

## Survival Rate of Patients with Squamous Cell Carcinoma of Larynx Undergoing Nonsurgical Treatments and Radiotherapy, From 2003 to 2015

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### Abstract

**Background:** The incidence rate of head and neck cancer in the world is about 560,000 new cases a year. Larynx cancer is the most common malignancy in head and neck in Iran. The most common head and neck carcinoma is the malignancy of squamous epithelial cells. This study was conducted to determine the survival rate of patients undergoing nonsurgical treatment methods for laryngeal squamous cell carcinoma in Kerman, Iran.

**Methods:** This retrospective study was conducted on patients with squamous cell carcinoma of larynx following nonsurgical treatment, who were referred to a radiation therapy center in Kerman, Iran, from 2003 to 2015. The likelihood of survival of patients based on the age, sex, stage of disease, non-surgical treatment, laryngeal preservation, as well as survival without progression and recurrence of the disease was determined.

**Results:** Mean age of the studied patients was 56.56 years. The patients had a mean survival rate of 52.92 months, mean disease free survival rate of 47.60 months and mean progression free survival rate of 11.29 months. The survival rate was higher in patients undergoing RT, followed by those undergoing CCRT and CT-RT ( $P < 0.001$ ). The patients had a one-year disease free survival rate of 69%, a three-year disease-free survival rate of 57% and a five-year disease-free survival rate of 44% and had a one-year progression free survival rate of 13% as well as a three- and a five-year progression free survival rate of 18%.

**Conclusion:** Overall survival rate was significantly different based on the type of non-surgical treatment, gender and the stage of cancer.

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### Introduction

The incidence of head and neck cancer in the world is about 560,000 new cases a year resulting in 300,000 deaths. Men are significantly more likely to be affected than women with a ratio of 2/1 to 4/1 (1). In the United States, head and neck cancer accounts for 3% of all cancers, with 52,000 cases per year

leading to 11,500 deaths (2). In the UK, there are 7,500 new cases of head and neck cancer annually (3). In total, oropharynx cancer is ranked the sixth in the world, while it is the seventh in the UK (4). Oral and nasopharyngeal cancer have the highest prevalence in India and Hong Kong, respectively (2). Larynx cancer is the most common malignancy in the head and neck in

Iran (5). The most common head and neck carcinoma is the malignancy of squamous epithelial cells. The most commonly occurring age is usually between 60 and 70 years. Further, 80% of cases of tumors are squamous cell carcinoma (SCC) and 20% occur in salivary gland and thyroid sites and are rare sarcomas tumors (6). The main methods of cancer treatment include surgery, radiotherapy and chemotherapy; other methods, including gene therapy, antiangiogenic, and hyperthermia, are also used to treat cancer (7–10).

Chemotherapy can be used in three different therapeutic phases: induction chemotherapy or neoadjuvant, concurrent chemoradiotherapy and sequential treatment. Induction chemotherapy is used to maintain organs and increase the survival rate. In spite of the positive results obtained from induction chemotherapy for organ conservation, the need to find a better treatment method to improve regional tumor control and obtain better results has yet remained (11). The risk of local tumor recurrence is high in operable patients undergoing induction chemotherapy. Therefore, the next generation of studies uses simultaneous chemoradiotherapy and sequential treatment. Sequential treatment involves induction chemotherapy and then concurrent chemoradiotherapy, which may sometimes require surgery to complete the treatment. Theoretically, this method has the benefits of both previous methods. Induction chemotherapy enhances response to local therapy or organ preservation, reduces metastasis and helps a therapist to check the response to the treatment. Simultaneous chemoradiotherapy improves regional control and survival rates. Induction chemotherapy can ultimately maintain the organ and quality of life. However, due to the ineffectiveness of induction chemotherapy to induce a profound effect on survival rate, a second generation of studies

has been undertaken, including simultaneous treatment with increased sensitivity to radiotherapy to improve local control of the tumor. Recent trials and meta-analyses have also shown that concurrent chemoradiotherapy is more effective in improving survival rate and local control than induction chemotherapy. The third generation of studies including Taxol (paclitaxel)-based regimens has been developed to improve the effect of induction chemotherapy. The results of these studies have shown that adding Taxol to the cisplatin and 5FU regimen results in improved outcomes. However, the question of where the three-drug regimen, as induction chemotherapy, can be equal to chemoradiotherapy is still unanswered. Therefore, to obtain the results of phase three trials in order to compare successive therapy with concurrent chemoradiotherapy, sequential treatment based on TPF (Taxol, Cisplatin, Flouropyrimidine) can be an acceptable alternative to concurrent chemoradiotherapy in advanced head and neck cancer (12).

