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Treatment selection for T4 laryngeal cancer: is organ-preserving approach possible with chemoradiotherapy or is multimodality treatment more effective?

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ABSTRACT

Aims: Organ-preserving approach is recommended as an evidence-based treatment option for advanced laryngeal cancer (LC) with similar survival results. However, the organ-preserving approach in T4 disease is controversial, and surgical treatment is primarily preferred. Today, chemoradiotherapy (CRT) is applied to T4 LC patients who are inoperable for medical or surgical reasons and upon the request of the patient who refuses the recommended surgical treatment. The aim of this study was to evaluate the treatment outcomes in patients with T4 LC who underwent CRT for these conditions and received adjuvant radiotherapy (RT)/CRT as the standard treatment regimen after surgery.

Methods: A retrospective review of T4 LC patients treated with CRT (17 patients) and adjuvant RT/CRT (26 patients) between 2015 and 2021 was conducted. Overall survival (OS), local regional recurrence-free survival (LRRFS), and disease-free survival (DFS) were compared between the groups. The organ preservation rate was determined for the CRT group.

Results: The median follow-up time for the entire cohort was 41 months, the 5-y OS, LRRFS, and DFS were 55.9%, 51.4%, and 51.9%, respectively. Statistically significant difference was found between the treatment groups in terms of 5-y OS, LRRFS, and DFS rates, and survival was found to be decreased in the CRT group (35.3% vs. 70.2%, p=0.007; 22.1% vs. 75.1%, p= 0.001; 22.1% vs. 75.7%, p=0.001). With respect to other clinicopathological factors, age was the only significant factor in on OS in multivariate analysis, whereas tumor size, nodal stage, and ECE (in the postoperative RT group, except LRRFS) were linked with OS, LRRFS, and DFS rates. Among the patients who underwent CRT, OS was found to be better in the group applied due to the patient's request compared to the patients referred for RT due to medical or surgical inoperability, and in multivariate analysis, the indication for RT remained an independent predictor of OS. In addition, the 3-y organ preservation rate was 81.5% in the CRT group.

Conclusion: The surgical arm had statistically significantly superior results in terms of OS, LRRFS, DFS compared to the CRT group. However, it is also noteworthy that OS was better in cases where RT is applied at the patient's request without inoperable disease. In addition, laryngeal protection was observed to a large extent in the CRT arm.

Keywords: Laryngeal cancer, advanced stage, organ preservation, radiotherapy, laryngectomy, treatment outcome

INTRODUCTION

Among head and neck squamous cell carcinomas, laryngeal malignancies are the most prevalent.[1] Treatment modalities for early-stage laryngeal cancer (LC) are either primary radiotherapy (RT) or endoscopic resection, both of which aim to preserve laryngeal function and share similar survival and functional outcomes, but the optimal primary treatment modality for advanced LC is controversial.[2] In the Veterans Affairs larynx study in 1991, an organ-preserving approach, provided by RT after induction chemotherapy (CT), was proposed as a valid alternative to total laryngectomy (TL) for locally advanced LC.[3] Subsequently, the Radiation Therapy Oncology Group (RTOG) 91-11 study, the results of which were announced in 2003, examined the timing of RT and the use of concomitant CT. It was shown that concomitant chemoradiotherapy (CRT) provides higher laryngeal protection rates than either RT following induction CT or RT alone.[4] Following these landmark prospective randomized studies, organ-preserving approaches have been adopted in advanced LC, and CRT has become the treatment of choice.

Although oncological results are very successful in T2, T3, and node-positive disease, this situation is controversial in T4 disease. The majority of patients

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enrolled in the RTOG 91-11 study were at stages T2 and T3. T4 tumors comprised approximately 10%, but only low-volume T4 tumors were included. Moreover, the Veterans Affairs study also showed a higher rate of local recurrence in the non-surgical arm of T4 disease. The results obtained from these studies have led clinicians to interpret that surgical treatment should be preferred instead of an organ-preserving approach in T4 disease.

However, TL causes deterioration of swallowing and speech functions and also decreases the quality of life due to the psychosocial problems it will bring, so patients may refuse surgical treatment and desire for CRT.[6] CRT is also indicated in patients who are surgically inoperable, as is the case with disease extending beyond the larynx. Apart from this, CRT may be the only alternative for patients who are in the high-risk group in terms of operation due to comorbid diseases. In addition, an organ-preserving approach may be preferred according to the decision of the multidisciplinary committee, as in the RTOG 91-11 study, in low-volume T4 tumors.

