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Treatment results, side effects and prognostic factors affecting survival in patients with larynx cancer

Larinks kanserli hastaların tedavi sonuçları, yan etkileri ve sağkalımını etkileyen prognostik faktörler

Birsen Yücel[1], Ayfer Ay Eren[1], Eda Erdiş[2], Nalan Akgül Babacan[3], Emine Elif Altuntaş[4]

[1]*Department of Radiation Oncology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
[2]*Department of Radiation Oncology, Antakya Government Hospital, Hatay, Turkey*
[3]*Department of Medical Oncology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
[4]*Department of Otorhinolaryngology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*

Abstract

Objective: Our aim was to determine the treatment results, side effects and the prognostic factors affecting survival in patients with larynx cancer treated in our clinic.

Methods: Data of a total of 90 patients with larynx carcinoma were included in the study. The patients' performance scores were evaluated according to the Eastern Cooperative Oncology Group (ECOG) system.

Results: Eighty-seven (97%) patients were male and three patients (3%) were female. The median age of the patients was 59 (37-86) years. Early-stage, locally advanced stage, and metastatic disease were detected in 43, 55, and 2% of the patients, respectively. Laryngeal cancers were observed in the glottic (53%), and supraglottic (47%) regions. Performance score (p=0.022), grade (p=0.033), lymph node metastasis (p=0.001), T stage (p=0.034) and disease stage (p=0.007) were significantly unfavourable in supraglottic cancers compared to glottic cancers. Recurrence was observed in 17% of the patients in a median 15 (range: 5-96) months. Distant metastasis was observed in 12% of the patients in a median 17 (range: 1-155) months. The factors affecting survival were the presence of comorbidities (p=0.032), performance status (p=0.022), hemoglobin level (p=0.003), T stage (p=0.006), disease stage (p=0.011), and weight loss (p=0.002). When RT- and CRT-associated side effects were compared, the incidence of adverse effects such as mucositis (p<0.001), nausea/vomiting (p<0.001), weight loss (p=0.005), neutropenia (p=0.001), and anemia (p=0.003) in patients under chemoradiotherapy was significantly higher than those associated with radiotherapy.

Conclusion: Hemoglobin level, T stage, presence of comorbidity and weight loss were independent prognostic factors.

Key words: Larynx cancer, survival, prognosis, side effect.

Özet

Amaç: Bu çalışmada, kliniğimizde tedavi edilen larinks kanserli hastaların tedavi sonuçları, tedavilerin yan etkileri ve hastaların sağkalımını etkileyen prognostik faktörlerin belirlenmesi amaçlanmıştır.

Yöntem: Çalışmada 90 hasta verisi analiz edilmiştir. Hastaların performans statüsü 2010'da revize edilmiş Doğu Onkoloji İşbirliği Grubu (*Eastern Cooperative Oncology Group*, ECOG) skorlama sistemine göre değerlendirilmiştir.

Bulgular: Hastaların %97'si erkek ve %3'ü kadın olup, medyan yaşı 59 (37-86) idi. Erken evre %43, lokal ileri evre %55, metastatik evre kanser %2 hastada saptandı. Hastaların %53'ünü glottik kanserler, %47'sini supraglottik kanserler oluşturmaktaydı. Supraglottik kanserlerin performans durumu (p=0.022), grade (p=0.033), T evresi (p=0.034), lenf nod metastazı (p=0.001), hastalık evresi (p=0.007) bakımından glottik kanserlere göre daha kötü özelliklere sahip olduğu saptandı. Medyan 15 (dağılım: 5-96) ayda hastaların %17'sinde nüks, medyan 17 (dağılım: 1-155) ayda da hastaların %12'sinde uzak metastaz tespit edildi. Hastaların sağkalımını komorbidite (p=0.032), performans durumu (p=0.022), hemoglobin düzeyi (p=0.003), T evresi (p=0.006), hastalık evresi (p=0.011), kilo kaybı (p=0.002) etkilemekteydi. Kemoradyoterapi uygulanan hastalarda mukozit (p<0.001), bulantı kusma (p<0.001), kilo kaybı (p=0.005), nötropeni (p=0.001) ve anemi (p=0.003), radyoterapi uygulanan hastalara göre daha fazla gözlenmiştir.

