JBUON 2017; 22(4): 996-1003
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Factors predicting survival in patients with early stage laryngeal cancer: A cohort study between 2000 to 2015

Mohammad Fararouei [1], Nima Daneshi [2], Mohammad Mohammadianpanah [3], Hamid Reza Tabatabaei [4], Mohammad Zare-bandamiri [4], Mostafa Dianatinasab [1,4]

[1]Shiraz HIV/AIDS Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz; [2]Student Research Committee, Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz; [3]Colorectal Research Center, Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz; [4]Department of Epidemiology, Faculty of Public Health, Shiraz University of Medical Sciences, Shiraz, Iran

Summary

Purpose: *In recent years, trends of treatment and survival of laryngeal cancer have received heightened attention. Despite the fact that most laryngeal cancers are diagnosed at early stage, a concern of worsening survival in patients with localized cancer has been raised but not consistently observed. This study aimed to determine factors affecting laryngeal cancer survival.*

Methods: *This was a cohort study from 2000 to 2015 in which clinical and demographic characteristics of patients at early stage of laryngeal cancer were collected. Medical records and telephone interviews were used to define patient's demographic and clinical status during the study period. Multivariate Cox model was used as the main method for analyzing data.*

Results: *Age at diagnosis, type of treatment, stage, and tumor grade were statistically associated with patient survival. Older patients were more prone to worse prognosis (HR=1.69, 95% CI: 1.03-2.75, p=0.03). The results also suggested that people who had surgery compared with those who received only radiation therapy (RT) survived longer (HR=0.44, 95% CI: 0.20-0.94, p=0.03). Furthermore, for those whose tumor was grade 3 at diagnosis, the risk of death was 2.45-fold higher than those with grade 1 (HR =2.45, 95% CI: 1.19-5.40, p=0.01). Stage II patients experienced worse prognosis than stage I patients (HR=1.77, 95% CI: 1.06-2.93, p=0.02).*

Conclusion: *This study revealed several factors that can influence patient survival rate, among them different therapeutic approaches.*

Key words: *Cox regression, laryngeal cancer, radiation therapy, surgery, survival*

Introduction

Laryngeal cancer is the second most common cancer of the upper aerodigestive system [1]. Each year, more than 150,000 new cases of laryngeal cancer are diagnosed worldwide [2]. According to previous studies, 30-40% of all malignant tumors of the head and neck and 1-5.2% of all malignancies are attributed to laryngeal cancer. The disease occurs most frequently in middle-aged men [3]. Among men, laryngeal cancer is responsible for about 2.4% of all cancers and also 2.1% of all cancer deaths [4]. Based on the pathologic type of cancer, 85-98 % of laryngeal cancers are diagnosed as squamous cell carcinoma [1]. The most common tumor localizations in such patients are glottic (60-65%), supraglottic (30-35%) and both subglottic and glottic (5%). Because glottic tumors cause hoarseness, generally patients with this localization are diagnosed in early stage (stages I,II). On the other hand, as supraglottic localization may not have obvious symptoms, these patients are

Correspondence to: Nima Daneshi, MSc. Student Research Committee, Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel & Fax: +98 7137251020, E-mail: daneshi.nima@gmail.com
Received: 04/02/2017; Accepted: 22/02/2017

diagnosed at later stages (stages III and IV). Approximately 50-60% of the cases of laryngeal cancers are diagnosed at early stages of disease [5].