The purpose of this study was to retrospectively screen the patients with a clinical diagnosis of T4 LC who underwent CRT for these conditions and patients with a pathological diagnosis of T4 LC who underwent postoperative RT/CRT (multimodality treatment), to compare survival rates between groups, and identify the variables that may have an impact on the oncological outcome.

METHODS

The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 12.04.2023, Decision No: 2023/7/17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[7]

Study Population

Between January 2015 and December 2021 in Samsun Training and Research Hospital, patients who were diagnosed with T4 LC clinically and treated with CRT with an organ-preserving strategy and patients with a pathological diagnosis of T4 LC who underwent postoperative RT/CRT were identified retrospectively. Patients who received palliative RT and had metastatic disease at the time of the initial diagnosis were not included in the study.

The patient's clinical data, including demographic information and treatment outcomes, was collected from the patient's medical records. The following data were recorded for each patient: age, gender, date of diagnosis, tumor location, tumor extent, tumor size, tumor volume, vocal cord fixation, thyroid-cricoid cartilage involvement, lymph node involvement, presence of surgery, lymphovascular invasion, perineural invasion, extracapsular extension (ECE), dose and fraction number of applied RT, concurrent CT information, total or partial laryngectomy, and type of lymph node dissection.

Treatment

A multidisciplinary head and neck tumor board decided whether to have surgery, taking into account the medical condition of each patient and the characteristics of the disease. In addition, the patient's request was also effective in the treatment decision. Most patients underwent surgical treatment consisting of TL with bilateral neck dissection, TL with bilateral neck dissection and hemithyroidectomy, or partial laryngectomy with bilateral neck dissection.

RT was delivered using with the intensity-modulated RT technique. Dose fractionation schedules for RT were implemented as follows: In definitive RT, a total of 70 Gy was given to the primary tumor and involved node(s), 60 Gy to the larynx and the high-risk lymph node groups, and 50-54 Gy to the low-risk lymph node groups with a daily fraction of 2 Gy. In some patients, the simultaneous integrated boost technique was used with a total dose of 69.96 Gy, 59.4 Gy, and 54.12 Gy in 33 fractions. In postoperative RT, a total of 60 Gy was delivered to the tumor bed and the high-risk lymph node groups, and 50-54 Gy to the low-risk lymph node groups with a daily fraction of 2 Gy. Patients with positive surgical margins or lymph nodes with ECE were given 66 Gy.

Concurrent CT was applied to patients who underwent definitive RT. In the presence of risk factors, CT was administered concurrently with adjuvant RT. Low-dose cisplatin (35-40 mg/m^2 weekly during RT) or high-dose cisplatin (75-100 mg/m^2 days 1, 22, and 43) were preferred regimens. Carboplatin or cetuximab are alternative concomitant systemic agents for patients deemed medically unfit to tolerate cisplatin.

Follow-up

The first clinical examination was performed 1 month after the completion of RT, and the response assessment was performed at 2 months. Further follow-up examinations were performed every 3 months for the first 2 years, every 6 months for the next 3 years, and once a year thereafter. Laryngoscopic and physical examinations were used to monitor patients. Head and neck MRI or CT scans and PET/CT were performed 2-3 months after the end of RT to assess response to

treatment and then when clinically necessary. Tumor re-development in the primary region was defined as local recurrence, and the detection of lymph nodes was defined as regional recurrence. Any metastasis found in solid organs was considered a distant metastasis. Salvage surgery was performed in patients with local regional recurrence and in the presence of residual disease after CRT. In the presence of distant metastases, CT and/or RT were applied.