Sonuç: Hemoglobin düzeyi, T evresi, komorbidite ve kilo kaybı bu hastalar için bağımsız prognostik faktörler olmuştur.

Anahtar sözcükler: Larinks kanseri, sağkalım, prognoz, yan etki.

Correspondence: Birsen Yücel, MD. Department of Radiation Oncology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey.
e-mail: yucelbirsen@yahoo.com

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Larynx cancers are the second most common cancers of the head, and neck region, following skin cancers, and constitute 2-5% of all malignancies.[1] According to the Surveillance, Epidemiology, and End Results data, annual incidence of larynx cancers was 3.4/100,000 between 2003-2007 (men, 6.1/100,000, and women, 1.3/100,000).[2] The larynx is divided anatomically into three regions as supraglottis, glottis, and subglottis. Glottic (60-65%), supraglottic (30-35%), and transglottic+subglottic (5%) tumors have been found in varying incidences.[3,4] As in the case of all head and neck cancers, the most common histopathological type in larynx cancers is squamous cell carcinoma.

As they cause hoarseness, glottic tumors are generally diagnosed in their early-stages. However, supraglottic tumors are generally diagnosed in the late-stage, as they don't manifest many symptoms. In addition they have a rich lymphatic network which explains higher incidence of metastatic lymph nodes.[4,5] Approximately 50-60% of larynx cancers are diagnosed in the early-stages (Stage I-II).[5]

Larynx cancers generally metastasize via direct invasion or through the lymphatic system. Therefore, surgery and radiotherapy (RT) are two important treatment modalities in these cancers. However, the role of chemotherapy (CT), which is a part of chemoradiotherapy (CRT) or induction treatment, is gradually increasing. Surgery or RT have similar local control, and survival rates in the early-stage tumors. With both treatment modalities, 5-year disease-free survival rates are approximately 90% in stage I and 80% in stage II.[6] Combination treatments (surgical and post-operative RT/CRT or primary CRT) are generally preferred for late-stage tumors.

To date, prognostic factors such as gender, age, smoking, late stage, supraglottic disease, and grade have been described in these cancers. In recent years, investigations on the importance of certain genetic and immunological markers (p53, Ki67, BNIP3, TGM2, and IGF1R) have begun.[7-12] The aim of this study was to determine the prognostic factors which have an impact on the treatment, in addition to side effects and survival rates in patients with larynx cancer.

Materials and Methods

Patients who were admitted to the Oncology Center at Training, Research and Application Hospital of Cumhuriyet University Medical Faculty between 2006 and 2012, and treated for larynx cancer were included in the study. The patients' data were obtained from the patients' medical records.

The patients' performance scores were evaluated according to the Eastern Cooperative Oncology Group (ECOG) scoring system. Disease staging was performed according to the TNM staging, which was revised in 2010. A hemogram was performed at the time of admission, and the hemoglobin concentration was used as a criterion during the evaluation process of survival. Weight loss was defined as a 5% reduction in the patient's weight. The data were obtained by subtracting baseline bodyweight (before treatment) from the final bodyweight (after treatment) in patients who received RT or CRT, and from anamnesis in patients who received surgical treatment.