Although morbidity from laryngeal cancer varies in different parts of the world, generally the trend of mortality is rising worldwide including Iran [3-6]. There are several epidemiological studies conducted on the survival of patients with laryngeal cancer and its related factors. Accordingly, factors that affect patient survival include age, cancer localization, tumor grade, disease stage, resection margin, nodal involvement, type of treatment and the characteristics of tumor biology [7,8]. Although several studies on the impact of different therapeutic approaches have been performed, and because the choice of treatment depends on factors such as tumor size, location and tumor stage, comparing the results of these approaches is difficult [4]. Partial laryngectomy, laser resection or RT are treatments that are preferred in early laryngeal tumors, while total or subtotal laryngectomy followed by RT is usually used in advanced disease [2]. Some previous studies reported that the survival rate of patients with early laryngeal cancer is about 73-92% and for advanced disease it is 50-64% [7]. As laryngeal cancer is one of the most common types of cancers of the head and neck, nevertheless, limited evidence is available regarding the factors associated with patient survival. To the best of our knowledge, no study has investigated survival of laryngeal cancer patients in Iran. Moreover, as laryngeal cancer may affect patient's quality of life and performance, we aimed to investigate factors associated with laryngeal cancer mortality hoping that the results may help physicians to choose better therapeutic strategies.

Methods

Settings

This retrospective cohort study was performed on 250 patients diagnosed with early stage laryngeal cancer (stages I and II) in order to identify factors affecting laryngeal cancer. The median time of patient follow-up was 35.20 months (range 18.38-61.16). Participants were selected among patients who were histologically diagnosed with laryngeal cancer during 2000 to 2015. Patient medical records were obtained from the cancer registry database of Namazi hospital, the biggest and the most referred medical center for all types of diseases, including cancer, in the southern part of the country [9].

Data collection

Data was collected using the patient medical records. In addition, a telephone interview was conducted in order to define the patient's current clinical status and, if happened, the date of death. Ethical approval was obtained from Shiraz University of Medical Sciences ethics committee.

Study variables

Variables under study included age, sex, diagnosis date, laryngectomy (yes, no), location, TNM stage, pathologic type, grade, treatment strategy and RT dose (Gy). The stage of disease was determined according to TNM staging classification (AJCC, 6th Edn) [10]. T1 and T2 are defined as early stage and patients at this stage were selected. Tumor location was categorized into three groups (supraglottic, glottic and unknown). Pathological types of cancer were divided into two groups: squamous cell carcinoma and others. Different therapeutic approaches were divided into two groups, namely: (1) patients treated with RT only, and (2) patients treated with surgery.

Statistics

In the present study, survival was the primary outcome variable. Survival was considered as the interval between diagnosis and death if the patient had died and date of the last follow-up if the patient was still alive or reached the end of follow-up period (July 2016). For those with incomplete follow-up or sensor cases, survival was considered from the date of diagnosis to the last time that they were contacted. One, 2- and 3-year survival was also calculated. All the covariates with significance level <0.2 entered into the multivariate Cox regression analysis.

In univariate analysis the association between laryngectomy and survival was assessed. However, since laryngectomy is part of surgical treatment and given the collinearity between these two variables, laryngectomy and surgical therapy were included in a separate multivariate Cox analysis and the one with smaller p value was selected to be included in the final model.

Kaplan-Meier overall survival curves were plotted and differences were compared with log-rank test. In this study, the relationship between the study variables and death from cancer was assessed using multivariate Cox proportional hazard regression analysis.

All the statistical analyses were performed using SPSS software, version 20. A two-sided p value <0.05 was considered statistically significant.

Results

Selected characteristics of the study subjects

Two hundred and fifty patients with early-stage laryngeal cancer were studied, of which 232 (92.8%) were male. The mean (± SD) age at diagnosis in men was 60.06 ± 11.01 and in women 59.33 ± 14.30 years. According to the therapeutic approach, only 40 (16%) patients had undergone laryngectomy. Concerning tumor location, 176 (70.4%) of the cases were glottic, 67 (26.8%) supraglottic and the remaining were unknown. Most

patients had TNM stage II (52.4%) and the rest had stage I (47.6%). With regard to histology, 99.6% of the patients had squamous cell carcinoma. Of all the patients, 148 (59.2%) had grade 1 tumor differentiation, 78 (31.2%) had grade 2 and the rest had grade 3. According to type of treatment, 64 (25.6%) of the patients had undergone surgery and 186 (74.4%) patients received RT. The average total dose of RT was 65.34 ± 6.33 Gy. Table 1 shows characteristics of the 250 study subjects and 1-, 3- and 5-year overall survival.