Endpoints

The primary endpoints analyzed were overall survival (OS), local regional recurrence free survival (LRRFS), and disease-free survival (DFS). OS was defined as the period of time from the time the patients were diagnosed with LC until the last follow-up or death. LRRFS was defined as the period of time from the time the patients were diagnosed with LC until the locoregional recurrence or death, whichever occurred earlier. DFS was defined as the period of time from the time the patients were diagnosed with LC until the locoregional recurrence, distant recurrence, or death, whichever occurred earlier. The secondary endpoint analyzed was the organ preservation rate. Organ preservation rate was defined as the the period of time between the date of diagnosis and the date of salvage surgery. The last follow-up date and survival status were updated in May 2023.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software (version V25.0; IBM Corporation, Armonk, NY, USA). Continuous variables are presented as medians after examining with normality tests, and categorical variables are presented as the frequency and proportion (%). Chi-square test or Fisher exact test were used to compare variables between the groups. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression was used to determine hazard ratios (HR). A p-value less than 0.05 was considered statistically significant.

RESULTS

Patients, tumor, and treatment characteristics were summarized in Table 1. A total of 43 eligible patients were identified, including 17 treated with definitive CRT and 26 receiving RT/CRT following surgery. There was no statistically significant difference between the treatment groups in terms of patient and tumor characteristics (Table 2). CRT was preferred in 8 of 17 patients due to the patient's request, and in 9 of them because they were surgically inoperable or in the high-risk group due to comorbid diseases.

Table 1. Baseline clinicopathological characteristics of the patients with laryngeal carcinoma

Variable	Patients (43) n (%)
Age (median)	59 (49-81)
Gender	
Female	2 (4.7)
Male	41 (95.3)
Smoking	
Yes	28 (65.1)
No	2 (4.6)
Not reported	13 (30.3)
Localization	
Glottic/Transglottic	21 (48.8)
Supraglottic	22 (51.2)
Comorbidity	
Diabetes	4 (9.3)
Hypertension	17 (39.6)
Heart disease	13 (30.3)
Lung disease	11 (25.6)
No	15 (34.9)
Anterior commissura invasion	
Yes	26 (60.5)
No	17 (39.5)
Subglottic extension	
Yes	25 (58.1)
No	18 (41.9)
Cartilage involvement	
Yes	40 (93)
No	3 (7)
T stage	
T4a	28 (65.1)
T4b	15 (34.9)
N stage	
N0-1	31 (72.1)
N2-3	12 (27.9)
Surgery	
Yes	26 (60.5)
No	17 (39.5)
Surgery Type	
TL	25 (96.2)
PL	1 (3.8)
Dissection	
BBD	13 (50)
BBD+HT	13 (50)
Lymphovascular invasion	
Yes	13 (50)
No	13 (50)
Perineural invasion	
Yes	7 (26.9)
No	19 (73.1)
Extracapsular extension	
Yes	2 (7.7)
No	24 (92.3)
Surgical margin	
Yes	1 (3.8)
No	16 (61.6)
Close	9 (34.6)
Treatment	
Definitive CRT	17 (39.5)
Adjuvant RT	4 (9.3)
Adjuvant CRT	22 (51.2)
RT Schedule/Dose	
Definitive	8 (50)
70 Gy, conventional	8 (50)
69.96 Gy, SIB	5 (19.1)
Adjuvant, conventional	2 (7.7)
66 Gy	19 (73.2)
64 Gy	
60 Gy	
Chemotherapy schema	
Once a week (35-40 mg/m²)	33 (87.2)
Once every 21 days (75-100 mg/m²)	5 (12.8)

BBD: Bilateral Neck Dissection; CRT: Chemoradiotherapy; HT: Hemithyroidectomy; PL: Partial Laryngectomy; RT: Radiotherapy; SIB: Simultaneous Integrated Boost; TL: Total Laryngectomy

Table 2. Baseline clinicopathological characteristics of the patients with definitve CRT and adjuvant RT/CRT

Variable	Adjuvant RT/CRT Patients, 26 (n,%)	Definitive CRT Patients, 17 (n,%)	p
Age			
<60	19 (67.9)	9 (32.1)	0.176
≥60	7 (46.7)	8 (53.3)	
Performance status			
ECOG 0-1	21 (67.7)	10 (32.3)	0.097
ECOG 2	5 (41.7)	7 (58.3)	
Gender			
Female	2 (100)	0 (0)	0.511
Male	24 (58.5)	17 (41.5)	
Anterior commissura invasion			
Yes	17 (65.4)	9 (34.6)	0.415
No	9 (52.9)	8 (47.1)	
Subglottic extension			
Yes	17 (68)	8 (32)	0.234
No	9 (50)	9 (50)	
Tumor size			
<3.5 cm	8 (50)	8 (50)	0.280
≥3.5 cm	18 (66.7)	9 (33.3)	
T stage			
T4a	17 (60.1)	14 (45.2)	0.964
T4b	9 (60)	3 (25)	
N stage			
N0-1	17 (54.8)	14 (45.2)	0.306
N2-3	9 (75)	3 (25)	
Cartilage involvement			
Yes	24 (60)	16 (40)	0.658
No	2 (66.7)	1 (33.3)	

