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Radiation Therapy for Early Glottic Carcinoma: Factors Influencing the Outcome

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ABSTRACT

To evaluate the influence of mid treatment hemoglobin level with the other prognostic factors on the outcome in patients with Tis-T1N0 glottic carcinoma treated with radiotherapy (RT). Between October 1995 and December 2008, a total of 84 patients diagnosed with Tis-T1N0 glottic carcinoma were treated with definitive RT. The influence of tumor, treatment, and patient-related factors on local control (LC) and overall survival (OS) were analyzed. The median follow up time was 30 months (ranges, 4-180 months). Local and/or locoregional relapse was observed in 11 patients (13%) (3 locoregional and 8 local). The estimated 5- and 10-year LC and OS rates were 87%, 85%, and 87%, 70% for the entire study group, respectively. Multivariate analyses revealed that older age (≥50 years) and the use of wedge-filter were found to be favorably influencing the LC (p= 0.025 and p= 0.030, respectively). Mid treatment hemoglobin level more than 13 g/dl was determined statistically significant for improving both LC and OS (p= 0.011 and p= 0.021). Older age and use of wedge filter were found to be independent prognostic factors for LC. Mid treatment hemoglobin level of more than 13 g/dl was correlated to superior LC and OS rates. Monitoring the changes of hemoglobin levels during therapy has to be considered to improve the outcome.

Keywords: Glottic carcinoma, Radiotherapy, Prognostic factors, Hemoglobin

ÖZET

Erken Glottik Karsinomada Radyoterapi: Sonuçları Etkileyen Faktörler

Radyoterapi (RT) ile tedavi edilen Tis-T1N0 glottik karsinomlu olgularda hemoglobin değeri ve diğeri prognostik faktörlerin tedavi sonuçlarına üzerine etkisini değerlendirmek. Ekim 1995 and Aralık 2008 tarihleri arasında Tis-T1N0 glottik karsinom tanılı 84 olgu definitif RT ile tedavi edildi. Tümör, tedavi ve hastaya bağlı faktörlerin lokal kontrol (LK) ve toplam sağkalım (TS) üzerindeki etkileri analiz edildi. Ortanca takip süresi 30 ay idi (sınır 4-180 ay). Lokal-bölgesel ve/veya lokal nüks 11 olguda (%13) izlendi (3 lokal-bölgesel ve 8 lokal). Tüm çalışma grubu için beklenen 5- ve 10-yıllık LK and TS oranları sırasıyla %87, %85 and %87, %70 idi. Çok değişkenli analizde geç yaşın (≥50 years) ve tedavide wedge kullanımının LK'u olumlu etkilediği ortaya çıktı (p= 0.025 ve p= 0.030). Tedavi ortasındaki hemoglobin değerinin 13 g/dl üzerinde olmasının ise hem LK hem de TS'ı istatistiksel olarak iyileştirdiği saptandı (p= 0.011 ve p= 0.021). Geç yaş ve wedge kullanımı LK için bağımsız prognostik faktörler olarak bulundu. Tedavi ortası hemoglobin değeri 13 g/dl'nin üzerinde olması daha üstün LK ve TS ile uyumluydu. Hemoglobin değerlerinin tedavi sırasında takibi ile aneminin önlenmesi tedavi sonuçlarını iyileştirmesi açısından dikkate alınmalıdır.

Anahtar Kelimeler: Glottik karsinoma, Radyoterapi, Prognostik faktörler, Hemoglobin

INTRODUCTION

Treatment options for early stage glottic carcinomas include conservation surgery, laser excision, and radiotherapy (RT).[1-5] While all these treatment approaches result in high local control (LC) rates, voice quality has been the most considered subject in recent years. It has been suggested that RT provides a high control rate associated with a better voice quality than the surgical procedures.[2] On the other hand, with RT being the initial treatment of choice, surgery can be reserved as a salvage option for treatment failures by allowing increased local control rates.[2,6,7] Although the high rates of local control and long term survival can be achieved by RT, there are various factors affecting the outcomes including hemoglobin. In spite of the discrepancies in these factors being documented widely in previous studies[6-16], as of today, there have not been published prospective randomized studies nor meta-analyses.

In current study, patterns of failures, the impact of mid treatment hemoglobin (midHb) within the other prognostic factors on local control and overall survival were evaluated as a single-center experience.