The mean (±SD) survival time in this study was 46.86 ± 38.66 months (median 35.20). One, 3- and 5-year overall survival rates were 98, 80, and 67%, respectively. Figure 1 shows the overall survival rate in laryngeal cancer patients during the 192 months of the study.

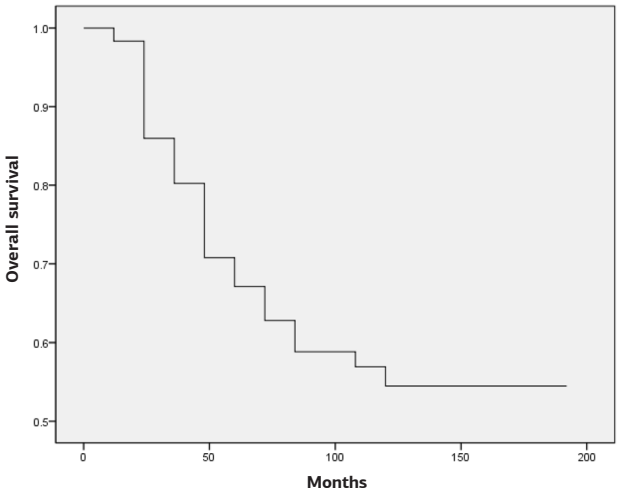

Figure 1. Overall survival in laryngeal cancer patients during the 192 months of the study.

Univariate analysis

The results showed that age over 60 years (p=0.04), grade 3 (p=0.01), laryngectomy (p=0.03), stage II (p<0.02) and RT (p=0.04) were negatively associated with survival. No statistically significant association between gender, tumor location and RT dose with survival was observed (p>0.05).

Figure 1 shows overall survival rate in laryngeal cancer patients during the 192 months of the study. According to Figure 2, patients who had been subjected to surgery had significantly higher survival rate than patients who received RT alone. Also, Figure 3 presents the laryngeal cancer cumulative survival according to different clinical stages.

Multivariate analysis

According to the results of the multivariate Cox regression analysis, age at diagnosis, stage and grade of tumor differentiation were negatively associated with survival. On the other hand, surgical treatment was positively related to patient survival. The results of the modeling using multivariate Cox proportional hazard model are presented in Table 2. Accordingly, the older patients were more prone to worse prognosis (HR=1.69, 95% CI: 1.03-2.75, p=0.03). The results of Cox regression analysis also suggested that people who had surgery, compared to those who received RT, had a lower risk of death (HR=0.44, 95% CI: 0.20-0.94, p=0.03). The risk of death among patients with grade 3 disease was higher than in those with grade 1 (HR=2.45, 95% CI: 1.19-5.40, p=0.01).

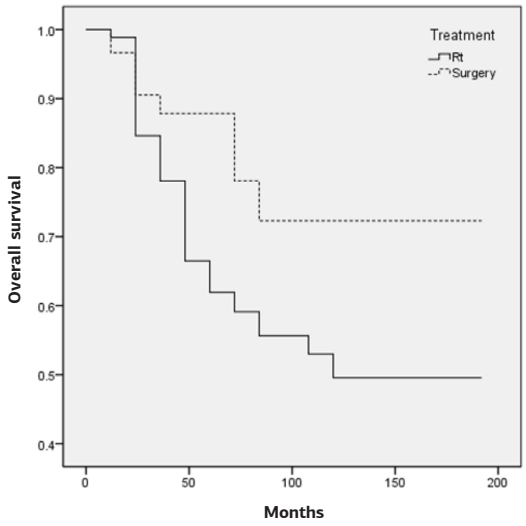

Figure 2. Overall survival as a function of treatment. Patients subjected to surgery had significantly higher overall survival than patients who received radiation therapy (p=0.03).