CRT: Chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; RT: Radiotherapy

The median follow-up time for the entire cohort was 41 months, with a range from 7 months to 97 months. Seventeen died at the end of the follow-up period. For the entire cohort, the 5-y OS was 55.9%, and the mean OS was 64.87 (HR=6.04, 95% confidence interval (CI): 53.05-76.69 months, and the median OS was not reached. A statistically significant difference was found between the treatment groups in terms of 5-y OS rates, with 70.2% in the adjuvant RT/CRT arm and 35.3% in the CRT arm (**Figure 1a**, p=0.007). With respect to other clinicopathological factors, patients <60 years old (p=0.037), tumor size <3.5 cm (p=0.035), tumor volume <20 cc (p=0.028), nodal stage 0-1 (p=0.013), and the absence of ECE (p=0.009) were associated with improved OS (**Table 3**). Among the patients who underwent definitive RT, OS was found to be better in the group applied due to patient demand compared to the patients referred for RT due to medical or surgical inoperability (**Figure 2a**, p=0.012). Primary treatment modality, age, tumor size, nodal stage, the indication of RT, and ECE (in the postoperative RT group) were independent predictors of OS on multivariable analysis (**Table 4**).

Table 3. Univariate analysis for factors influencing OS, LRRFS and DFS in patients with laryngeal cancer

Variable	OS			LRRFS			DFS		
	3-y	5-y	p	3-y	5-y	p	3-y	5-y	p
Age									
<60	73.3	66.7	0.037	66	58.7	0.107	67.2	59.8	0.139
≥60	53.3	38.1		40	0		40	40	
Localisation									
Supraglottic	56.5	33.5	0.124	47	47	0.498	47.7	47.7	0.302
Glottic/Transglottic	75.9	70.5		66	58.7		66.3	59	
Tumor Size (cm)									
<3.5	87.1	79.1	0.035	85.7	71.4	0.034	85.7	71.4	0.033
≥3.5	49.5	41.3		42.3	42.3		43	43	
Tumor Volume (cc)									
<20	71.6	62.5	0.028	63	56.7	0.076	63.4	57.1	0.119
≥20	17.9	0		19	0		19	0	
Cartilage involvement									
Yes	69.1	63	0.097	61	55.5	0.007	61.3	55.89	0.009
No	33.3	0		0	0		0	0	
T stage									
T4a	66.8	62	0.597	62.9	55.9	0.282	63.2	56.1	0.354
T4b	58.2	43.6		45	45		45.7	45.7	
N stage									
N0-1	76.6	68.8	0.013	66.6	59.2	0.018	66.4	59.4	0.013
N2-3	38.9	25.9		30	30		31.3	31.3	
Treatment									
Adjuvant RT/CRT	791	70.2	0.007	75.1	75.1	0.001	75.7	75.7	0.001
Definitive CRT	41.2	35.3		29.4	22.1		29.4	22.1	
RT indication									
Patient request	66.7	66.7	0.012	33.3	33.3	0.073	33.3	33.3	0.073
Inoperable	11.1	0		11.1	0		11.1	0	
Extracapsular extension									
Yes	0	0	0.009	0	0	0.039	0	0	0.014
No	86.7	77		82.5	82.5		82.6	82.6	

CRT: Chemoradiotherapy; DFS: Disease-Free Survival; LRRFS: Local Regional Recurrence Free Survival; OS: Overall Survival; RT: Radiotherapy

Table 4. Multivariate analysis for factors influencing OS, LRRFS and DFS in patients with laryngeal cancer

