

# Clinicopathological Characteristics and Survival Rate of Patients with Laryngeal Squamous Cell Carcinoma: A Retrospective Study during 2011–2017 in Yazd, Iran

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## ABSTRACT

**Background:** The aim of the current study is to determine the clinicopathological characteristics of patients with laryngeal squamous cell carcinoma and evaluation of the effect of prognostic factors on survival rate.

**Materials and methods:** The archives of all patients with laryngeal squamous cell carcinoma (2011–2017) were studied. Patients' data were extracted using a checklist that included age, gender, tumor stage, treatment methods used, and survival rate in months. All data were analyzed by the SPSS-17 software with the Chi-square test, the Kaplan–Meier test, and the log-rank test at a statistical significance level of  $p < 0.05$ .

**Results:** Out of 109 patients with laryngeal cancer, 99 were males and 10 were females. Patients in stages I and II and also in stage III had a longer overall survival compared to patients in stage IV. The mean survival rate was found to be significantly lower in patients in stage IV compared to those in the other stages of the disease. Patients in the age group of 35–59 years had a longer overall survival compared to the older age group (60–89 years). Patients at stage III of the disease who had not undergone chemotherapy had a greater longevity compared to the ones who had undergone the therapy. Patients at stage IV who had not undergone laryngectomy had a much lower survival rate compared to those who had used both surgery and radiotherapy or chemoradiation.

**Conclusion:** Surgery and radiotherapy can positively affect the mean survival rate in patients at stages I and II of laryngeal carcinoma. Together surgery and chemotherapy or chemoradiation have a positive effect on the survival of patients in advanced stages of the disease.

**Keywords:** Chemotherapy, Larynx, Radiotherapy, Squamous cell carcinoma.

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## INTRODUCTION

Speech and voice are humans' means of communication with the environment around them and with other humans.<sup>1,2</sup> Malignant laryngeal tumors can be life-threatening in addition to causing speech disorders and the loss of voice. Laryngeal cancer comprises about 2.2% of all the cases of cancer in males and about 0.4% of all the cases of cancer in females.<sup>3,4</sup> Squamous cell carcinoma is the most common type of laryngeal cancer. Approximately 3.2 new cases of laryngeal cancer are reported per 1,00,000 men and women, with an annual mortality rate of about 1.1 per 1,00,000 men and women.<sup>3–6</sup> Most patients are in their fifth or sixth decades of life at the time of diagnosis but this cancer has also been reported in younger age groups. Men make up about 96% of the cases of laryngeal cancer.<sup>5–7</sup> In Iran, about 90,000 people are affected by different types of cancer each year, and the 11 million cases of cancer reported in 2005 are anticipated to reach 18 million by 2020.<sup>8</sup> Nevertheless, according to the statistics provided by the Cancer Research Center of Iran, laryngeal cancer is not among the 10 most common types of cancer in the country.<sup>9,10</sup> Several risk factors have been reported for laryngeal cancer, including smoking cigarettes and the *hookah* and the excessive consumption of alcohol.<sup>10–12</sup> Several factors affect the prognosis of laryngeal cancer, including the stage; site; size; grade of the tumor; the patient's age, gender, and general health status.<sup>6–8</sup> Treatment may be based on the stage of the disease, the site affected by the tumor, the size of the tumor, the patient's attempt at preserving his speech, eating habits, recurrence of the tumor, and the state of breathing.<sup>10–12</sup> The type of treatment may vary based on the affected site and the tumor stage and may involve radiotherapy, surgery, and chemotherapy either alone or in combination.<sup>1–10</sup> The most popular method of treatment

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used for these patients includes partial or total laryngectomy. In the early stages of the disease (stages I and II), radiotherapy or local surgery is considered the first steps in treatment.<sup>5–10</sup> In the more advanced stages (stages III and IV), the treatment options considered include chemoradiation or total laryngectomy combined with radiation or chemotherapy.<sup>11,14,15</sup> Each of these treatment options has their own advantages and disadvantages (e.g., complications).<sup>14</sup> There are different reports on patients' survival rate based on their chosen method of treatment.<sup>5–18</sup> Given the lack of comprehensive studies conducted on this type of cancer in Iran, the present study aims to investigate cases of laryngeal cancer and the factors affecting the prognosis of this cancer over a 5-year period.