PATIENTS AND METHODS

Patients: Between October 1995 and December 2008, a total of 92 previously untreated patients diagnosed as Tis-T1N0 glottic carcinoma, were treated with definitive RT at the Uludag University Faculty of Medicine. Eight patients were lost to follow up and excluded from the study. The study was approved by the university ethic committee and all the patients were provided inform consent. The decision on whether to refer the patient to RT was due to the discretion of the surgeon, patient's choice and compatibility.

All 84 patients had diagnosis with histopathologically squamous cell carcinoma. Eighty male (95%) and 4 female (5%) patients were included in this retrospective study. The median age was 58 years (range, 32-85 years) and 34 of the patients (40%) were older than 50 years old. There were 10 (12%), 54 (64%), and 20 (24%) patients with Tis, T1a, T1b tumors, respectively. Fifty-three patients (63%) had well differentiated, 24 (28%) moderately differentiated, and 4 (5%) poorly differentiated tumors. In three of them, differentiation could not be verified. Patient and tumor characteristics are presented in Table 1.

Table 1. Patient and tumor characteristics

Characteristics	No. patients	%
Sex		
Male	80	95
Female	4	5
Age (years)		
<50	51	60
≥50	34	40
Smoking history		
Yes	69	82
No	16	18
Stage		
T is	10	12
T1a	54	64
T1b	20	24
Histologic differentiation		
Well	53	63
Moderate	24	28
Poor	4	5
Undetermined	3	4
Anterior commissure involvement		
Yes	25	30
No	59	70
Vocal cord localization		
Right	37	44
Left	32	38

Staging was obtained with direct laryngoscopy with biopsy and/or computed tomography (CT) of larynx. Pretreatment evaluation consisted of complete blood counts, biochemical tests, and chest x-ray. The hemoglobin levels at the beginning of RT (preHb), midtreatment of RT (midHb), and end of RT (postHb) were also recorded (Table 2). The response to treatment was assessed at the first and two months after the end of RT, and a clinically complete response was documented in all the patients by laryngoscopy.

Treatment: Patients were treated with a planned, continuous course of RT with definitive intent.

Table 2. The distribution of the Hb levels

	<13 g/dl	(%)	≥13 g/dl	(%)	Median (range)
PreHb	10	11	74	89	14 (9-16 g/dl)
MidHb	11	13	73	87	14 (10.3-16 g/dl)
PostHb	14	17	70	83	14 (10-16.8 g/dl)

Hb: Hemoglobin

Elective nodal RT and elective neck dissection were not performed in any of the patients. All patients were evaluated with the treatment planning CT scan. RT was delivered with a parallel-opposed lateral 6 MV photon beams by linear accelerators (Siemens Mevatron KD2 and MD2). Wedge filter was used to obtain a homogenous dose distribution in 51 (61%) of the patients regarding the involvement of anterior commissure and anterior portion of the cord. The median time between the date of diagnosis and the first date of therapy was 25 days (range, 3-133 days). In one patient, the reason for admitting RT 133 days after diagnosis was related to patient incompatibility. A median dose of 63 Gy (range, 60-70 Gy) was given in 2-2.1 Gy/fraction over a median period of 42 treatment days (range, 30-57 days). Seven patients were given a break due to the holidays or technical problems during the treatment.

Following the completion of RT, evaluation was made by laryngoscopy and physical examination monthly in the first year, and less frequently thereafter. Computed tomography of the larynx was performed every six months for two years.

Statistics: All statistical calculations were accomplished using the SPSS-13 software. The primary end point was local control and overall survival (OS) and they were assessed using Kaplan-Meier method. Outcomes were analyzed from the end of RT to the last follow up or to the date of the first recurrence for LC, and from the date of diagnosis to the last follow up or to the date of death for OS. The mean survival analysis table was processed for the 5- and 10-years survival rates. Univariate analyses were made by using the log-rank test, and in the multivariate analyses, Cox regression analysis was used. The results were considered statistically significant at the level of $p \leq 0.05$. The variables analyzed in this study included patient, tumor, and treatment characteristics.

RESULTS

Follow-up and survival: The median follow-up period was 30 months with a range of 4-180 months, and the median OS was 69.5 months with a range of 2-180 months. The 5- and 10-year OS rates were calculated as 87% and 70% for the entire group. At the time of analysis 18 of the patients were deceased. While 7 patients (40%) died of the disease, the rest of the patients died of intercurrent diseases (4 had myocardial infarction, 3 cerebrovascular disease, 2 lung cancer, 1 prostate cancer, and 1 gastrointestinal bleeding). Lung metastases developed in one patient and second primary tumor occurred in 8 patients (10%).