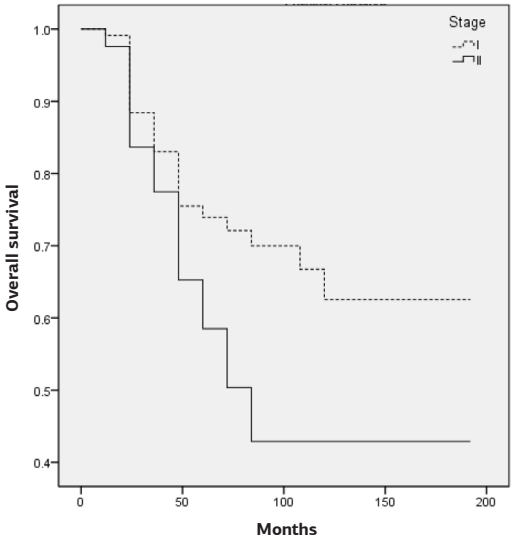

Figure 3. Laryngeal cancer overall survival according to different clinical stages (p=0.02).

Table 1. Characteristics of the 250 study subjects and 1,3 & 5 year overall survival

Characteristics	*Category*	*Alive n (%)*	*Dead n (%)*	*Total n(%)*	*1-Year OS (%)*	*3-Year OS (%)*	*5-Year OS (%)*
Age, years	<60	100 (76.9)	30 (23.1)	130 (52.0)	99	87	73
	>60	84 (70.0)	36 (30.0)	120 (48.0)	97	73	61
Sex	Female	13 (72.2)	5 (27.8)	18 (7.2)	100	61	61
	Male	171 (73.7)	61 (26.3)	232 (92.8)	98	82	68
Laryngectomy	No	148 (70.5)	62 (29.5)	210 (84.0)	98	78	63
	Yes	36 (90.0)	4 (10.0)	40 (16.0)	100	96	96
Treatment	RT	129 (69.4)	57 (30.6)	186 (74.4)	99	78	62
	Surgery	55 (85.9)	9 (14.1)	64 (25.6)	97	88	88
Location	Supraglottic	46 (68.7)	21 (31.3)	67 (26.8)	100	74	59
	Glottic	135 (76.7)	41 (23.3)	176 (70.4)	98	83	71
	Unknown	3 (42.9)	4 (57.1)	7 (2.8)	100	67	50
Stage	I	91 (76.5)	28 (23.5)	119 (47.6)	99	83	74
	II	93 (71.0)	38 (29.0)	131 (52.4)	98	77	59
Grade	1	109 (73.6)	39 (26.4)	148 (59.2)	99	81	64
	2	60 (76.9)	18 (23.1)	78 (31.2)	96	85	80
	3	15 (62.5)	9 (37.5)	24 (9.6)	100	58	32
RT dose*	<60	35 (61.4)	22 (38.6)	57 (22.8)	100	73	61
	>60	94 (72.9)	35 (27.1)	129 (51.6)	98	81	61

*for those who received RT

Table 2. The relationship between the study variables and laryngeal cancer mortality using univariate and multivariate Cox regression analysis

Variables	*Univariate*			*Multivariate*		
	HR	*95%CI*	*p value*	*HR*	*95%CI*	*p value*
Age, years						
<60	1 *	-	-	1*	-	-
>60	1.63	1.005-2.65	0.04	1.69	1.03-2.75	0.03
Sex						
Female	1*	-	-			NI
Male	0.81	0.32-2.02	0.65			
Laryngectomy						
No	1*					NI
Yes	0.34	0.12-0.93	0.03			
Treatment						
RT	1*	-	-	1*	-	-
Surgery	0.48	0.24-0.98	0.04	0.44	0.20-0.94	0.03
Location						
Supraglottic	1*	-	-			NI
Glottic	0.75	0.44-1.27	0.29			
Unknown	1.50	0.52-4.46	0.43			
Stage						
I	1*	-	-	1*	-	-
II	1.75	1.06-2.87	0.02	1.77	1.06-2.93	0.02
Grade						
1	1*	-	-	1*	-	-
2	0.72	0.41-1.26	0.25	0.82	0.46-1.46	0.50
3	2.49	1.19-5.22	0. 01	2.45	1.19-5.40	0.01
RT dose (Gy)						
<60	1*	-	-			NI
>60	0.91	0.53-1.57	0.75			