About 60% of patients are diagnosed in stages III and IV and their prognosis is extremely poor at the beginning of treatment, especially with new therapies.

Since head and neck contain many organs for vital activities such as eating, breathing, talking, etc., surgical resection may destroy or damage these vital activities. Thus, nonsurgical treatments for these tumors have become more and more important and have been further developed (13).

Studies on the survival of such patients and their follow-up can show the effect of these methods.

Through determining the survival rate in nonsurgical treatment methods for laryngeal tumors and comparing them with other studies, the efficacy of these methods can be investigated. If appropriate effects and survival rate are

sustained, the methods continue; otherwise, other methods will be used.

## Materials and Methods

This retrospective study was conducted on patients with SCC of larynx following nonsurgical treatment, who were referred to a radiation therapy center in Kerman, Iran, from 2003 to 2015. Factors retrieved from the computer database included age, gender, type of nonsurgical treatment, tumor stage and pathologic report of the biopsy specimen. The database also provided us with information on overall survival, survival without disease progression, disease-free survival, and number of patients who managed to preserve complete larynx without surgery. In the case of a defect in the database, comprising information was received via phone call, and any unresponsive case was excluded from the study. Moreover, they were later surgically treated.

## Data evaluation

After collecting data, a survival curve was used to determine the overall survival response, survival without progression, and survival without the disease. Moreover, log-rank test was used to determine the survival rate difference in different groups, and if required, Kaplan-Meier and life-table tests were used.

## Results

In this retrospective study, the outcomes of 223 patients with SCC of larynx following nonsurgical treatment were analyzed in a 12-year follow-up, suggesting that the survival rate was significantly different according to the type of nonsurgical treatment, gender and cancer stage.

In this study, 223 patients were examined of whom, 202 were males (90.6%) and 21 were females (9.4%). Mean age of patients was 56.56 years (SD = 10.93), ranging from 35 to 87 years.

The frequency of patients based on the cancer stage has been shown in table 1.

**Table 1.** The frequency distribution of patients based on the cancer stage

Stage	TNM	Percent	Frequency number
Stage 1	T1	11.7	26
Stage 2	T2	29.1	65
Stage 3	T3, N1	39.5	88
Stage 4a	T4, N2	18.8	42
Stage 4b	N3	.9	2
<b>Total</b>		100.0	223

In terms of the location of tumor, in 154 patients (69.1%), tumor was in glottis, in 66 ones (29.6%), it was in supraglottis and in 3 patients (1.3%), tumor site was subglottic area.

Types of nonsurgical treatment used for the studied patients were: Definitive radiotherapy (RT) in 89 patients (39.9%),

CCRT in 55 patients (24.7%) and CT-RT in 79 patients (35.4%).

The voice of the patients was preserved in 180 ones, while 42 patients lost their voice (missed data in one patient).

During the follow-up period, 117 patients (52.5%) died.

The mortality rate was significantly different in the patients ( $P < 0.001$ ) according to the therapeutic methods used for them. On this basis, the lowest mortality rate was observed in patients treated with RT (16.9%), followed by those treated with CCRT (56.4%) and CT-RT (89.9%). Moreover, the therapeutic methods used for the patients led to significantly different voice statuses in them ( $P < 0.001$ ). Accordingly, the lowest rate of loss of voice was observed in patients treated with RT (2.2%), followed by those treated with CCRT (18.2%) and CT-RT (38.5%).