Local control: The estimated 5- and 10-year LC rates for all 84 patients were 87% and 85%. A total of 11 patients had local recurrences during the follow up and all recurrences were confirmed by biopsy. Three patients developed recurrent disease both at the primary site and the lymph node (regional) and 8 patients (73%) developed recurrent disease at the primary site alone with the median time to recurrence of 15 months (range, 3-67 months). Six of 54 patients with stage T1a (11%), and 5 of 20 patients with stage T1b (25%) revealed recurrent disease. Of the recurrences, 4 patients had well differentiated (36%), 5 had moderately differentiated (45%), and one had poorly differentiated tumor (9%). It wasn't observed any recurrences in the female patients and the patients with stage Tis disease. Only 4 patients had anterior commissure involvement (ACI) through all the recurrences and 4 lo-

Table 3. Factors that influenced the local control, univariate analysis

Factors (n)	**5 year LC %1**	**10 year LC %**	**Survival** (mean±SD)	**p**
Sex				
Male (80)	87	84		0.421
Female (4)	100	100	–*	
Age (years)				
<50 (51)	71	71	127±18.8	0.017
≥50 (34)	92	89	148±5.64	
Smoking history				
Yes (69)	85	83		0.182
No (16)	100	100	–*	
Smoking habits				
<30 cigarettes/day (42)	94	90	150±5.8	0.034
≥30 cigarettes/day (30)	76	76	136±13	
<20 years (8)	95	95	146±7.7	0.325
≥20 years (64)	85	83	150±7.7	
Stage				
Tis (10)	100	100	–*	
T1a (54)	90	87		0.094
T1b (20)	73	73		
Histologic differentiation				
Well (53)	92	92	163±6.2	
Moderate (24)	83	75	113±11	0.881
Poor (4)	75	75	93±25	
ACI				
Yes (25)	81	81	145±6.5	0.401
No (59)	89	87	146±14.2	
Localization				
Right (37)	89	89	158±8.9	
Left (32)	86	81	138±10	0.736
Bilateral (15)	85	85	126±12.2	
Wedge filter				
Yes (51)	94	91	128±11.6	0.038
No (33)	76	76	164±6.2	
Overall treatment time				
<45 days (67)	88	86	155±6.7	0.505
≥45 days (17)	78	78	133±18.7	
Treatment interruption				
Yes (7)	88	86	154±6.7	0.912
No (77)	78	78	142±19.4	
MidHb				
<13g/dl (11)	64	64	89±17.2	0.012
≥13 g/dl (73)	91	89	160±6.2	

* Survival mean value was not able to be evaluated regarding the patients had no recurrences at the time of analysis.
LC: Local control, SD: Standart Deviation

Table 4. Factors that influenced the overall survival, univariate analysis

Factors (n)	**5 year OS** (%)	**10 year OS** (%)	**Survival** (mean±SD)	**p**
Sex				
Male (80)	86	72	140±8.4	0.783
Female (4)	100	67	141±13.3	
Age (years)				
<50 (51)	76	76	141±13.3	0.697
≥50 (34)	89	68	133±7.3	
Smoking history				
Yes (69)	85	71	135±13.4	0.677
No (16)	100	67	139±8.8	
Smoking habits				
<30 cigarettes/day (42)	88	66	130±8.3	0.590
≥30 cigarettes/day (30)	85	79	151±11.8	
<20 years (8)	81	59	119±14.1	0.436
≥20 years (64)	88	73	143±8.8	
Stage				
Tis (10)	100	86	135±11.6	
T1a (54)	85	66	138±9.6	0.507
T1b (20)	84	75	116±12.5	
Histologic differentiation				
Well (53)	90	75	151±8.7	
Moderate (24)	81	56	111±11.7	0.281
Poor (4)	75	75	97±23.4	
ACI				
Yes (25)	82	74	137±7.3	0.327
No (59)	89	69	129±16.2	
Localization				
Right (37)	83	83	153±10.2	
Left (32)	88	62	129±9.8	0.644
Bilateral (15)	93	72	120±13.9	
Wedge filter				
Yes (51)	88	74	116±14.4	0.228
No (33)	80	51	148±8.6	
Overall treatment time				
<45 days (67)	87	75	143±8.5	0.357
≥45 days (17)	82	77	106±20.3	
Treatment interruption				
Yes (7)	60	60	140±8.4	0.951
No (77)	87	70	104±43.8	
MidHb				
<13 g/dl (11)	66	41	92±17.5	0.002
≥13 g/dl (73)	90	77	153±7.5	

OS: Overall survival; SD: Standart Deviation

cal recurrences were observed in the patients who treated with using wedge filter in RT field.