Variable	OS		LRRFS		DFS	
	HR	p	HR	p	HR	p
Age <60 vs ≥60	3.55(1.17-10.74)	0.029	-	-	-	-
Tumor Size (cm) <3.5 vs ≥3.5	3.78(1.14-12.50)	0.024	3.46(1.00-11.95)	0.049	3.49(1.01-12.04)	0.048
N stage N0-1 vs N2-3	10.43(2.80-38.76)	< 0.001	2.86(1.14-7.18)	0.025	2.99(1.19-7.49)	0.019
Treatment Adj RT/CRT vs Def CRT	7.69(2.07-23.67)	<0.001	9.35(2.28-27.63)	<0.003	8.53(2.12-24.98)	<0.002
RT indication Patient request vs Inoperable	0.16(0.03-0.81)	0.027	-	-	-	-
Extracapsular extension Yes vs No	0.07(0.009-0.67)	0.020	0.20(0.03-1.11)	0.066	0.15(0.02-0.85)	0.032
Cartilage involvement Yes vs No	-	-	4.85(1.35-17.45)	0.015	4.49(1.24-16.23)	0.022

CRT: Chemoradiotherapy; DFS: Disease-Free Survival; HR: Hazard Ratio; LRRFS: Local Regional Recurrence Free Survival; OS: Overall Survival; RT: Radiotherapy

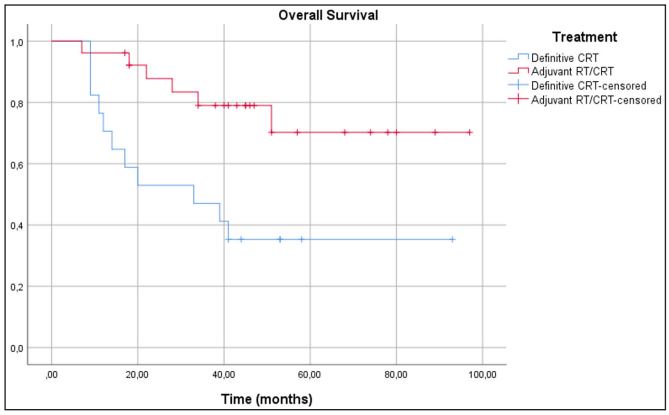

Figure 1a. Kaplan-Meier graph of OS comparing definitive CRT versus adjuvant RT/CRT.

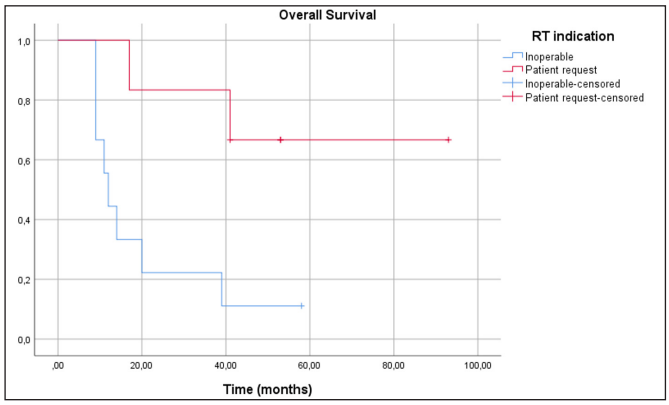

Figure 2a. Kaplan-Meier graph of OS evaluating definitive CRT according to RT indication.

At a median time of 13 months (range: 7-52) after RT, 9 individuals experienced recurrence. Most recurrences were in the definitive CRT group, with 7 patients, of whom 2 patients without distant metastases underwent salvage surgery. Lymph node excision was performed in one patient who developed regional recurrence in the adjuvant treatment group. Distant metastases were detected previously or simultaneously in four of the patients who relapsed, and CT was initiated in these patients. A recurrence in one patient was detected during the last follow-up, and a treatment plan has not been made yet. The best supportive care was applied to one patient because of poor performance.

For the entire cohort, the 5-y LRRFS was 51.4% and the mean LRRFS was 60.22 (HR=6.27, 95% CI: 47.92-75.51) months, and the median LRRFS was not reached. A statistically significant difference was found between the treatment groups in terms of 5-y LRRFS rates, with 75.1% in the adjuvant RT/CRT arm and 22.1% in the CRT arm (**Figure 1b**, p=0.001). There were significant correlations between improved LRRFS and tumor size <3.5 cm (p=0.034), the absence of cartilage involvement (p=0.007), the absence of ECE (p=0.039), and nodal stage 0-1 (p=0.018) (**Table 3**). There was no difference between the patients who underwent definitive RT in terms of RT indication (**Figure 2b**, p=0.073). Primary treatment modality, tumor size, nodal stage, and cartilage involvement were independent predictors of LRRFS on multivariable analysis (**Table 4**). The 3-y organ preservation rate was 81.5% in the CRT group.