*reference category, NI= not included

Discussion

Multivariate Cox regression analysis showed that age at diagnosis, stage, type of treatment, and tumor grade can affect the survival of laryngeal cancer patients. According to log-rank test, no significant association between gender, tumor location and RT dose with survival was found. The results of the present study showed that the 1-, 3- and 5-year survival rate in patients with laryngeal cancer were 98, 80 and 67%, respectively. The median survival of the patients was 35.20 months.

Yucel et al. suggested that the 3-year survival rate for early-stage patients was 83%, but they did not report 1- and 5-year survival [5]. Terhaard et al. reported the 5-year survival rate of stage I glottic and supraglottic types as 97 and 74%, respectively. The difference between survival rate in the Terhaard study and the present study is that here only stage I patients were included [11]. A similar study suggested that 1- and 2-year survival rates for patients with early-stage disease were 79.3 and 59.3%, respectively [12]. Another study by Sarada et al. on patients with T1 stage laryngeal cancer suggested that 5-year survival rate of the patients was 77.4% [13]. Cellal et al. suggested that 3- and 5-year survival in patients with T1 disease were 86 and 77%, respectively [14]. Lower survival rate was reported by another study where the 5-year survival was reported as 67.6%. This study included both advanced and early stages of patients, most of which were in early stage (of all 275 patients only 17 were in the advanced group) [15]. Another study on the effect of RT on 5-year survival rate of patients with T2 supraglottic cancer reported a 5-year survival rate of 56%. However, only patients with RT in stage T2 supraglottic disease were included in the study [16]. John et al. reported a 65% 5-year survival rate of the study participants. However, although they examined patients in early-stage disease, only those with RT were enrolled in the study [17]. In a study by Chen et al., 5-year survival rate for early-stage patients was reported to be 78%. The authors studied patients who received RT in the supraglottic area of the tumor, while other treatments and others tumor types were excluded [18]. Comparing survival rates in different studies is challenging because of the following reasons: different types of disease, selection of patients that may occur based on certain therapeutic methods or tumor location and limited sample sizes. Univariate analysis showed no significant association between survival and gender. This association is a controversial issue, since some studies suggested that gender is associated with laryngeal cancer survival [16,19], while others agree with our findings [7,20,21]. According to univariate analysis there was no significant statistical association between tumor location and overall survival. Petrakos et al. reported no significant association between survival and tumor location. Although Petrakos et al. included patients in different stages, the stages were not specifically reviewed [22]. Jones et al. in a study reported that the 5-year survival rate of glottic cancer patients was better than in patients with supraglottic disease [23]. Moreover, our findings contrasted the resuts of the Megwalu et al.study [19].

The results of the present study showed no significant association between RT dose and overall survival rate. To the best of our knowledge, no previous studies examined this association. Although Sarada et al. did not investigate the association between RT dose and survival of their patients, the impact of RT dose was measured on the local control. The authors showed that (based on the results of univariate analysis) patients who received higher RT dose experienced higher rate of local control [13].