### Survival analysis

The patients had a mean survival rate of 52.92 months ( $SD = 35.80$ ), mean disease-free survival rate of 47.60 months ( $SD = 36.50$ ) and mean progression-free survival rate of 11.29 months ( $SD = 25.34$ ).

Moreover, the patients had a one-year survival rate of 75%, a three-year survival rate of 59%, and a five-year survival rate of 45%, which decreased over time (Fig. 1). The survival rate of patients was significantly different based on the gender (fewer survivors in female group). Accordingly, the estimated survival rate was 80.88 months ( $SEM = 5.13$ ) in males and 54.02 ( $SEM = 10.42$ ) in females ( $P = 0.040$ , fig 2).

### The survival rate based on the tumor stage

The survival rate of the patients was significantly higher in patients with lower tumor stages ( $P < 0.001$ ), as expected (Fig.3).

### The survival rate based on the type of nonsurgical treatment

As it is shown in figure 4, the survival rate was higher in patients undergoing RT, followed by those undergoing CCRT and CT-RT ( $P < 0.001$ ).

### The survival rate based on the voice preservation

The mean survival rate was 95.88 months ( $SEM 5.39$ ) in patients who preserved their voice whereas it was 50.67 months ( $SEM 8.70$ ) in patients who lost their voice, which was significantly different ( $P < 0.001$ , fig 5).

Organ preservation (voice preservation) in a locally advanced lesion (T3-4, N+) was better in concurrent chemoradiation (CTRT) than in CT-RT (81.8% vs. 61.5%).

### Disease free survival rate

The patients had a one-year disease free survival rate of 69%, a three-year disease-free survival rate of 57% and a five-year disease-free survival rate of 44% (fig 6).

### Progression free survival rate

The patients had a one-year progression-free survival rate of 13% and a three- and a five-year progression-free survival rate of 18% (fig 7).

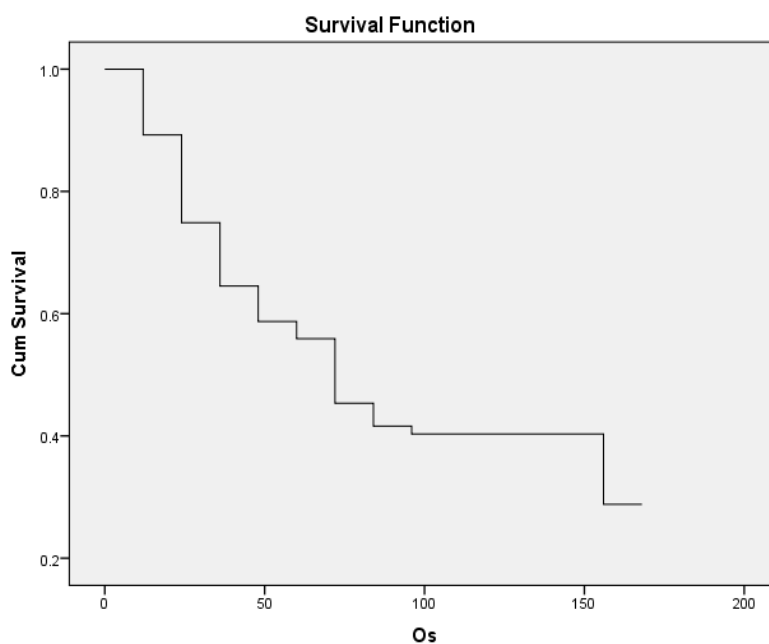


Figure 1. The overall survival rate of the studied patients with SCC of larynx following non-surgical treatments