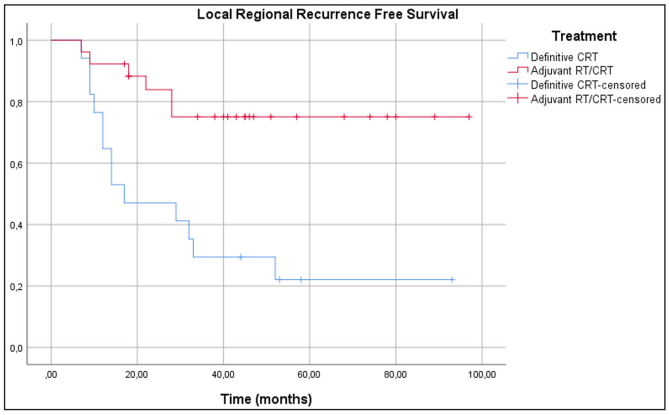

Figure 1b. Kaplan-Meier graph of LRRFS comparing definitive CRT versus adjuvant RT/CRT.

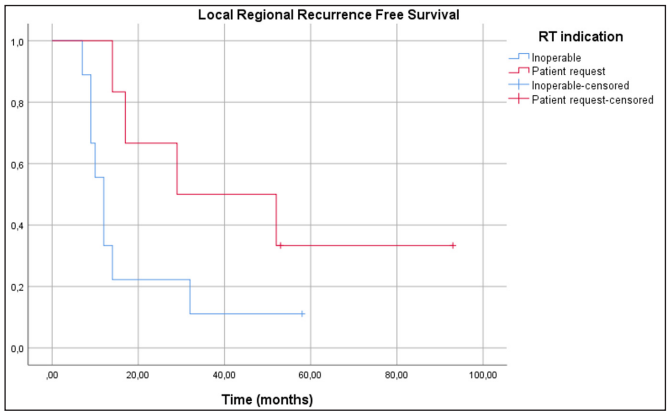

Figure 2b. Kaplan-Meier graph of LRRFS evaluating definitive CRT according to RT indication.

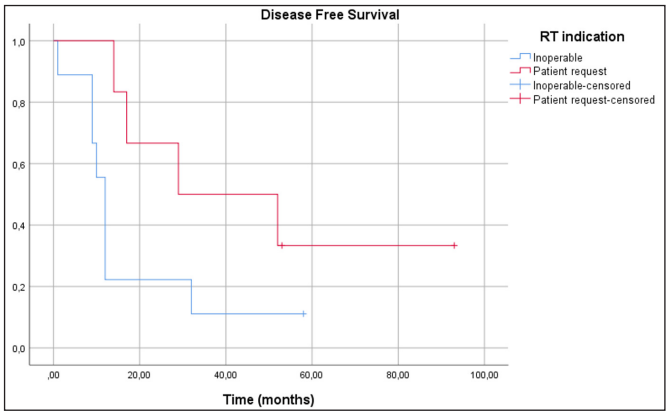

Figure 2c. Kaplan-Meier graph of DFS evaluating definitive CRT according to RT indication.

Distant metastases were seen in 8 individuals over a median 12.5-month period (range: 1-40) after RT. Distant metastases sites were lung (n=8, 100%), and liver (n=1, 12.5%). CT was applied to all patients after metastasis was detected. All patients who developed metastases died within a median of 13 (7-33) months. During the follow-up, lung cancer, a second malignancy, developed in 2 patients (4.34%). The primary malignancies of these patients were under control, and they were being treated for lung cancer.