## MATERIALS AND METHODS

This descriptive analytical survival study was conducted on all registered patients with primary laryngeal squamous cell carcinoma in Shahid Sadoughi and Shahid Rahnemon educational General Hospitals (two referral centers for Shahid Sadoughi University of Medical Sciences and Health Services in Yazd, Iran) during 2011–2017. The study protocol was reviewed and approved by the medical ethics committee at Shahid Sadoughi University. The samples were selected through the census method. The inclusion criteria were positive laryngeal biopsy or laryngectomy specimens. Patients who had terminated their treatment (for whatever reason) or whose records were not available or whose malignancy involved cases other than squamous cell carcinoma were excluded from the study. All patients are asked to sign an informed consent form upon their freewill agreeing that their medical records be used for research purposes. Patients' demographic information such as age at diagnosis, gender, history of smoking or otherwise, type of lesion, month and year diagnosed with laryngeal cancer, type of cancer and tumor stage, treatment protocols, and telephone number were extracted from the available data. The researchers then visited oncologists and Shahid Ramezanzadeh Radiotherapy Center to identify the type of treatments used for the malignant cases, including surgery, radiotherapy, laryngectomy, and chemotherapy. The data collected were entered into a predesigned checklist. The tumors were divided into three groups based on the anatomical site they involved: group I (supraglottis), group II (glottis), and group III (subglottis). As for the staging of the disease, patients were divided into four stages according to the American Joint Committee on Cancer staging of laryngeal cancer (AJCC) and (TNM), so that stages I and II were considered the early stages and stages III and IV were considered the advanced stages. Tumors were eventually divided into three main groups, including group I (stages I and II), group II (stage III), and group III (stage IV). Following the pathological evaluation, patients were contacted via telephone to acquire information regarding their current status (free of tumor). In case of death, condolences were expressed to patients' family members. The follow-up time was as the interval between the diagnosis time and the time of death or last contact with the patient. Survival was defined as the patient being alive upon the telephone contact.

## STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS software version 17 for windows (IBM Inc., NY, US). Categorical variables are demonstrated as proportions and continuous variables as mean and standard deviation (SD). In all analyses, continuous variables with non-normal distribution are reported using the median (interquartile range). The Kaplan–Meier method was used to assess the impact of different categorical predictors on patients' survival. Differences in distribution of events between classes of categorical variables are evaluated using the log-rank test.

## RESULTS

Totally, 109 patients were included in the study, 99 (90.8%) males and 10 (9.2%) females (male/female ratio = 9.9).

Younger patients in the age group of 35–59 years had a longer overall survival (HR: 0.535, CI 95%, 0.293–0.977, PV = 0.02) compared to the older age group (60–89 years).

The mean duration of survival in each stage irrespective of the prognostic factors was  $64 \pm 5$  months in stages I and II,  $65 \pm 6$  months in stage III, and  $38 \pm 5$  months in stage IV, with significant

differences between the rates obtained for the different stages (log-rank test, PV = 0.007). Patients in stages I and II (HR: 0.343, CI 95%, 0.171–0.690, PV = 0.003) and also in stage III (HR: 0.324, CI 95%, 0.145–0.723, PV = 0.006) had a longer overall survival compared to patients in stage IV (Fig. 1A).

Survival of patients based on the location of the tumor showed that patients with subglottic tumors had the lowest survival rate; however, the difference was not statistically significant between groups (log-rank test,  $p = 0.25$ ) (Fig. 1B).