According to the results of multivariate analysis, there was a significant association between stage and survival of the patients. Jay et al., in a study on both early and advanced cases, also suggested that stage of disease was associated with patient survival and 5-year survival for stage I and II were reported as 78 and 67%, respectively [24]. Another study, using Cox regression model showed that, compared with T2 stage, patients with T1 stage experienced longer survival [19]. In a study by Jones et al., significant association between T1 and T2 stage of disease with survival was observed, as the 5-year survival for T1 and T2 stage was 91 and 69.5%, respectively [23]. According to Calkovsky et al. study [2], 3- and 5-year survival rates for stage 1 were both 100% and for stage 2 were 100% and 87.5%, respectively. One explanation for this inconsistency is difference in sample size, as in the Calkovsky's et al. study, 3-year and 5-years survival rates of patients in stage I was assessed using data from 6 and 8 patients respectively [2]. Yu et al. reported that 1-year survival rate for T1 and T2 stages were 73.1 and 76.8%, respectively [1]. In a study by Papadas, 5-year survival rate for stage 2 disease was 60% [7]. According to Christine et al. study, 5-year survival rate for stage I and II was 58 and 77%, respectively. However, this finding was not statistically significant in the multivariate analysis [20]. In a study by Petrakos et al., the 5-year survival rate for stage I and II were reported as 78.2 and 71%, respectively, though these differences were

not statistically significant [22]. One explanation for this finding is that in stage I about 75% of the patients underwent RT and 60% experienced recurrence, whereas in stage II although only 15% of the patients received RT and 65.5% had surgical treatment, the relapse rate was 60% [22]. Our results showed that survival rate of stages 1 and 2 was lower compared with other studies. This finding can be explained by the difference in treatment strategies. In the present study, only 21% of stage I patients and 29.8% of stage II were subjected to surgery and the rest underwent RT. However, since most studies have reported that surgical treatment offers longer survival [19,20,25], shorter survival rate in the present study could be due to the treatment strategies used. The results of the present study showed lower survival rate for older age at diagnosis. Several studies have shown no significant association between overall survival and patient age [12,20]. Similarly, in some studies the survival rate of the patients was higher among younger patients [4,9,24]. As shown in the results section, compared with grade 1 tumors, patients with grade 3 bore a higher risk of death. Yu et al. reported that patients with grade 3 tumors experienced lower survival and this association was statistically significant [12]. However, in their study with all stages included Yucel et al., based on univariate analysis, found no significant difference in 3-year survival rate between grade 1, 2 and 3 [5]. Jay et al. reported no significant association between grade of tumor and survival [24].

In this study, treatment of laryngeal cancer was also an important factor influencing survival. The risk of death in patients who had undergone surgery was lower than in patients with RT. Another study suggested that patients treated by surgery had better survival than patients who received RT. Compared to RT, surgical treatment in glottic subtype, supraglottic subtype, T1 stage and T2 stage patients achieved higher survival rates [19]. Amy et al. showed that 4-year survival rate among patients with local operation as main treatment had better survival than those with RT. In addition, they reported that surgical treatment may have protective effect on disease progression without speculating about possible mechanism(s) connected with their observation [25]. The same association was reported by Christine et al. who compared RT and chemotherapy with surgery and concluded that operated patients achieved longer survival [20]. In a study by Henry et al., patients at any stage were increasingly subjected to non-surgical treatment (RT and chemo-RT) and at the same period the survival rates of the patients declined [26]. In contrast, few studies suggested that there was no survival difference between patients treated with partial laryngectomy and RT [23,27]. In a study by Zhang, the 5-year survival rate of patient with RT was not decreased, but they did not compare the survival rate of patients with RT and surgery [28]. Previous studies showed that after cancer diagnosis, treatment choices can influence the patient's quality of life . Although total laryngectomy is a more effective treatment for laryngeal cancer patients, this choice adversely impacts the patient's ability to speak and therefore quality of life [4]. Recently, the combination of RT and chemotherapy was considered as an effective alternative, because it can maintain the patient's ability to talk [28]. According to previous studies, therapeutic approaches vary substantially. For example, in America, Canada and northern Europe the most frequent treatment for patients in early-stage glottic carcinoma is RT . Some studies also reported that, although patients who were subjected to surgical treatment had achieved better survival than patients who received RT, over the time the use of RT has been increasing [19]. In line with the present study, Carvalho et al. revealed that 5-year survival rate of laryngeal cancer was declining in the past decade. Although the reason for this reduction is not well understood, observations have shown that in the same period of time the decrease in surgical treatment accompanied with an increase in non-surgical treatments such as RT and chemotherapy may be responsible for this negative finding [29].