Radiothetapy was performed in all patients using a Varian Clinac DHX instrument (Varian Medical Systems, Inc., Palo Alto, CA, USA) and a 6 MV x-ray. RT planning was performed three-dimensionally using ECLIPS version 8.6 software (Varian Medical Systems, Inc., Palo Alto, CA, USA). Radiotherapy fields were determined according to the disease stage, and localization. A total dose of 60-66 Gy was given in 2 Gy/fractions starting from the region containing the tumor bed or neck lymph nodes to patients who were scheduled for post-operative RT. In patients with early-stage disease who were scheduled for definitive RT, a total dose of 58.5, 63, 65.25, 70 Gy RT was given in 2-2.25 Gy/day fractions or a total dose of 72-74.4 Gy was given hyperfractionatedly in 1.2x2/day fractions. In patients with locally advanced disease who were scheduled for definitive RT, a total dose of 70 Gy RT was given in 2 Gy/day fractions concurrently with CT. In CRT, weekly cisplatin (40 mg/m^2) or weekly cisplatin (25 mg/m^2) + docetaxel (25 mg/m^2) schemes were used. During RT, the side effects of the treatment were evaluated weekly according to the RTOG/EORTC (Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer) side effect criteria.[13]

Statistical analysis was performed using the Statistical Package for Social Sciences 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Frequency tests and the chi-square test were performed. Overall survival was estimated by the Kaplan-Meier method. Multivariate analysis (Cox regression analysis) was performed to evaluate the independent factors effective on survival. p values <0.05 were considered statistically significant.

Results

A total of 90 patients with larynx carcinoma were included in the study. Eighty-seven (97%) patients were male and 3 patients (3%) were female. The median age was 59 (range: 37-86) years. Demographical features of the patients are presented in Table 1.

Clinical, and histopathological differences between glottic and supraglottic cancers and treatment protocols according to the stage of the disease are summarized in Table 2 and Table 3. Performance score (p=0.022), grade (p=0.033), lymph node metastasis (p=0.001), T stage (p=0.034) and disease stage (p=0.007) were significantly different in supraglottic cancers compared to glottic cancers.

Surgical Treatment

As surgical treatments, total (n=28; 31%), and subtotal laryngectomies (n=11; 12%), cordectomy (n=3; 3%), functional (n=17; 49 %), and modified radical (n=18; 51%) neck dissections were performed.

RT and CRT

The median RT doses were 70 Gy, and 60 Gy in patients who received definitive or adjuvant RT, respectively. Cisplatin protocol was implemented on 17 patients (61%) who received CRT, and cisplatin+docetaxel protocol was applied on 11 patients (39%) who received CRT.

The mean follow-up period was 22 (range: 1-158) months. Recurrence was observed in 15 patients within a median 15 (range: 5-96) months. Recurrence was observed in 5 out of 39 patients (13%) with early-stage, and in 10 out of 49 patients (20%) with locally advanced stage disease (p=0.258). Recurrence was detected in the tumor bed in 7 (78%), and in the neck in 2 patients (22%). Recurrences were noted in patients who received surgical treatment (n=5; 38%), CRT (N=5; 31%), surgery+RT (n=2; 17%), surgery+RT (n=2; 12%), and RT (n=1; 4 %).

Table 1. Demographic characteristics of the patients and the disease states.

		Patients, n (%)
Sex	Male Female	87 (97) 3 (3)
Smoking		83 (92)
Alcohol use		23 (26)
Family history		27 (30)
Comorbidity		33 (37)
Performance status	ECOG-0 ECOG-1	56 (62) 34 (38)
Hemoglobin	≥12 mg/dl ≥12 mg/dl	62 (69) 28 (31)
Weight loss		36 (40)
Localization of the tumour	Glottic Supraglottic	48 (53) 42 (47)
Histopathology	In situ carcinoma Squamous cell carcinoma	3 (3) 87 (97)
Grade	Grade I Grade II Grade III	26 (32 44 (55) 10 (13)
Levels of lymph node involvement	Level I Level II Level III Level IV Level V	5 (6) 21 (23) 10 (13) 4 (4) 4 (4)
Disease stage	Early stage (I-II) Locally advanced stage (III-IV) Metastatic stage	39 (43) 49 (55) 2 (2)

Metastasis was observed in 14 patients (12%) within the median17 months (1-155 months). Eight metastatis foci (57%) were in the lung, 4 (29%) in the bone, 1 (7%) in the

Table 2. Clinical and histopathological differences in glottic and supraglottics cancers, according to stage of the disease, locations of tumors, and treatment modalities.