For the entire cohort, the 5-y DFS was 51.9%, and the mean DFS was 59.43 (HR=6.42, 95% CI: 46.83-72.03) months. A statistically significant difference was found between the treatment groups in terms of 5-y DFS rates, with 75.7% in the adjuvant RT/CRT arm and 22.1% in the CRT arm (**Figure 1c**, p=0.001). There were significant correlations between improved DFS and the tumor size <3.5 cm (p=0.033), the absence of ECE (p=0.014), the absence of cartilage involvement (p=0.009), and nodal stage 0-1 (p=0.013) (**Table 3**). There was no difference between the patients who underwent definitive RT in terms of RT indication (**Figure 2c**, p=0.073). Primary treatment modality, tumor size, nodal stage, stage, cartilage involvement, and ECE (in the postoperative RT group) were independent predictors of LRRFS on multivariable analysis (**Table 4**).

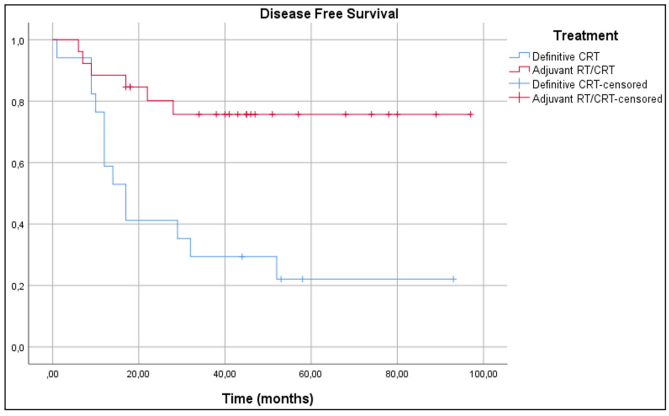

Figure 1c. Kaplan-Meier graph of DFS comparing definitive CRT versus adjuvant RT/CRT.

DISCUSSION

In this study, patients who applied to our clinic with the diagnosis of T4 LC and underwent primary CRT or postoperative RT/CRT were examined to determine survival rates and related factors. According to the analysis, the OS, LRRFS, and DFS rates in T4 patients were considerably lower in the primary CRT group than in the postoperative RT/CRT group. Among the patients who underwent CRT, OS was found to be better in the group applied due to the patient's request compared to the patients referred for RT due to medical or surgical inoperability, and in multivariate analysis, the indication for RT remained an independent predictor of OS. With respect to other clinicopathological factors, age was the only significant factor in OS in multivariate analysis, whereas tumor size, nodal stage, and ECE (in the postoperative RT group, except LRRFS) were linked with OS, LRRFS, and DFS rates.

The Veterans Affairs study, which was published in the early 1990s, was a turning point in the field of LC treatment that prioritized organ preservation.[3] In this trial, 332 patients were randomized to induction CT followed by definitive RT or laryngectomy and postoperative RT. Looking at the 2-y outcomes between the two groups, there was no difference in OS for both arms, with a rate of 68%. The larynx was preserved in 64% of patients who received induction CT followed by RT. Thus, there has been a fundamental change in the management of LC, and it has subsequently become conceivable to discuss laryngeal preservation with promising results in the treatment of patients requiring TL at an advanced stage. When the 2-y results were analyzed in our study, it was found that the survival of the operated patients was quite good compared to definitive CRT (83.4% vs. 47.1%), in contrast to the Veterans Affairs study. However, in the Veterans Affairs study, it was stated that there was no difference in OS between the two groups according to the stages, but

since the survival results for T4 tumors were not given separately, we could not compare them with the results of our study.

The Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) study, which had the same design as the Veterans Affair study, included only T3 tumors, independent of nodal stage, as a more homogeneous group.[6] About half of the 68 patients were in the induction CT arm, and a statistically significant worsening of OS was reported in the CT arm, with 2-y results of 69% vs. 84%. Comparing the results of this study with our own results would not be helpful as the study design did not include T4 disease, but it is worth noting that survival worsened with nonsurgical treatment across treatment arms.