Strengths and limitations

The present study used all patient data during a long period of time in a referral center in Iran. Recruiting participants who visited the biggest referral center makes the results generalizable to the population of the country. No data on delay of diagnosis was available in this study. This factor can affect the stage of disease and the survival of the patients [30].

Conclusions

The present study revealed that several factors may influence patient survival. Different therapeutic approaches that apply for laryngeal cancer affect patient survival. Generally, choosing a treatment is a complex and important process and when all factors are considered (stage, age, grade and location), it is possible to select the best treatment and improve survival. As previous studies have suggested, surgical treatment contributes to

better survival in laryngeal cancer patients. However, regarding the patient quality of life, this approach seems not to be the best option. Although in most of the studies RT was associated with lower survival, but because RT affects less the patient quality of life than surgery, using this nonsurgical alternative treatment has been rising. Finally, we maintain that further studies on this subject are necessary.

Acknowledgement

The present study was financially supported by Shiraz University of Medical Sciences, Shiraz, Iran (No:11822).

The present study is part of MSc thesis written by Nima Daneshi under the supervision of Dr. Mohammad Fararouie. We also would like to thank the staff of the Center for Cancer Registry at Namazi hospital for providing us with clinical data.

Authors' contributions

ND contributed in the conception of the study, conducted the study and prepared the draft. MD contributed in the conception of the study, drafted and revised the draft. MF contributed in the conception of the study, conducted the study, revised the draft, approved the final version of the manuscript, and agreed for all aspects of the work. HT contributed in the conception of the study, revised the draft, approved of the final version of the manuscript, and agreed for all aspects of the work. MM and MZ contributed in the conception of the study, conducted the study, revised the draft, approved of the final version of the manuscript, and agreed for all aspects of the work. All authors approved the final version that has been submitted to JBUON.

Conflict of interests

The authors declare no confict of interests.

References

1. Megwalu UC, Sikora AG. Survival outcomes in advanced laryngeal cancer. JAMA Otolaryngology–Head Neck Surg 2014; 140: 855-860.
2. Calkovsky V, Wallenfels P, Calkovska A, Hajtman A (Eds): Laryngeal Cancer: 12-Year Experience of a Single Center. In: Advances in Respiratory Cancerogenesis. Springer 2015, pp 9-16.
3. Markou K, Christoforidou A, Karasmanis I et al. Laryngeal cancer: epidemiological data from Northern Greece and review of the literature. Hippokratia 2013;17:313-318.
4. Ramroth H, Schoeps A, Rudolph E et al. Factors predicting survival after diagnosis of laryngeal cancer. Oral Oncol 2011;47:1154-1158.
5. Yücel B, Eren AA, Erdis E et al. Treatment results, side effects and prognostic factors affecting survival in patients with larynx cancer. ENT Updates 2013;3:69.
6. Fararouei M, Parisai Z, Farahmand M et al. Cancer incidence appears to be rising in a small province in Islamic Republic of Iran: a population-based cohort study. East Mediter Health J 2015;21: 319.
7. Papadas TA, Alexopoulos EC, Mallis A et al. Survival after laryngectomy: a review of 133 patients with laryngeal carcinoma. Eur Arch Oto-Rhino-Laryngol 2010;267:1095-1101.
8. Matsuo JMS, Patel SG, Singh B et al. Clinical nodal stage is an independently significant predictor of distant failure in patients with squamous cell carcinoma of the larynx. Ann Surg 2003;238:412-422.
9. Dianatinasab M, Fararouei M, Mohammadianpanah M et al. Hair coloring, stress and smoking increase the risk of breast cancer: A case–control study. Clin Breast Cancer 2017.
10. Greene F, Page D, Fleming I et al. AJCC Cancer Staging Manual. Springer-Verlag, New York, 2002.
11. Terhaard C, Snippe K, Ravasz L et al. Radiotherapy in T1 laryngeal cancer: prognostic factors for locoregional control and survival, uni-and multivariate analysis. Int J Radiat Oncol Biol Phys 1991;21:1179-1186.
12. Yu Q, Zhang X, Ji C et al. Survival analysis of laryngeal carcinoma without laryngectomy, radiotherapy, or chemotherapy. Eur Arch Oto-Rhino-Laryngol 2012;269:2103-2109.
13. Reddy SP, Hong RL, Nagda S, Emami B. Effect of tumor bulk on local control and survival of patients with T1 glottic cancer: a 30-year experience. Int J Radiat Oncol Biol Phys 2007;69:1389-1394.
14. Cellai E, Frata P, Magrini SM et al. Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers. I. The case of T1N0 disease. Int J Radiat Oncol Biol Phys 2005;63:1378-1386.
15. Preuss S, Cramer K, Klussmann J et al. Transoral laser surgery for laryngeal cancer: outcome, complications and prognostic factors in 275 patients. Eur J Surg Oncol 2009;35:235-240.
16. Rutkowski T, Wygoda A, Składowski K et al. Predictors of radiotherapy outcome in patients with T2 supraglottic carcinoma. Eur Arch Oto-Rhino-Laryngol 2012;269:923-929.
17. Holland JM, Arsanjani A, Liem BJ et al. Second malignancies in early stage laryngeal carcinoma pa-