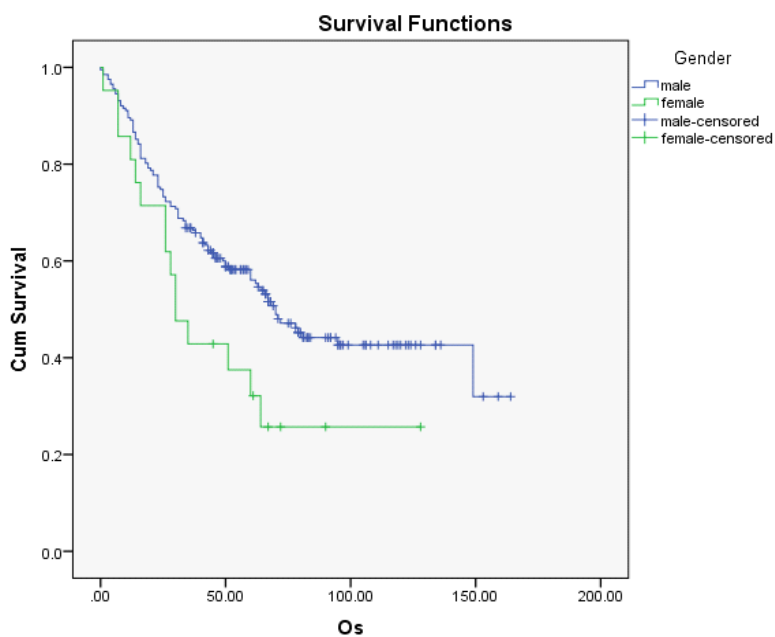


Figure 2. The survival rate based on the gender in patients with SCC of larynx following non-surgical treatments

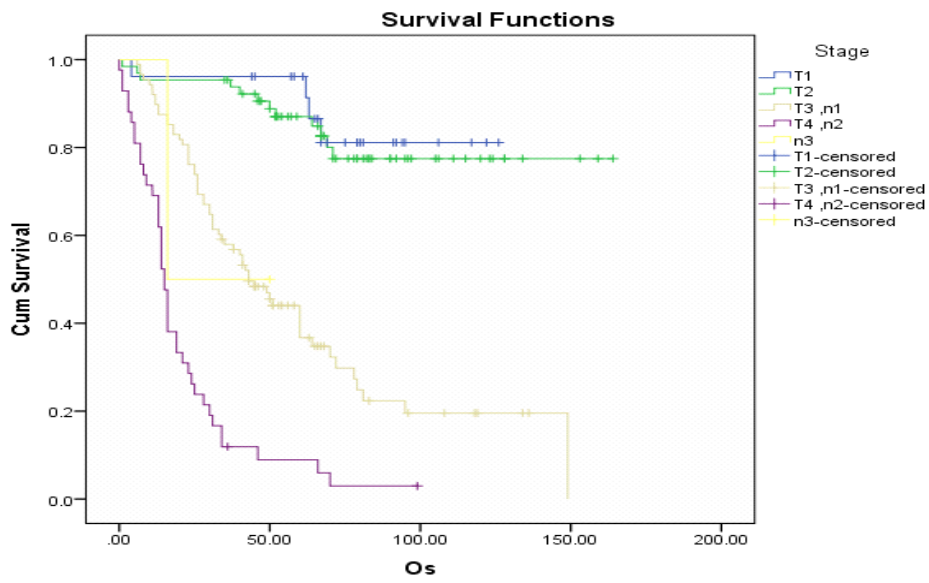


Figure 3. The survival rate based on the stage of disease in patients with SCC of larynx following non-surgical treatments