Survival of patients based on stage of tumor and age groups is given in Table 1. Patients in stages I and II had a significantly lower survival rate in the 60–89 age group compared to the 35–59 age group, comprising a statistically significant difference (log-rank test,  $p = 0.02$ ). In stage III, however, no significant differences were observed between the two age groups, and the mean survival rate was not affected by age in patients in this stage of the disease (log-rank test,  $p = 0.81$ ). In stage IV, no significant differences were observed between the two age groups in the mean survival rate (log-rank test,  $p = 0.51$ ) (Fig. 1C1 to 3).

No significant relationship was observed between the mean duration of survival and the stage of the disease or gender (Fig. 1D1 to 3).

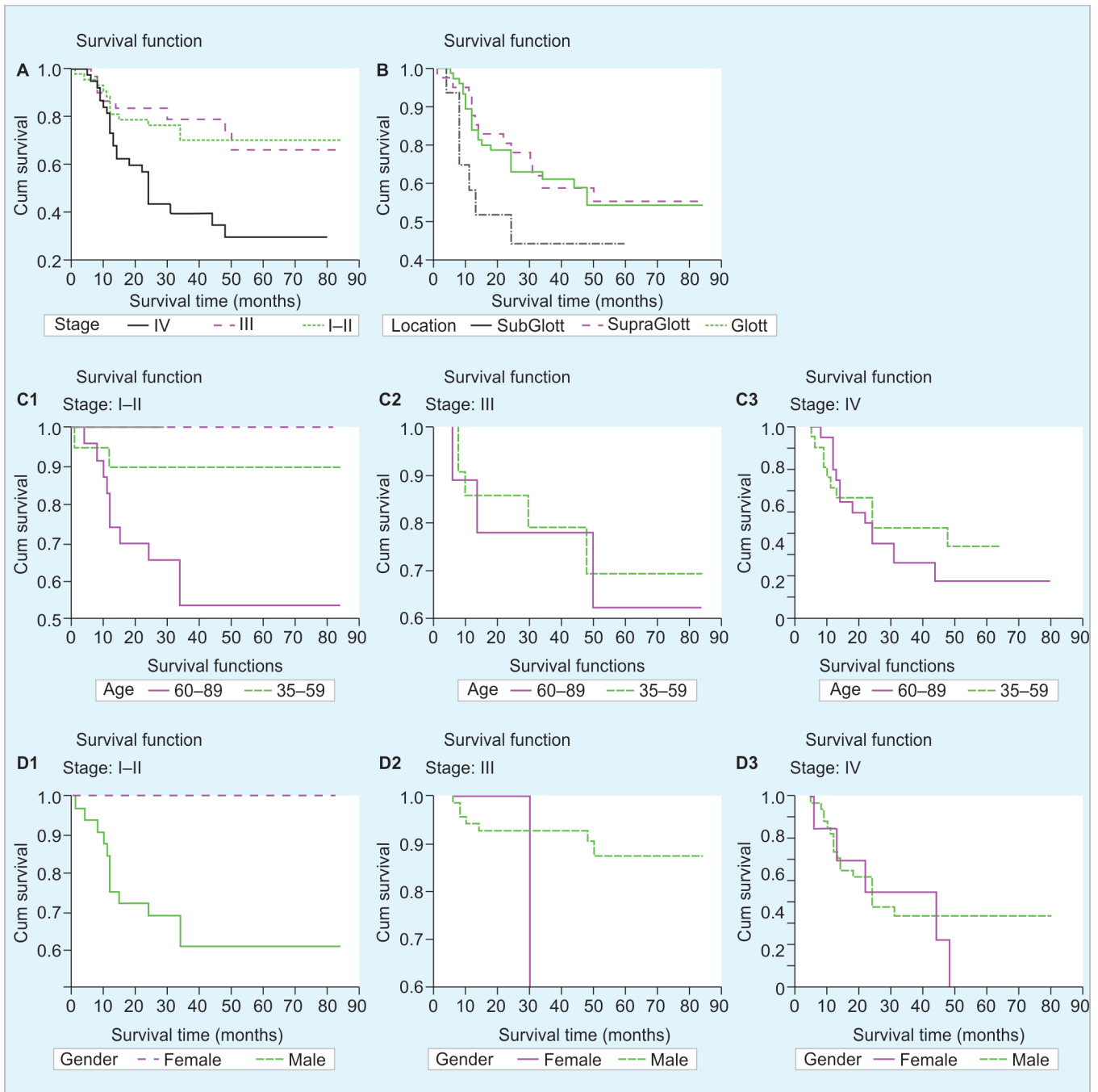
No significant differences were observed between the groups in their mean survival rate by the location of tumor and the stage of the disease in either of the stages, including stages I and II (log-rank test,  $p = 0.73$ ), stage III (log-rank test,  $p = 0.31$ ), and stage IV (log-rank test,  $p = 0.87$ ) (Fig. 2A1 to 3).