tients treated with radiotherapy. J Laryngol Otol 2002;116:190-193.

18. Chen M-F, Chang JT-C, Liao C-T et al. Radiotherapy of early-stage glottic cancer: analysis of factors affecting prognosis. Ann Otol Rhinol Laryngol 2003;112:904-911.
19. Megwalu UC, Panossian H. Survival Outcomes in Early Stage Laryngeal Cancer. Anticancer Res 2016; 36: 2903-2907.
20. Gourin CG, Conger BT, Sheils WC et al. The effect of treatment on survival in patients with advanced laryngeal carcinoma. Laryngoscope 2009;119:1312-1317.
21. Kao J, Lavaf A, Teng MS et al. Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer: an analysis by primary site and nodal stage. Int J Radiat Oncol Biol Phys 2008;71:362-370.
22. Petrakos I, Kontzoglou K, Nikolopoulos T et al. Glottic and supraglottic laryngeal cancer: epidemiology, treatment patterns and survival in 164 patients. J BUON 2012;17:700-705.
23. Jones AS, Fish B, Fenton JE, Husband DJ. The treatment of early laryngeal cancers (T1–T2 N0): surgery or irradiation? Head Neck 2004;26:127-135.
24. Piccirillo JF, Sasaki CT, Wells CK, Feinstein AR. New clinical severity staging system for cancer of the larynx: five-year survival rates. Ann Otol Rhinol Laryngol 1994;103:83-92.
25. Chen AY, Fedewa S, Zhu J. Temporal trends in the treatment of early-and advanced-stage laryngeal cancer in the United States, 1985-2007. Arch Otolaryngol Head Neck Surg 2011;137:1017-1024.
26. Hoffman HT, Porter K, Karnell LH et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. Laryngoscope 2006;116:1-13.
27. 27. Orus C, Leon X, Vega M, Quer M. Initial treatment of the early stages (I, II) of supraglottic squamous cell carcinoma: partial laryngectomy versus radiotherapy. Eur Arch Oto-Rhino-Laryngol 2000;257:512-516.
28. Zhang H, Travis LB, Chen R et al. Impact of radiotherapy on laryngeal cancer survival. Cancer 2012; 118: 1276-1287.
29. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int J Cancer 2005;114:806-816.
30. Dianatinasab M, Fararouei M, Mohammadianpanah M, Zare-Bandamiri M. Impact of social and clinical factors on diagnostic delay of breast cancer: A Cross-sectional Study. Medicine 2016; 95 (38):e4704.