		Glottic (n=48)	Supraglottic (n=42)	p value
Performance status	ECOG0 ECOG1	35 (68) 13 (38)	21 (38) 21 (62)	0.022
Hemoglobin	≥12 mg/dl ≥12 mg/dl	36 (58) 12 (43)	26 (42) 16 (57)	0.133
Grade	Grade 1 Grade 2 Grade 3	19 (73) 18 (41) 5 (50)	7 (27) 26 (59) 5 (50)	0.033
T stage	T1-2 T3-4	27 (63) 18 (41)	16 (37) 26 (59)	0.034
Lymph node involvement	Present Absent	41 (64) 7 (28)	23 (36) 18 (72)	0.001
Stage	Early stage (I-II) Locally advanced stage (III-IV)	27 (69) 20 (41)	12 (31) 29 (59)	0.007

Table 3. Treatment modalities in glottic and supraglottic cancers according to the disease stages.

		Glottic (n=48)	Supraglottic (n=42)	Total
Treatment of early stage	Surgery	5 (19)	7 (58)	12 (31)
	RT*	22 (78)	5 (42)	27 (67)
Treatment of locally advanced stage	Surgery	1 (5)	-	1 (2)
	Radiotherapy	-	2 (8)	2 (4)
	CRT†	5 (25)	11 (42)	16 (33)
	Surgery +RT/CRT	14 (70)	13 (50)	27 (55)

*RT: Radiotherapy, †CRT: Chemoradiotherapy

brain, and 1 (7%) in the mediastinum. Distant metastases were observed in 5 (13%) patients with early-stage and in 6 (12%) cases with locally advanced stage (p=0.592).

Secondary metastases of primary malignancies developed in 8 (9%) patients. These primary malignancies were pulmonary squamous cell carcinoma (n=4; 50%), renal cell carcinoma (n=1;13%), rectal adenocarcinoma (n= 1;13%), gastric cancer (n=1; 13 %), and skin basal cell carcinoma (n=1; 13%)

Three-year overall survival rate was 69% for all patients, while the median survival rate was not calculated. The factors affecting survival in the univariate analysis were the presence of comorbidity (p=0.032), ECOG performance score (p=0.022), hemoglobin level (p=0.003), T stage (p=0.006), disease stage (p=0.011), and weight loss (p=0.002). The factors affecting survival rates independently in the multivariate analysis were hemoglobin level (p=0.002), T stage (p=0.026), presence of comorbidity (p=0.001), and weight loss (p<0.001). The prognostic factors affecting survival in larynx cancer are presented in Tables 4 and 5.

Radiotherapy- and CRT-associated side effects were observed in 77 patients (85%). Radiotherapy was interrupted in 13 of these patients (14%) due to the side effects of RT and CRT. When RT- and CRT-associated side effects were compared, the incidence of mucositis (p<0.001), nausea/vomiting (p<0.001), weight loss (p=0.005), neutrope-

Table 4. Univariate analysis of the prognostic factors affecting survival in laryngeal cancer.