Survival rate based on the stage of tumor and chemotherapy/radiotherapy is given in Table 2.

Survival rate based on the stage of tumor and treatment type is given in Table 3. Moreover, no significant differences were observed in the mean survival rate between the patients who had undergone laryngectomy and those who had not undergone the procedure, regardless of whether their laryngectomy was partial or total, and in either of the stages I, II, III, or IV. In stages I and II (log-rank test,  $p = 0.18$ ) and III (log-rank test,  $p = 0.09$ ), no significant differences were observed between the groups in their mean survival rate by the type of therapy; however, the difference between the groups was statistically significant in stage IV, so that the mean survival rate was significantly lower in patients who had not undergone laryngectomy, but much higher in patients who had undergone a combination of laryngectomy, chemotherapy, and radiotherapy or a combination of laryngectomy and radiotherapy (log-rank test,  $p = 0.03$ ) (Fig. 2B1 to 3).

## DISCUSSION

Previous studies have shown a significantly higher frequency of laryngeal cancer in men than in women with an approximate ratio of 7:1,<sup>5–13</sup> while the present study found this ratio to be slightly higher at (9:1). Laryngeal cancer tends to mostly affect the age group over 50, and the present study also reported the mean age of the patients as 60, which was not inconsistent with the findings reported in various other countries.<sup>3–13</sup> Smoking cigarettes is considered the main etiologic factor in laryngeal cancer.<sup>1–3</sup> In the present study, 87.2% of the patients were smokers. In stages I and II, the patients' survival rate was higher in the younger age group compared with the older age group, which is almost consistent with the findings reported by the American Cancer Society, and this finding was also true in patients in stages III and IV of the disease; however, the difference was not statistically significant in the latter stages.<sup>6,7</sup>

