurrence+, n (%)	p-value
Gender	Male	168 (31.1)	
	Female	8 (24.2)	0.525
Age	<65	123 (31.5)	
	≥65	53 (29.1)	0.572
Smoking	≤30 PY	58 (26.6)	
	>30 PY	105 (33.2)	0.173
Localization	Supraglottic	66 (39.1)	
	Glottic	107 (26.7)	**0.004**
Stage	Early stage	71 (22.1)	
	Advanced stage	105 (41.7)	**<0.001**
Stage	Carcinoma *in situ*	11 (20.8)	
	Stage I	35 (21.1)	
	Stage II	25 (24.5)	
	Stage III	61 (40.4)	
	Stage IV	44 (43.6)	**<0.001**
Clinical T	T *in situ*	11(20.8)	
	T1	35 (21.1)	
	T2	34 (29.6)	
	T3	72 (41.4)	
	T4	24 (36.9)	**<0.001**
Clinical N	N0	126 (26.3)	
	N1+N2a	24 (56.1)	
	N2b and above	26 (51.9)	**<0.001**
N0/N+	N0	126 (26.3)	
	N+	50 (53.8)	**<0.001**
Histopathology	Carcinoma *in situ*	13 (24.5)	
	Well-differentiated	55 (24.7)	
	Moderately differentiated	75 (33.3)	
	Poorly differentiated	33 (45.2)	**<0.001**
Anterior commissure involvement	No	95 (29.1)	
	Yes	81 (32.8)	0.348
Type of treatment	ELS	32 (17.6)	
	OPS	17 (24.6)	
	RT	27 (36)	
	TL	24 (29.6)	
	CRT	76 (45.8)	**<0.001**

LSCC: Laryngeal squamous cell cancer, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, PY: Package-year, RT: Radiotherapy, TL: Total laryngectomy

The AC is a focal point of anatomical, diagnostic, and therapeutic controversies and challenges in laryngeal oncology. AJCC divided the glottis into three regions as AC, posterior commissure, and vocal cords, but AC involvement was not considered as a separate parameter in the current T staging system (14, 15). Reportedly, 20% of all glottic cancers have AC involvement (16). There are different opinions in the literature regarding the effect of AC involvement on prognosis in patients treated with ELS in early-stage glottic LSCC (17). Carta et al. (18) found that AC involvement shows worse survival outcomes. Hendriksma and Sjögren (19) presented a compilation of 58 publications that examined AC involvement in early-stage glottic SCC in the English literature between 1998 and 2018. The study found that only one of the 14 publications reported that AC involvement in T1b and T2 tumors significantly affected five-year OS, but no difference was observed in T1a. In the other 13 studies, no significant differences were found in Tis-T1-T2 tumors. In the same review, in four out of 13 publications, AC involvement was reported to decrease DSS significantly; and regarding local control rates, it was reported that AC involvement decreased local control rates significantly in about one-third of the studies (19). In our study, no statistically significant differences were observed in OS, DSS, LRFS, and DFS with AC involvement in all tumor stages. However, in early-stage glottic LSCC, though AC involvement did not show a significant difference in OS (p=0.27), it was seen that DSS (p=0.04), DFS (p=0.01) and LRFS (p=0.01) rates decreased significantly with the AC involvement.

Early-stage and locoregionally advanced-stage treatments differ from each other in laryngeal cancer. In the advanced stages, the standard treatment was TL and adjuvant RT until the early 90s, and 1991 VALCSG (8) and Forastiere et al.'s (20) studies pioneered the use of CRT regimens as a standard treatment option.

The advantages of partial surgery and RT over each other in the early stages are still controversial. Upon the review of the publications comparing ELS and RT, Mo et al. (21) in a meta-analysis of 11 studies involving T1 tumors stated that ELS increased OS significantly compared to RT, and no differences were found between local control rates. In the meta-analysis of T1a glottic patients, Abdurehim et al. (22) found no statistically significant differences between the two treatment groups in terms of OS and DSS rates. In the meta-analysis comparing RT and ELS in early-stage glottic tumors (Tis-T1-T2), Higgins et al. (23) found no differences between the two treatment arms in local control and laryngectomy-free survival, whereas OS rates were significantly higher in ELS. In our study, when we compared ELS with RT in early-stage laryngeal cancers (Tis-T1-T2), the five-year OS rate was found significantly lower in RT compared to ELS (71.5% vs. 85%); but in DSS, there were no significant differences between RT and ELS (87.3% vs. 94.4%). Further, the five-year LRFS rate was significantly higher in ELS than in RT (82.5% vs. 70.8%). In summary, when RT and ELS were compared in our study, OS, DFS, and LRFS rates showed a significant difference in favor of ELS, while no significant difference was found between the two groups in terms of DSS. When OPS and RT were compared, no statistically significant differences were found between these two treatment arms regarding OS and DSS. However, it was observed that OPS was statistically superior to RT in local control rates (p=0.009).