Of all the recurrences, 36% were seen within the 6 months, 45% within the first year, and 81% within the second years. A second recurrence after salvage surgery occurred in one patient with stage T1a, poorly differentiated tumor at the initial site. Surgery was the first attempt for salvage therapy in all recurred patients. While the most common type of salvage approach was total laryngectomy (81%), all but one patient underwent elective and/or therapeutic neck dissection within the same procedure. Re-irradiation was considered in 3 patients after surgery for the persistent tumor. Four of the recurred patients (36%) were alive without any evidence of disease at their last follow up.

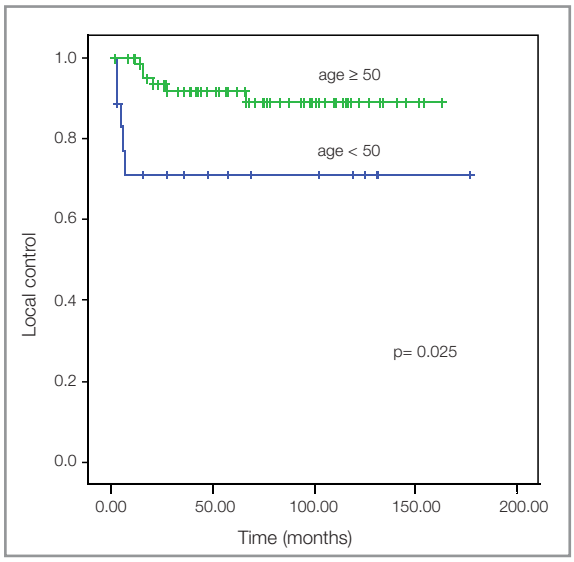

Figure 1. Local control by age

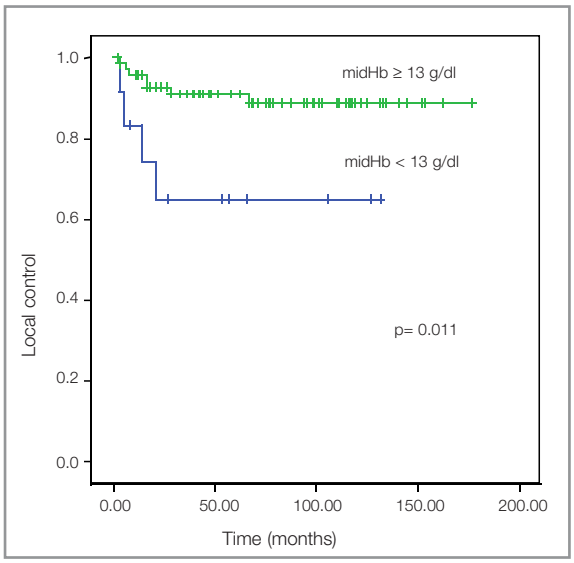

Figure 2. Local control by midHb level

Prognostic factors: Univariate analyses of LC and OS are shown in Table 3 and Table 4. Smoking less than 30 cigarettes per day was found favorable for LC (p= 0.034). The patients more than 50 years old had significantly better LC (p= 0.017) (Figure 1). The overall treatment time (<45 days vs. ≥ 45 days) and treatment interruption affected neither LC nor OS. Use of wedge filter was significantly found to improve the 5- and 10-year LC compared to the patients treated without wedge filter (94% and 91% vs. 76% and 76%, p= 0.038). The influence of pre-mid and post hemoglobin levels on LC was analyzed and midHb ≥13 g/dl were only determined statistically significant on 5 and 10 year LC compared to midHb < 13 g/dl (91%, 89% and 64%, 64%, p= 0.012) (Figure 2). The similar outcome was obtained for the 5 and 10 year OS; 66%, 41% for midHb level <13 g/dl and 90%, 77% for midHb ≥13 g/dl (p= 0.002) (Figure 3). There was no statistically difference between the patients regarding the stage and histopathological grading in the univariate analysis for LC and OS.