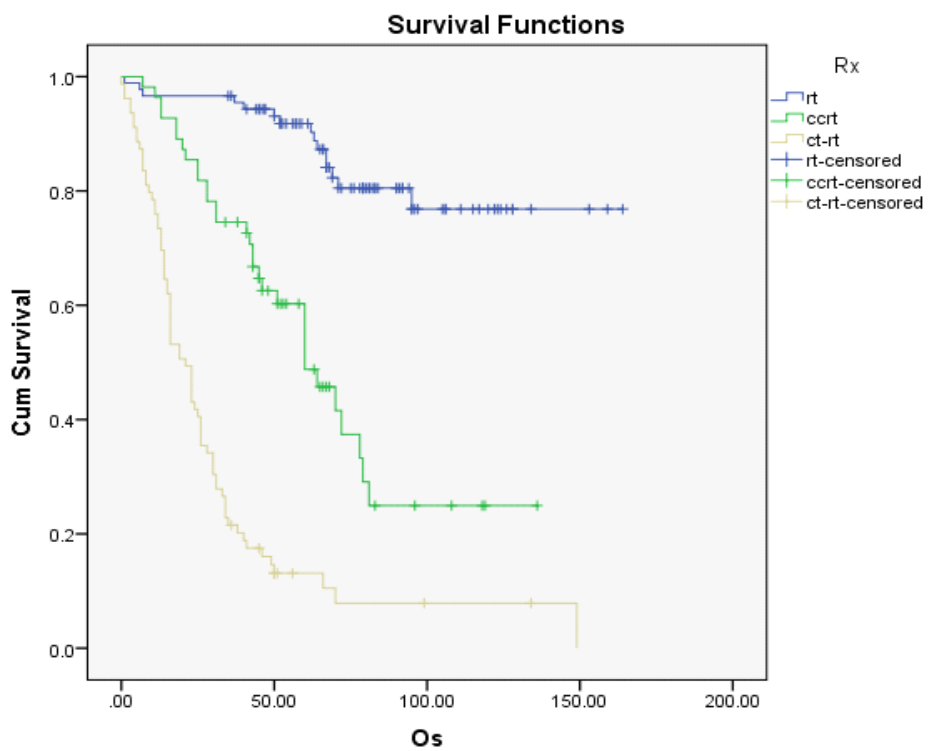


Figure 4. The survival rate based on the type of treatment in patients with SCC of larynx following non-surgical treatments

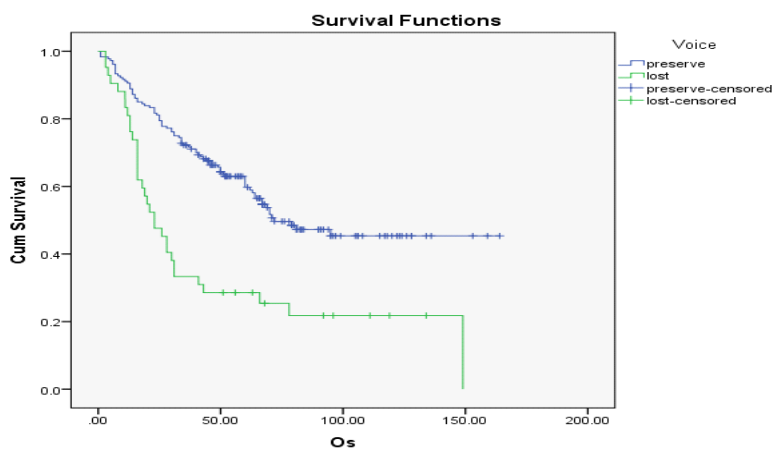


Figure 5. The survival rate based on the voice preservation in patients with SCC of larynx following non-surgical treatments