Treatment options are TL or CRT in locoregionally advanced LSCC. The social and psychological situation created by TL still prompts clinicians to investigate laryngeal preservation methods that would provide the same survival rates. In a meta-analysis comparing non-surgical organ preservation therapies with TL, Tang et al. (24) reported that there was no statistically significant difference in T3 tumors in OS, but OS was higher in T4 tumors in patients who underwent TL. In addition, this meta-analysis reported that the DSS and local control rates were statistically significantly higher in TL. However, no significant difference was found between the two treatment arms in terms of DFS. Rosenthal et al. (25) compared TL and CRT cases in T4 tumors. While no statistically significant differences were found between OS and DSS, a significant superiority of TL was observed in locoregional control rates. In a 10-year study in which 182 patients were evaluated, Timmermans et al. (26) applied CRT to T3 tumors and adjuvant RT after TL to T4 tumors. They did not detect any significant OS differences between T3 and T4 tumors, between stage 3 and stage 4 tumors, and between CRT and TL, and based on their findings they concluded that the optimal treatment for T3 tumors was CRT. Our current strategy is compatible with the aforementioned metanalysis as we perform CRT in T3 tumors and T1-2-3 tumors with N+ necks. We prefer TL and adjuvant treatments in T4 tumors regardless of neck status. In the present study, when all locally advanced-stage tumors were evaluated together, no statistically significant differences were found between the two treatment arms in OS and DSS, while the rates of DFS (p=0.003) and LRFS (p=0.002) were found to be significantly higher in TL compared to CRT. Getting similar results between TL and CRT and knowing that TL is applied in more advanced T4a tumors and CRT in T3 tumors, suggests that TL is a good option in the treatment of T4a laryngeal cancer. Therefore, our strategy is to give the larynx the chance of preservation and to protect the patients' quality of life. It is important to recommend CRT in the first place for T3 tumors along with close follow-up. The fact that there were no statistically significant differences between the two treatment arms in terms of OS and DSS in our study also supports that approach. In our study, overall TL was applied in 14% of all laryngeal cancer cases.

Recurrence rates vary according to the laryngeal sub-regions and stages, where the tumor originates, although recurrence is observed in 15% to 30% of patients (27, 28). Haapaniemi et al. (29) advocated that World Health Organization performance status, female sex, supraglottic localization, and primary non-surgical treatments were independent predictors of laryngeal cancer recurrence. Brandstorp-Boesen et al. (30) reported that the risk of recurrence was affected by age, location, T stage, and treatment type, and N+ status did not increase the risk of recurrence in supraglottic cancers; but increased in glottic cancer. In their article, salvage surgeries performed in 241 patients with recurrent laryngeal cancer, Mimica et al. (31) used TL in 74% of the patients, OPS in 16%, and transoral laser surgery in 10%, and reported the rate of DSS after salvage surgery to be 57%.

In our study, the recurrence rate was 30.7%. Similar rates have been reported in the literature (28, 29). The factors that affected recurrence were: N positivity, advanced-stage tumors, supraglottic localization, and AC involvement in early stage glottic tumors. Recurrence rates were also higher in non-surgical treatments than in surgical treatments. Salvage laryngectomy should be considered as the first option in case of recurrence.

The limitations include that our study is a retrospective one due to the nature of cancer studies that contain heterogeneous data and do not provide functional results. The high number of cases and the long follow-up period are the strengths of our study.

Conclusion

In patients diagnosed with LSCC, the most appropriate treatment plan can be determined with careful diagnosis and staging, and approximately two out of three patients can be safely cured. The presented study shows that ELS provides higher rates of OS, DFS, and LRFS compared to RT in the

treatment of early-stage LSCC. In early-stage glottic SCC, AC involvement decreases DFS and increases the local recurrence rate. Supraglottic tumors, advanced-stage tumors, and clinical N positivity significantly increase recurrence. In the treatment of advanced LSCC, the CRT option can be considered primarily in T3 tumors and TL should be reserved as salvage therapy.

Ethics Committee Approval: This retrospective study was conducted following the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 76/10, date: 25.11.2019).

Informed Consent: Informed consent was not obtained from the patients because of the anonymous and retrospective design of the study.

Authorship Contributions

Surgical and Medical Practices: Ö.B., E.Ç.T., G.S., M.H.K., Concept: A.C.S., Ö.B., Design: A.C.S., Ö.B., Data Collection and/or Processing: A.C.S., Ö.B., G.T., Ş.A., S.K., V.Y., Analysis and/or Interpretation: A.C.S., Ö.B., G.T., Ş.A., S.K., V.Y., Literature Search: A.C.S., Ö.B., V.Y., Writing: A.C.S., Ö.B.

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Main Points

- In early-stage glottic tumors, anterior commissure involvement decreases disease-free survival and increases local recurrence.
- Endolaryngeal laser surgery provides higher rates of survival compared to radiotherapy early-stage laryngeal cancer.
- For laryngeal cancer, only necks with clinically positive nodes or high potential of occult metastasis should be treated.
- Recommending chemoradiotherapy in the first place for T3 tumors along with close follow up is important.

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