When multivariate analysis was performed for the age, stage, histologic differentiation. ACI, wedge, smoking habits, treatment break, overall treatment time and midHb, age at the diagnosis (≥50 years old) and usage of wedge filter in treatment were found to be efficient on improving LC (odds ratio [OR]= 6.511, 95 % confidence interval [CI]= 1.265-33.522, p= 0.025 and OR= 6.823, 95% CI= 1.195-38.969, p= 0.031, respectively). As a similar outcome of the univariate analyses for midHb, it was statistically demonstrated significant as a predictive factor for both LC and OS (OR= 9.519, 95% CI= 1.660-54.575, p= 0.011 and OR= 4.083, 95% CI= 1.239-13.453, p= 0.021, respectively).

Toxicities: Sixty-two out of 84 patients (74%) did not develop any mucosal reactions. Grade 1 and 2 skin reactions were seen in 48 (57%) and in 21 (25%) of the patients. Edema was assessed after the completion of RT through the first, third, and sixth months. First and third month evaluations showed high rates of edema (30 and 26%, respectively) compared to the following visits. No patient had a complication requiring total laryngectomy.

DISCUSSION

The main purpose of the early stage glottic carcinoma treatment is to cure the disease with minimal side effects, and to provide a better voice quality as much as possible. While both the surgery and RT are equally effective modalities, RT is widely preferred as the initial treatment of choice in many centers due to a well-preserved voice.[1,3,6-10,17-20] Despite the high rates of LC with RT, tumor recurrences are still being observed in a small group of patients which might be related with the prognostic factors. Until now, there have not been any publis-

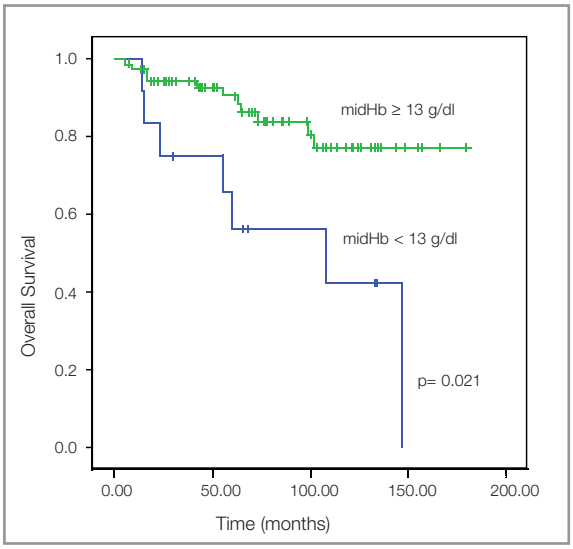

Figure 3. Overall survival by midHb level

hed meta-analyses or randomized trials about the prognostic factors in the early stage glottic carcinoma; and the ones in the literature are reports with conflicting results and conclusions.

The 5- and 10-year LC rates were 87% and 85%, and the 5- and 10-year OS rates were 87% and 70% for the entire group; being correlated with those described in the literature.[13,20-23]

Local recurrence was the initial site of all recurrences. Isolated regional recurrence was not seen in any of the treatment failures. The median time to recurrence was 15 months, which is in alignment with the previously published series.[24,25]

While several authors concluded the fact that age was not a prognostic factor for LC.[6,7,22,23,26] In a study by Gultekin et al., showed a significantly improved difference on LC in the younger patients[27], however, Sjogren et al., did not observe any influence on OS, expecting poorer survival with younger ages. [21] In the present study, older patients appeared to have better prognosis on LC without affecting the overall survival. This finding might be a predictive factor for the agressivity of tumor in the younger laryngeal cancer patients as in the breast cancer. On the other aspect, regarding the small number of the patients it is difficult to advocate this result.

While gender was reported as not having any statistically significant impact on the outcomes in previous series, female patients had better LC rates than male patients.[6,21,22] Even though being female seemed to be a favorable factor for LC and OS, it is highly likely to be related to the lack of the number of female patients in most of the studies including the present study.

Many studies have documented high LC rates in the patients with lower stages.[6,19,24,26] Franchin et al. also showed a significant correlation between the stage and the disease free survival.[26] In contrast to those results, stage was not demonstrated as a prognostic factor influencing LC, however, the 5-year LC rates were 100%, 90%, and 73% for Tis, T1a, and T1b disease, respectively, in present study (p= 0.094). This could be related with most of the studies included also T2 stage patients in their analysis but we did not. In similar, several authors reported no significant effect of T1a and T1b stage on LC, but the results were superior for T1a stage.[1,23,28]

The influence of histological differentiation on LC is another debating subject. Mendenhall et al. showed that poorly differentiated tumors were observed with poorer LC29, however, this observation was not supported by all the authors.[6,7,20,23,26] Consistently, we did not show any relationship between the differentiation and the LC.