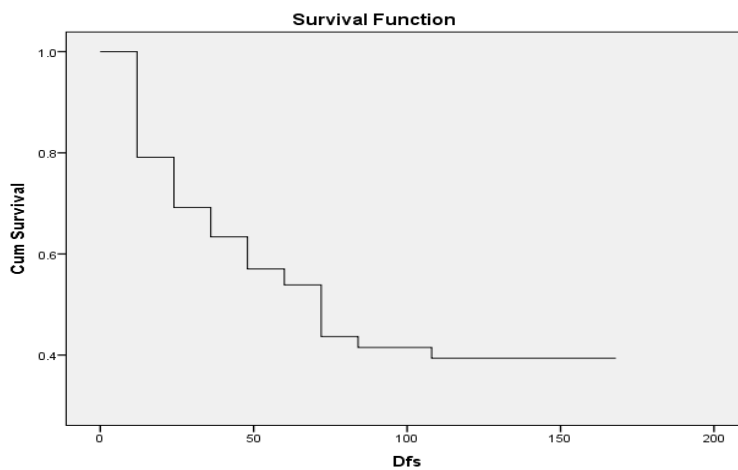


Figure 6. The one, three and five-year disease free survival

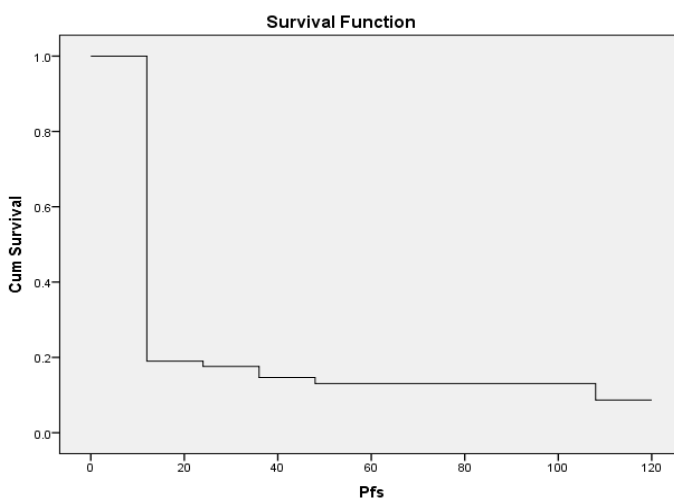


Figure 7. The one, three and five-year progression free survival

## Discussion

This study showed higher prevalence of laryngeal cancer in men. According to the results, 202 (90.6%) patients were males and 21 (9.4%) patients were females. Other Iranian researchers such as Jafari et al. (14) and Larizadeh et al. (15) similarly showed the overall male to female ratio of 2.74:1 in head and neck cancer. Moreover, as it was seen in the literature, larynx is the most commonly affected site in head and neck tumors (46.76%) and SCC is the most common diagnosis (77.5%) (15–17).

In head and neck cancer, the male to female ratio reported by large scale epidemiological studies and national cancer registries varies from 2:1 to 15:1, depending on the site of disease (18).

In this study, the mean age of the studied patients was 56.56 years, ranging from 35 to 87 years. However, the mean age of patients with SCC of larynx has been 60 years in a study by Jafari et al. (14) in Tehran, Iran, and 63 years in the study by Ramroth et al. (19).

In our study, the patients had a mean survival rate of 52.92 months, a one-year survival rate of 75%, a three-year survival rate of 59%, and a five-year survival rate of 45% in a 12-year follow-up. In the study of Jafari et al., patients with laryngeal cancer had a one-year survival rate of 90.5%, a three-year survival rate of 62.7% and a five-year survival rate of 57.7% (14). The five-year survival rate was reported to be 66% in another study (19).

In the study of Al-Gilani et al., the median OS for the entire cohort was 34 months and the 5-year OS for nonsurgical management, surgery alone, and surgery plus adjuvant treatment was 36%, 41% and 41%, respectively (20).

This study showed that the survival rate in the patients was significantly different based on the gender, with females having fewer survivors. Accordingly, the estimated survival rate was 80.88 months in males and 54.02 months in females. However, a matched-pair analysis by Roberts et al. showed no significant differences between women and men with head and neck cancer in terms of recurrence-free, disease-specific, or overall survival rate. Their analysis also showed no evidence of a disparity in the survival rate associated with gender even when the analysis was restricted to individual sites (21). Surely, this result is in line with our results due to the higher stage of laryngeal cancer in females in the study group.

By comparing the survival rates of the patients based on the disease stage in our study, as expected, the survival rate was significantly higher in lower stages. For example, 5-year survival was 81% in stage 1, 77% in stage 2, 31% in stage 3 and 3% in stage 4. In a study by Daneshi et al. (22), analyses indicated a significant relationship between patients' survival rate and the disease stage ( $P = 0.002$ ).