		No. patients	3-year overall survival rates (%)	p value
Comorbidity	Absent	57	76	0.032
	Present	33	43	
Performance status	ECOG 0	56	79	0.022
	ECOG I	34	55	
Localization	Glottic	48	75	0.132
	Supraglottic	42	58	
Hemoglobin	≥12 g/dL	28	47	0.003
	≥12 g/dL	62	76	
Grade	Grade I	26	66	0.291
	Grade II	44	69	
	Grade III	10	38	
T stage	T1-2	43	81	0.006
	T3-4	44	56	
Lymph node status	N0	63	71	0.426
	N+	24	62	
Disease stage	Early stage	39	83	0.011
	Locally advanced stage	49	61	
RT* interruption	No	66	74	0.179
	Yes	13	56	
Weight loss	No	54	78	0.002
	Yes	36	52	

*RT: Radiotherapy

Table 5. Multivariate analysis of the prognostic factors affecting survival in laryngeal cancer.

		p value	HR*	%95 CI†
Multivariate analysis	T3-4	0.026	2.64	1.12-6.20
	Presence of Comorbidity	0.001	4.49	1.88-10.73
	Weight loss	0.001	5.98	2.50-14.28
	Hemoglobin ≥12 g/dL	0.002	0.30	0.14-0.64

*HR: Hazard ratio, †CI: Confidence interval

nia (p=0.001), and anemia (p=0.003) was significantly higher among CRT-associated side effects. The comparison of RT- and CRT-associated side effects is presented in Table 6.

Discussion

Larynx carcinoma is the second most common cancer among the head, and neck cancers. The incidence of larynx cancers is higher in males compared to females. Şengül et al. determined that among 323 patients with larynx cancer only 3% of them were of female gender, whereas Raitiola et al. found that female cases had constituted only 5% of 312 patients with larynx cancer.[14,15] Similar to previous studies, 3% of the patients were of female gender in the current study.

Larynx cancers with glottic and supraglottic localization differ as for incidence, tumor features, clinical progression, and histopathological features. One of the most important factors underlying these differences is the rich lymphatic network in the supraglottic region. Many researchers stated that glottic cancers have higher incidence rates compared to supraglottic cancers.[14,15] Raitiola et al. reported that larynx cancers were observed in the glottic, and supraglottic localizations in 57, and 43% of the cases, respectively. Şengül et al. reported that larynx cancers were localized in the glottis in 52% of the cases, and followed by in the descending order of frequency they are seen in supraglottis (32%), and transglottis (16%). Since the lymphatic drainage of both regions is different, the incidence of lymph node metastasis of these regions is not similar. The incidence of neck-lymph node metastasis in glottic cancers is below 10%, while it ranges between 10-50% in supraglottic cancers.[16-18] Raitiola et al. demonstrated that both regions showed differences in their T stages, and stated that supraglottic cancers had significantly higher T stages. In this study, glottic, and supraglottic localizations were observed in 53%, and 47% of the patients, respectively. Metastasis to the neck lymphatic sys-

Table 6. Comparison of RT- and CRT-induced side effects.

			RT* (n=44)	CRT† (n=28)	p value
Early side effects	Skin	Grade 1-2	38 (86)	24 (86)	0.430
		Grade 3-4	2 (5)	3 (11)	
	Mucositis	Grade 1-2	14 (32)	19 (68)	<0.001
		Grade 3-4	-	6 (21)	
	Pharynx/osephagus	Grade 1-2	32 (73)	22 (79)	0.750
		Grade 3-4	1 (2)	1 (4)	
	Neutropenia	Grade 1-2	1 (2)	7 (25)	0.001
		Grade 3-4	-	3 (11)	
	Thrombocytopenia	Grade 1-2	-	1 (4)	0.199
		Grade 3-4	-	1 (4)	
	Anemia	Grade 1-2	3 (7)	10 (36)	0.003
		Grade 3-4	-	-	
	Nausea/vomiting		13 (29)	24 (86)	<0.001
	Weight loss		11 (39)	17 (61)	0.005
Late side effects	Xerostomia	Grade 1-2	19 (43)	18 (64)	0.080
		Grade 3-4	1 (2)	2 (7)	

*RT: Radiotherapy, †CRT: Chemoradiotherapy

tem was observed in 15% of the glottic cancers and 43% in supraglottic cancers. The observed difference in metastasis was also statistically significant. Additionally, supraglottic cancers were associated with poorer patient performance scores, tumor grade, T, and disease stages compared to glottic cancers.