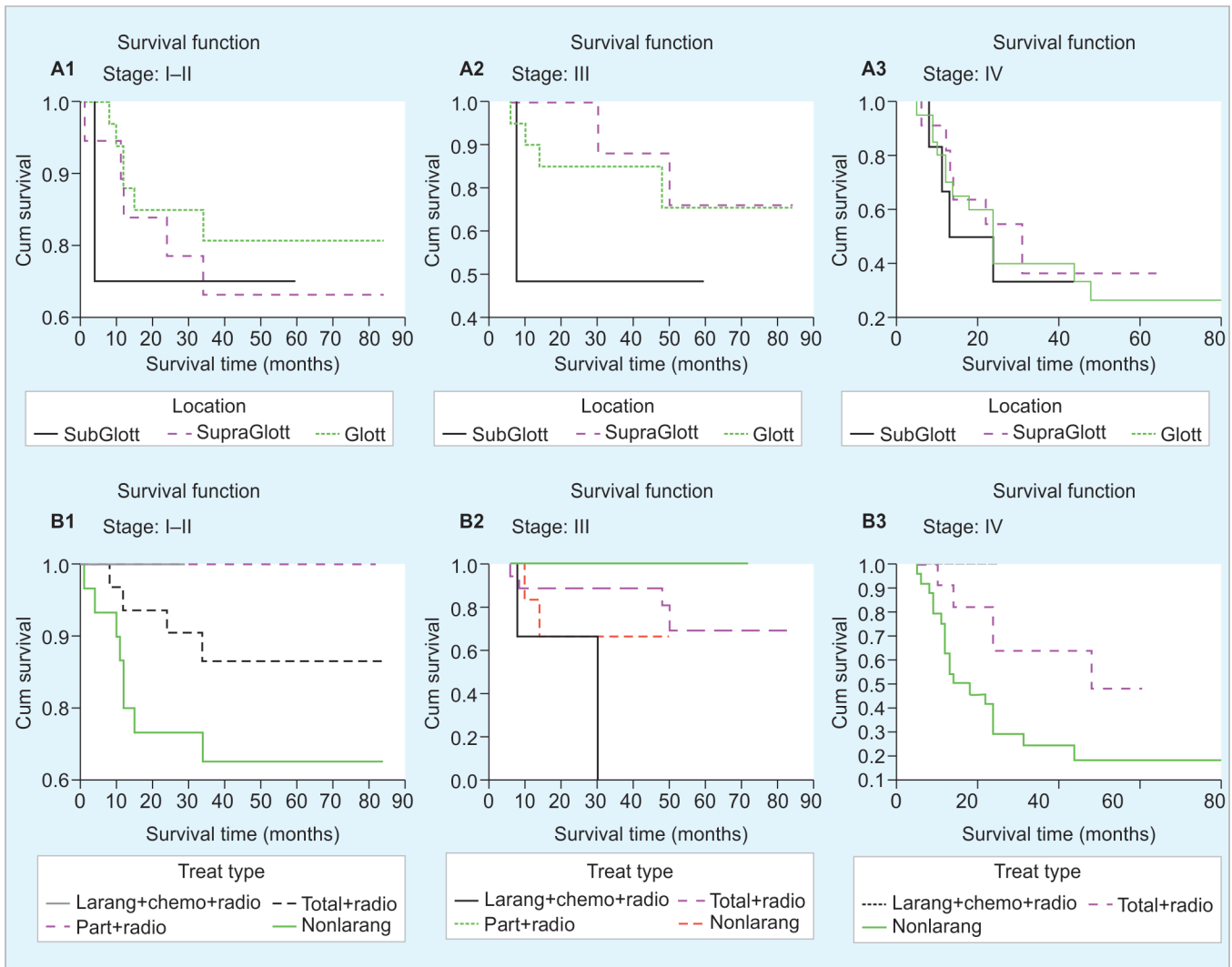


**Figs 1A to D:** (A) Kaplan–Meier survival estimates for laryngeal carcinoma in patients stratified by different stages (I–IV); (B) Kaplan–Meier survival estimates for laryngeal carcinoma in patients stratified by location of tumor; (C1 to 3) Kaplan–Meier survival estimates for laryngeal carcinoma in patients stratified by different stages (I–IV) and patients’ age; (D1 to 3) Kaplan–Meier survival estimates for laryngeal carcinoma in patients stratified by different stages (I–IV) and patients’ gender

**Table 1:** Survival of patients based on stage of tumor and age groups

Stage	Age group	Mean + SE*	CI 95%	Death (N)	Censored (%)	p value
I-II	35-59	76 + 5	65-87	2	89.47	0.0235
	60-89	53 + 7	39-67	10	56.52	
III	35-59	66 + 7	53-80	5	76.19	0.819
	60-89	62 + 10	42-83	3	66.67	
IV	35-59	36 + 6	25-47	11	42.11	0.511
	60-89	32 + 7	20-45	13	27.78	

\*SE is the standard error



**Figs 2A and B:** (A1 to 3) Kaplan–Meier overall survival and survival estimates for laryngeal carcinoma in patients stratified by different stages (I–IV) and tumor location; (B1 to 3) Kaplan–Meier survival estimates for laryngeal carcinoma in patients stratified by different stages (I–IV) and treatment types