We found that the survival rate was higher in patients undergoing RT than those undergoing CCRT and CT-RT, respectively. In the study by Dziegielewski et al (23), the overall 2- and 5-year survival rates were respectively 89% and 70% in T3 cancer patients undergoing TL-R/CT (total laryngectomy with radiotherapy or chemoradiotherapy), 48% and 18% in patients undergoing RT, and 66% and 52% in patients undergoing CRT. Moreover, as reported in the mentioned study, the overall 2- and 5-year survival rates were respectively 60% and 49% in T4a cancer patients managed by TL-R/CT, 12% and 5% in patients undergoing RT, and 32% and 16% in patients treated by CRT. In the study by Forastiere et al., it was found that the proportion of patients who had an



intact larynx after radiotherapy with concurrent cisplatin (88%) differed significantly from that of patients given induction chemotherapy followed by radiotherapy (75%,  $P=0.005$ ) or radiotherapy alone (70%,  $P<0.001$ ). The rate of locoregional control was also significantly better with radiotherapy and concurrent cisplatin (78% vs. 61% with induction cisplatin plus fluorouracil followed by radiotherapy and 56% with radiotherapy alone). Both the chemotherapy-based regimens suppressed distant metastases and resulted in a better disease-free survival rate, as compared to radiotherapy alone. However, the overall survival rate was similar in all three groups (24). In Anschuetz et al. study (25), the crude rate of functional larynx preservation was 74.6%. Radiotherapy +/- chemotherapy was the dominant treatment modality ( $n=359$ , 75.3%), followed by primary surgery ( $n=118$ , 24.7%) and adjuvant treatment ( $n=69$ , 58.5%). Our study showed that the mean survival rate was 95.88 months in patients who preserved their voice (organ preservation) whereas it was 50.67 months in patients who lost their voice, which was significantly different ( $P < 0.001$ ). Moreover, the best group in organ preservation was CRT (81.8%), followed by CT-RT (61.5%) in locally advanced lesions. Treatment for laryngeal SCC has been predominantly surgical for decades. However, in the last 20 years, nonsurgical modalities (radiotherapy), with the aim of organ preservation, have also become predominant in advanced stages. Bussu et al., in their study explained that among irradiated patients, 2-year organ preservation was 86% for cT2, 43% for cT3, and 17% for cT4a ( $p=.037$ , Wilcoxon test). With respect to the survival, the only significant difference between surgery and radiotherapy was detected in cT4a SCCs ( $p=.03$ , Wilcoxon test), in favor of surgery (26). In another study, RT and conservation laryngeal surgery showed equivalent results in

early laryngeal cancer. CRT is the standard treatment in stage III and IV laryngeal cancer with intact cartilage and functional larynx. Patients with cartilage destruction or dysfunctional larynx are not candidates for organ preservation (27). In a meta-analysis by Fu X et al. who compared the efficacy between total laryngectomy and nonsurgical organ-preservation modalities in the treatment of advanced-stage laryngeal cancer, there were no significant differences between TL and NOP for 5-year local control and no significant difference in 2-year disease-specific survival rate was detected between the two groups but the advantage of TL was especially obvious in T4 subgroups, but not in T3 subgroups (28).

In this study, the mean disease-free survival rate was 47.60 months and the mean progression-free survival rate was 11.29 months. Moreover, the one-year disease free survival rate was 69%, the three-year disease-free survival rate was 57% and the five-year disease-free survival rate was 44%. Additionally, the one-year progression-free survival rate was 13% whereas the three- and five-year progression-free survival rate was 18%. In a study by Rosenthal et al. who examined long-term outcomes after surgical or nonsurgical initial therapy for patients with T4 SCC of larynx, the overall 5-year and 10-year survival rates were 52% and 29%, respectively, and the corresponding disease-free survival rates were 57% and 48%, respectively. Moreover, the overall 5-year and 10-year locoregional control rates were 78% and 67%, respectively (29). In the study of Chedid et al. on the assessment of the disease-free survival rate in patients with laryngeal SCC treated with radiotherapy with or without chemotherapy, it was shown that the disease-free survival rate of patients undergoing radiotherapy was 62.5% (30). Larizadeh and Damghani studied patients with T3, T4 and N+ laryngeal cancer who had refused a laryngectomy or had

the unresectable disease (medically or surgically) for sequential chemoradiotherapy and realized that the 2-year laryngeal preservation rate was 75%. They also observed actuarial progression-free survival rates of 71% and 67% at 2 and 3

years, respectively. Moreover, actuarial overall survival rates were observed to be 83% and 71% at 2 and 3 years, respectively (31).

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