Given the fact that supraglottic cancers have more invasive phenotypes compared to glottic cancers, it is believed that supraglottic cancers generally have a poorer prognosis.[19] The high incidence of lymphatic node metastases in supraglottic cancers may be one of the underlying reasons of this deterioration. In a study of 196 patients with laryngeal squamous cell carcinoma, Teppo et al. stated that the prognosis of glottic and supraglottic cancers were different. In their study, 5-year disease-specific survival rate was over 75% in 57 patients with glottic cancer, whereas this rate was 22% in patients with supraglottic cancer.[10] Raitiola et al. reported that the 5-year disease-specific survival rate was 81% in glottic cancers and 71% in supraglottic cancers.[15] Different from the study by Teppo et al., there was no significant difference in the 5-year disease-specific survival rates between glottic and supraglottic cancers in the study by Raitiola et al. Similar to the results of Raitiola et al., there was no correlation between tumor localization and survival rates in this study. However, the 3-year overall survival rate of the patients with supraglottic cancer was lower compared to patients with glottic cancer.

Survival rates in the early-stage larynx cancers are higher relative to the patients with late-stage disease. According to the literature, survival rates for early (stages I and II), and late stage (stages III and IV) larynx cancers range between 73-92% and 35-64%, respectively.[20-22] Şengül et al. reported that in the 50th month after the onset of therapy, the cumulative survival rate estimated for 172 patients in all disease stages was 69 percent. The cumulative survival rates in various disease stages were as follows: Stage I, 84%; II, 77%; III, 68%, and IV, 56%.[14] Zhang et al. reported that the 3-year disease-free survival rates were as follows in 205 patients with squamous cell larynx carcinoma under surgical treatment: Stage 1, 80%; II, 81%; III, 77%, and IV, 53%.[23] Similarly, the 3-year overall survival rates in the current study was 69% for all patients, 83% for early-stage, and 61% for late-stage disease .

According to the literature, recurrence rates range between 5-27% in the early-stage larynx cancers.[24,25] Mercante et al. reported that the recurrence rate was 15% within a average of 16 months in 143 patients with early-stage glottic larynx cancer under radiotherapy.[26] Çaloğlu et al. determined that 27% of 34 patients with larynx cancer who received surgery+RT and 35% of 26 patients under curative RT had experienced recurrences in a median 18 months.[27] Ataman et al. observed that 13% of 144 patients with early-stage larynx cancer (Tis, T1 and T2) had recurrences (33, 78, and 83% within the first one, two, and three years, respectively).[28] In the RTOG 91-11 study (locally advanced stage, n=547), the authors observed recurrences in patients under induction CT+RT (70/ 173), CT+RT+CRT (34/172), and radiotherapy (80/ 173) and in 32% of all patients.[29] Parallel to the literature findings, recurrence was observed in 17% of the patients in a median15 months in this study. Thirteen percent of the recurrences were observed in the early-stage, and 20% of them in the locally advanced stage. According to the treatment type, the lowest recurrence rate was 4% which was observed in patients who received RT.

According to the early results of the RTOG 91-11 study (late-stage, n=547) distant metastasis was observed in 3% of all patients, in 5% of 173 patients who received induction CT+RT, in 5% of 172 patients under concomitant CRT, and in 9% of 173 patients who were given RT.[29] Regarding the RTOG 9501 study, Cooper et al. reported that the incidence of distant metastasis was 23% in patients with larynx cancer who received post-operative RT, whereas Bernier et al. reported that this rate was 25 percent.[30,31] Çaloğlu et al., on the other hand, stated that the incidence of distant metastasis was 18% in the patient group that received post-operative RT.[27] In this study, distant metastasis was observed in 12% of the cases in a median 17 months, and most of the metastases were present in the lung. Metastasis was observed in 13% of the patients in the early-stage and in 12% of the patients in the locally advanced stage; there was no significant difference between both groups as for the occurrence of metastasis.