**Table 2:** Survival rate based on stage of tumor and chemotherapy/radiotherapy

Stage	Chemotherapy	Mean + SE (month)	CI 95%	Death (N)	Censored (%)	p value
I–II	No	68 + 5	58–79	7	78.13	0.076
	Yes	46 + 11	24–68	5	50	
III	No	70 + 6	59–81	5	80	0.011
	Yes	22 + 5	12–33	3	40	
IV	No	43 + 8	28–58	10	41.18	0.325
	Yes	29 + 5	19–39	14	30	
Stage	Radiotherapy	Mean + SE (month)	CI 95%	Death (N)	Censored (%)	p value
I–II	No	36 + 10	16–57	3	57.14	0.175
	Yes	66 + 5	56–76	9	74.29	
III	No	40 + 9	23–57	1	75	0.9556
	Yes	65 + 6	53–77	7	73.08	
IV	No	27 + 9	9–46	7	22.22	0.143
	Yes	36 + 4	27–44	17	39.29	

Previous studies and the American Cancer Society have reported the male to female ratio of mortality in all races and ethnicities to be 1.9:0.4.<sup>6,7</sup> In the present study, however, the mean survival rate was lower in women compared with that in men in all the stages

of the disease; nevertheless, the disparity of findings might have been due to the small female sample size assessed in the present study.<sup>6,7,11</sup> Laryngeal tumors occur on three anatomic sites, and different survival rates and prognoses were reported for them

**Table 3:** Survival rate based on stage of tumor and treatment type

Stage	Treatment type	Mean + SE (month)	CI 95%	Death (N)	Censored (%)	p value
I-II	Non-laryngectomy	52 + 9	35-68	8	55.56	0.187
	Partial laryngectomy + radiotherapy	-	-	0	100	
	Total laryngectomy + radiotherapy	70 + 6	57-82	4	78.95	
III	Non-laryngectomy	37 + 7	23-52	2	66.67	0.094
	Partial laryngectomy + radiotherapy	-	-	0	100	
	Total laryngectomy + radiotherapy	69 + 7	55-82	4	77.78	
	Laryngectomy + chemo + radio	23 + 8	6-39	2	33.33	
IV	Non-laryngectomy	29 + 5	18-39	19	20.83	0.037
	Total laryngectomy + radiotherapy	43 + 6	31-55	5	54.55	
	Laryngectomy + chemo + radio	-	-	0	100	

depending on the affected site.<sup>9-11</sup> Given the extensive lymphatic drainage in the supraglottis, the tumors on this site appear to spread earlier and to have a worse prognosis compared to other tumors on the other sites of the larynx, whereas in the glottis, tumors have a poorer lymphatic access and a lower chance of early spread. Tumors in the subglottis spread to areas such as the lymphatic vessels around the trachea, the inferior jugular vein, and the mediastinum via cricothyroid and cricotracheal lymphatics. In a cohort study conducted in Canada by MacNeil et al. on the survival of patients with laryngeal cancer, the mean survival rate was reported as about 54.4% when the glottis was involved and patients with subglottis tumor had a shorter longevity compared to those whose glottis was affected.<sup>18</sup> In the present study, subglottic tumors had the lowest survival rate; however, no significant differences were observed in the mean survival with respect to the location of the tumor in the different stages of the tumor. In a previous study of Canada, the number of patients admitted in early stages (stages I and II) of the disease was higher than the number of patients admitted in advanced stages (stages III and IV) and our study is not in line with their study.<sup>18</sup> In a study published by the American Cancer Society, only 38.5% of the patients admitted to their center were in early stages (stages I and II) and 62.5% were in advanced stages (stages III and IV).<sup>7</sup> Also, in the present study, the number of patients admitted at advanced stages (stages III and IV) was higher compared with the ones admitted at early stages (stages I and II). In addition, the mean survival rate (irrespective of the prognostic factors) was much lower in stage IV than in the other stages, which is consistent with the findings of other studies, indicating that patients in stage IV appear to have a shorter chance of survival compared to patients in the other stages of laryngeal cancer.<sup>6,7,17,18</sup>