A decade later, the landmark RTOG 91-11 study highlighted the role of definitive CRT in the management of LC.[4] There was no surgical arm in this study. 547 patients were randomized to induction CT followed by RT, CRT, or RT alone. While no difference was found between the groups in terms of OS, the addition of CT to RT reduced the frequency of distant metastases and contributed to DFS compared to the RT alone arm. The larynx preservation rate was found to be significantly higher in the CRT arm compared to the other two arms (88% vs. 75% vs. 70%). Locoregional control was achieved at the highest rate in the CRT arm (78% vs. 61% vs. 56%). The 5-y OS was 54% in the CRT arm, but it should be kept in mind that T4 tumor rate in this study comprised 9.3% of patients, and only low-volume T4 patients were included in the study. In our study, which included only T4 tumors without any discrimination in terms of tumor volume or spread, the 5-y OS rate in the CRT arm was found to be 35.6%. However, in the subgroup analysis performed according to RT indication, 5-y OS was found to be 66.7% in patients who applied for RT upon the request of the patient, not because of inoperability. According to the long-term results of the RTOG 91-11 study, no survival advantage was observed between the 3 arms, and larynx preservation rates were still found to be highest in the CRT arm.[8] However, it was emphasized that the incidence of deaths not related to cancer due to late side effects was higher in the CRT arm.

In a cohort study examining The National Cancer Data Base data, in the subgroup analysis according to T stages, OS was found to be decreased in those who underwent CRT in T4 disease.[9] The 5-y OS was 57.5% with the upfront TL and 37.8% in the CRT arm. This study showed that there was a difference in OS between the treatment arms for T4 tumors compared to other T stages. Similar to our study, lower OS rates were reported with CRT compared to the surgical arm.

While the efficacy of the organ-preserving approach has been demonstrated in randomized controlled trials, it is frequently reported that this efficacy is lower in the results of observational studies.[3,4,6,9,10] This may be due to the more systematic recruitment of randomized trials. In daily practice, surgical treatment is the preferred method in advanced stages. In particular, patients who cannot tolerate surgery or whose tumor spread is more common and whose operability is difficult are referred for CRT. Among the patient groups compared in observational studies, important factors affecting survival such as decreased performance status and comorbidity may be higher in the CRT group, and treatment responses may be relatively lower in this group. In our study, there was no statistically significant difference between the treatment groups in terms of patient and tumor characteristics; however, it is also noteworthy that OS is better in cases where RT is applied at the request of the patient without inoperable disease.

In the Veterans Affairs study, high local recurrence rates were observed in the induction CT arm, and the rate of salvage laryngectomy was found to be significantly higher for T4 stage compared to other stages (56% vs 29%).[3] In our study, local recurrence was observed in 7 patients in the CRT arm, but salvage surgery was performed in only 2 patients, the 3-y organ preservation rate was 81.5%. We think that the low need for salvage surgery may be due to the fact that 4 of these 7 patients already had distant metastases before and during the detection of local recurrence and that they were receiving CT for this purpose.

Apart from local recurrence, TL may be required in the follow-up period due to long-term side effects after CRT such as laryngeal and/or swallowing dysfunction, long-term tracheotomy, and/or gastrostomy tube dependency resulting from functional failure of the larynx. It has also been reported in important randomized studies that patients who died due to this long-term toxicity were not associated with cancer.[3,4,8] Therefore, some clinicians are concerned about the choice of CRT in advanced stages. In our study, salvage surgery was not required due to the loss of laryngeal function.

Regarding the analyzed variables, age is also known to be a predictor of OS, patients aged <60 years were better OS rates in our results.[11] It is known that there is an important link between nodal stage and survival, and this relationship was also found in our study.[12-14] Tumor size is another important parameter, especially in terms of local control.[15] Increased tumor volume was associated more frequently with local failure. In our study, it was observed that the treatment outcomes were worse for those who were over 3.5 cm. The presence of ECE is clearly known to be associated with a poor prognosis,

requiring an increased radiation dose in areas where it is present and adding CT to RT.[16] Our results were consistent with the literature, and it was determined that the presence of ECE changed the treatment outcomes in operated patients.

The strengths of this study are as follows: Since only T4 tumors were taken in our study, the distribution of patients is more homogeneous. Both groups do not differ in terms of patient characteristics. Thus, more reliable results can be given when making comparisons. However, there are limitations to this study, some inherent to a retrospective study design with inherent confounding factors. In addition, despite the 7-y time period being screened, the number of patients included in the study is relatively low.

CONCLUSION

In T4 disease, the surgical (multimodality treatment) arm had statistically significantly superior results in terms of OS, LRRFS, and DFS compared to the organ-preserving approach with the CRT group. However, it is also noteworthy that OS is better in cases where RT is applied at the request of the patient without inoperable disease. In addition, laryngeal protection was observed to a large extent in the CRT arm.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 12.04.2023, Decision No: 2023/7/17).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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