Findings for ACI have still been controversial since it would be an indication for surgery rather than RT. While ACI has been indicated as a poor prognostic factor for LC, regarding the proximity to the thyroid cartilage[2,6,7,25,29], other studies failed to find a significant correlation.[2,28] In a retrospective study by Fein et al., it was not demonstrated any differences between the patients who had ACI and the ones who did not have ACI with respect to LC 30. Similarly, in this current study, ACI was not found to be a predictive factor for local recurrence in both univariate and multivariate analyses.

In most of the studies, fraction size was emphasized to be an important factor in the LC of the glottis cancer.[7,24] Kim et al. reported superior LC rates in patients treated with higher daily fraction sizes (2 Gy per fraction).[9] The effect of prolonged treatment time has also been reported to be associated with locoregional failure by several authors.[7,22,26] These results are constantly compatible with the behavior of tumor cells related to the repopulation. In a large series of 1350 patients, Wang et al. showed prolonged treatment time adversely affecting local tumor

control of both advanced glottic and supraglottic lesions but to a lesser degree for the early tumors.31 In contrast, Fein and Selek et al. did not find a significant correlation between the overall treatment time and the LC.[30,31] Based on the same aspect, it has been well known that prolonging overall treatment time due to the interruptions had a negative impact on LC.[8,32] It is very obvious that avoiding prolonged treatment time would lead to better LC rates.[8,18,20] In our study, the fraction size was homogenous and therefore we did not analyse it as a prognostic factor. Furthermore, overall treatment time differed due to the interruptions during treatment. Local control and OS rates were demonstrated to be higher for patients who completed RT in less than 45 days compared to those who completed more than 45 days; however, it did not reach the significant level.

The interval between diagnosis and the start of RT was investigated as a prognostic factor; however, it did not appear to influence LC in some series.[6,26] Our study is in agreement with those in the literature.

A few of the published series up until now have addressed the influence of the use of a wedge filter on LC. While Van der Voet et al. showed a decrease on LC in the use of wedge filter, Chatani et al. stated that wedge filter was useful for avoiding adverse effects while providing a benefit on LC rates.[33,34] In a study of Jin et al., local failure was found to be high likely related with not using wedge filter in the patients who had ACI.[35] LC was found significantly better in the patients who were treated with using wedge filter in the current study (p= 0.038). We assume that this result might be related with two factors; the first one is, presence of small number of patients in our study and the second one is, the status of the patients with ACI progressed poorly who we did not prefer to use wedge filter.

Smoking was evaluated as a prognostic factor in the study of Marshak et al.[6] and smoking more than 30 packs per year was shown a significant unfavorable factor for LC. Fein et al. also investigated the effect of the tobacco use on the LC but failed to show any relationship.[10] In the present study, we analysed the use of cigarette per day and found more than 30 cigarettes per day was related to a decreased LC (p= 0.034).

The prognostic value of Hb has been evaluated in a few of the studies including cervix, pharynx, and larynx carcinoma; and preHb level was mostly found efficacious on outcomes.[10,36] Fein et al. reported that preHb levels of more than 13 g/dl, had a major favorable effect on LC and survival in patients with glottic carcinoma.10 Grantz et al. emphasized a significant relationship between preHb and the LC alone.[37] Overgaard et al. demonstrated preHb as a prognostic factor with respect to LC in supraglottic larynx carcinoma.[36] On the other hand, in a study by Van Acht et al., anemia at the beginning and at the end of RT within any drop in Hb level during RT were found to be significant factor for disease-free survival.[38]

Despite of the prognostic significance of preHb level was not shown in Jin et al.'s study, they found an association between Hb drop with LC rate.[34] It appeared there have been many series experiencing Hb effect on LC and OS in glottic carcinoma, however, most of them focused on either the influence of preHb level[10,28,37] or decrease in Hb level during therapy.[8,35,37] In this study, as an exception, only Hb level midtreatment of RT (≥13 g/dl) influenced LC and OS.

CONCLUSION

The results of this retrospective study supports the literature, advocating radiation therapy as an initial and highly curable treatment option in patients early glottic carcinoma; however, the outcomes are related to variable factors. Older age and use of wedge filter appeared to be favorable prognostic factors for LC in our study. Mid treatment hemoglobin level of more than 13 g/dl was also correlated to superior LC and OS rates. In our opinion, an attempt to maintain Hb level higher during therapy would ensure high LC rates.

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