At its early stages, laryngeal squamous cell carcinoma is treated with surgery alone (laser surgery) or combined with radiotherapy, and the choice of treatment methods depends on the affected site and the decision to preserve the laryngeal function. Small tumors that have not spread to the lymph nodes have good prognoses and can have a recovery rate of 75-95% depending on the affected site and the degree of infiltration.<sup>19,21</sup> Radiation or surgery can be used for treating these early-stage tumors (stages I and II), whereas total laryngectomy and postoperative chemoradiation appear to be appropriate methods for the treatment of tumors in advanced stages (stages III and IV).<sup>22-24</sup> Today, the focus of treatment for tumors in advanced stages is to use a treatment protocol including chemoradiation without a total laryngectomy; however, according to previous published articles, the patients' survival rate seems to have reduced with this method of treatment (Gourin).<sup>25</sup> Previous studies have examined and compared two

treatment protocols for stages I and II of the disease, including surgery and/or radiotherapy, and showed no significant differences between them in terms of the patients' survival rate, although surgery was associated with a slightly higher mean survival rate compared to only radiotherapy.<sup>20,21</sup> In the present study, patients in stages I and II who had not undergone laryngectomy showed a lower mean survival rate compared to those who had undergone a total or partial laryngectomy, although the difference was not statistically significant. Today, the treatment of patients in advanced stages involves the treatment protocol of preserving the larynx function, through chemoradiation for instance.<sup>26</sup> Nevertheless, recent studies have shown that most patients who have used this treatment method have suffered late toxicity; as a result, it has been recommended to revise the decision to use this treatment and to seriously consider surgery, which is still a very effective treatment method, in case the tumors are large. In a study by Gourin et al. on survival rate in patients with advanced stage IV laryngeal cancer, the survival rate was found to be significantly higher in patients who had undergone surgery compared with those who had received only chemotherapy or a combination of chemotherapy and radiotherapy.<sup>25</sup> In the present study, the best prognosis for patients in stage IV was observed in those who had received a combination of chemotherapy, radiotherapy, and surgery, followed by those who had received a combination of radiotherapy and surgery, and those who had not undergone surgery had a lower survival rate. In a study conducted by Lai et al. on patients in stage IV of laryngeal cancer, no significant difference was observed between the patients who had undergone surgery and those who had not.<sup>27</sup> Based on the present study and the study conducted by Gourin et al., it appears that, even in stage IV of laryngeal cancer, better outcomes and higher survival rates can be expected with surgery.<sup>25</sup>

The important things to consider in the treatment of patients with laryngeal cancer include the quality of life and postoperative complications. Researchers have, therefore, come to believe that, in early stages (stages I and II), the best option is to use minor surgeries combined with radiation. In a study conducted by Lim et al.<sup>28</sup> on the prognosis of patients in stages I and II of laryngeal cancer undergoing radiation, higher rates of recovery were observed in patients receiving this method of treatment (laser surgery combined with radiotherapy). Moreover, none of the patients in the present study had received only radiation without laryngectomy. Levy et al. conducted a study on the type of treatment and prognosis in patients in stages I and II of the disease and concluded that preserving the larynx and using one method of treatment alone or with radiation result in a good prognosis, which was inconsistent with the results of the present study.<sup>29</sup> Harada et al. conducted a



study on stages I and II of laryngeal cancer and their method of treatment and concluded that an initial radiation therapy together with the preservation of the larynx comprised the best treatment strategy.<sup>30</sup> Stankovic et al. conducted a study on patients with advanced laryngeal cancer (stages III and IV) and observed that patients who had received radiotherapy or chemoradiation prior to laryngectomy had greater local complications compared to patients who had undergone surgery from the outset; however, they found that a 5-year survival depended on the stage of the tumor and its TNM status rather than the type of treatment.<sup>31</sup>

## CONCLUSION

Overall, surgery and radiotherapy can be said to produce better survival rates in patients in stages I and II of laryngeal cancer compared to the other methods of treatment. In this stage, survival rate and the response to treatment are much better in younger patients compared with that in older ones. In patients in advanced stages (stages III and IV) of laryngeal cancer, a combination of surgery and radiotherapy or surgery and chemoradiation produces better survival rates and a greater response to treatment compared to when laryngectomy is not performed.

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