The standardized incidence of developing second primary malignancy in head-neck cancers is 2.18 (95% CI, 2.15-2.21) and the most frequent regions of second primary malignancies are esophagus and lungs.[32,33] According to the literature, the incidence of second primary malignancy in larynx cancers ranges between 11-29%.[34-36] In a population-based study performed between 1986-2008, Liao et al. determined that 9,996 patients out of 93,891 patients with head neck cancer (11%) had second primary malignancies. In this study, the most frequent organ associated with the second primary malignancy was the nasopharynx (39%), whereas this frequency was 14% for the larynx.[37] Mehdiyev et al. determined that this rate was 3% in 629 patients with larynx cancer.[38] In this study, second primary malignancies were observed in 9% of the patients, and similar to the previous studies, second malignancy developed in the lung (50%).

Various patient- and disease-related factors affect the survival rates in larynx cancers. Teppo et al. stated that the tumor region (glottic-supraglottic) and the disease stage affected the patient's prognosis.[10] Esassolak et al. reported that T stage and RT interruption for more than five days were prognostic factors for the disease survival in 83 patients with glottic cancer who were given curative RT.[39] Zhang et al. demonstrated that the surgical margin, disease stage and comorbidity were the independent factors that affected the prognosis of 205 patients with larynx cancer under surgical treatment.[25] Rutkowski et al. stated that female gender, hemoglobin concentration, and body-mass index were the independent prognostic factors for overall survival in 78 patients who had T2 supraglottic cancer.[40] In this study, patient comorbidity, performance score, weight loss, hemoglobin level, T stage, and disease stage were the prognostic factors for survival. However, tumor localization, RT interruption, lymph node condition, and grade did not affect survival. Hemoglobin level, T stage, comorbidity, and weight loss were also independent prognostic factors for the patients. These results indicate that early diagnosis and the overall condition of the patients are important parameters for patient survival.

In the RTOG 91-11 study, the induction CT+RT, concomitant CRT, and RT only groups were compared and evaluated for the acute side effects in these three groups. When concomitant CRT and RT groups were compared, the incidence of Grade 3 and 4 hematological side effects, mucositis, pharyngeal/esophageal side effects, and nausea were higher in the concomitant CRT relative to RT group. When concomitant CRT group was considered, Grade 3 and 4 hematological side effects were observed in 47% of the patients. Other adverse effects including mucositis (43%), pharyngeal/esophageal (35%), laryngeal (18%), dermatological (7%) side effects, nausea-vomiting (20%) were also observed with incidence rates indicated in parentheses. In the RT group, Grade 3 and 4 hematological side effects (3%), mucositis (24%), pharyngeal/esophageal (19%), laryngeal (16%), dermatological (9%) side effects were noted as indicated. In this group nausea and vomiting was not observed.[29] According to the long-term results of the same study, the most frequent long-term side effects for all three groups were related to subcutaneous tissue, salivary gland, pharynx/esophagus, and larynx. The incidence rates of 10-year cumulative grade 3-4 side effects were also determined for patients receiving CT+RT (31%), concomitant CRT (33%), and RT (38%) protocols.[41] In this study, the incidence of side effects including mucositis, nausea-vomiting, weight loss, neutropenia, and anemia was higher in patients who received CRT rather than RT. The incidence of xerostomia was similar in patients who received RT or CRT.

The limitations of the present study include its short follow-up period, retrospective design of the study and the scarce number of patients included in the study.

Conclusion

In the present study, 3-year overall survival rate was 83% in the early, and 61% in the locally advanced stage disease, while the independent prognostic factors were hemoglobin levels, weight loss, T stage, and comorbidity. The frequency of treatment-associated side effects was higher in patients who received CRT relative to RT.

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