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Outcomes of radiotherapy in early stage glottic laryngeal carcinoma: a single center experience

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Abstract

Our aim was to determine the treatment outcomes and the prognostic factors affecting local control in early stage glottic carcinoma (ESGC) treated with definitive radiotherapy (RT). Between April 2003 and May 2015, 76 patients with ESGC were treated at Inonu University Hospital. There were 58 patients with T1a, 7 T1b and 11 with T2 tumors. Twenty-two patients were treated with conformal radiotherapy, 31 patients were treated with conventional RT and 23 patients were treated with intensity modulated radiotherapy as initial treatment. During a median follow-up of 51 months (range 6-136), 11 patients had failures. Five year overall survival rates were 73.7% in T1 and 81.8% T2. Local control rate was 85.5% in our patients. Patients who were over 61 years had significantly lower local control ($p = 0.042$). One patient treatment was interrupted because of grade 3 edema. One patient had grade 3 dermatitis, 2 patients grade 3 mucositis and 4 patients grade 3 edema, respectively. Our results suggest that curative radiotherapy is an effective treatment modality in ESGC without increasing toxicity. Age proved to be the only independent prognostic factor affecting local control after primary radiotherapy according to the results of this study.

Keywords: Glottic cancer, radiotherapy, treatment, side effect

Introduction

Early stage glottic carcinomas are highly curable disease by using radiation therapy and surgery [1]. The goal of treatment is to accomplish the best local control with the least toxicity. Voice preservation is usually admitted to be better following radiotherapy (RT) alone compared with any surgical modalities, based on retrospective data [2,3].

Currently, RT with surgical salvage is the preferred treatment option. RT provides successful treatment outcomes with local control ratios of 80-95% and disease-specific survival of 92-97% in some studies [4,5]. Rendering high cure ratios and what is usually accepted as good voice quality, irradiation remains the cornerstone of treatment in many institutions [6].

Recent trends in RT for early glottic carcinomas include a better understanding of the role of fractionation and RT techniques which considers both, the dose administered at each treatment and the frequency of treatments. Selection of the initial treatment for early glottic carcinomas are based on patient factors and availability of expertise and suitable support and rehabilitation services [7-9].

In this study, we aimed at assessing the patterns of failure and prognostic factors, including RT techniques, lower conventional doses and anterior commision extension in the treatment of early-stage glottic carcinomas.

Materıal and Methods

Patients

Seventy-six patients with previously untreated T1N0 and T2N0 biopsy proven squamous cell carcinoma of the glottic larynx, who were treated with RT alone at the Turgut Ozal Medical Center, Inonu University, Malatya, Turkey, between April 2003 and May 2015, were involved in this retrospective study. Details of patiens and tumor characteristics are shown in Table 1.

All of the patients had well-differentiated tumors. Male-to-female rate was 74:2, and median age 61 years (range: 22–94 years). All patients were evaluated in a multidisciplinary approach in head and neck cancer

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council. Our patients underwent complete clinical examination and panendoscopy. Patients, who had anterior commisure involvement were evaluated with computed tomography (CT). When indicated, magnetic resonance imaging (MRI) and chest X ray was also performed. Tumor staging was done according to the 2002 version of the AJCC (American Joint Committee on Cancer) classification criteria. In our institution RT alone is generally chosen for early stage glottic cancer and surgery is performed when the patients refuses the RT and also when the tumor developed local recurrence.

Table 1. Patients characteristics

	n	%
Age (median:61; gap=22-94)		
≤61	38	50
>61	38	50
Gender		
Male	74	97
Female	2	3
Histopathology		
Epidermoid	76	100
Other	0	-
Smoking		
Yes	74	97
No	2	3
Localization		
Right cord	38	50
Left cord	28	37
Bilateral cord	10	13
Anterior commissure extension		
Yes	25	33
No	51	67
Subglottic extension		
Yes	6	8
No	70	92
Supraglottic extension		
Yes	7	9
No	69	91
T-classification		
T1a	58	76
T1b	7	9
T2	11	15
RT fraction dose		
2 Gy/day	66	87
2.25 Gy/day	10	13
Total RT doses		
<66 Gy	17	22
≥66 Gy	59	88
Overall treatment time (38-55 days)		
<46	42	55
≥46	34	45
Treatment gap		
<5 days	74	97
≥5 days	2	3
Treatment device		
LINAC	22	29
Cobalt-60	31	40.5
Helical Tomotherapy	23	30.5

Radiotherapy

Our patients were treated with external beam radiotherapy using high energy photons. Treatment characteristics and RT techniques are summarized in Table 2. Patients were immobilized using a thermoplastic mask, and CT images were acquired in the treatment position. The volume treated covered the larynx only, allowing for movement, and excluded cervical lymph nodes. The typical borders for patients would be the prevertebral fascia posteriorly, below the hyoid bone superiorly, below the cricoid cartilage inferiorly, and at the fall-off (1–2 cm) anteriorly. Especially, patients with anterior commissure involment were carefully considered and planned to obtain a homogenous dose distribution. A median dose of 66 Gy (range, 58–70 Gy) was given over a median period of 46 days (range, 38–55 days). Most of the patients were treated 5 days per week with 2 Gy daily fractions. Some patients were treated with 2.25 Gy daily fractions. Concomitant or adjuvant chemotherapy was not administered for all patients.

Table 2. Local control rates of our patients

	local control (%)	p
Age		
≤61	94.7	0.042
>61	78.9	
Gender		
Male	86.5	<0.001
Female	100	
Localization		
Single cord	88	0.492
Bilateral cord	80	
Anterior commissure extension	92	
Yes	84	0.352
No		
Subglottic extension		
Yes	100	0.320
No	86	
Supraglottic extension		
Yes	71.4	0.205
No	88.4	
T-classification		
T1	87.7	0.594
T2	81.8	
RT fraction dose		
2 Gy/day	84.8	0.187
2.25 Gy/day	100	
Total RT doses		
<66 Gy	84.7	0.314
≥66 Gy	94	
Overall treatment time (days)		
<46	95	
≥46	79.4	0.221
Treatment gap		
<5 days	86.5	0.577
≥5 days	100	
Treatment device		
LINAC	86.3	0.052
Cobalt-60	77.4	
Helical Tomotherapy	100	

After completion of radiotherapy, all patients were evaluated by using video laryngoscope and physical examination every 3 months for the first 2 years, every 6 monts thereafter, for a total of at least 5 years by radiation oncologists, medical oncologists and head and neck surgeons in head and neck cancer council. When recurrence was suspected, biopsy was performed for confirmation. Patients developing local recurrence were treated with salvage surgery.

Statistical Analyses

All statistical analyses were conducted using SPSS version 17.0.0 (SPSS Inc., Chicago, IL, USA). Time to event was calculated from the first day of RT to the event of interest. Local control-free survival ran from the first day of treatment to the date of first recurrence.

Follow-up was calculated in months from the first day of radiotherapy to the date of the last follow-up or time of death. For overall survival, the event of interest was death due to any cause, and for recurrence ratios, the event of interest was the confirmation of local recurrence based on biopsy results. The Kaplan Meier method was used to plot survival and recurrence curves. Univariate analysis was carried out by means of log-rank testing. Multivariate analyses were done using the Cox stepwise-regression analysis to determine the independent contribution of each prognostic factor.

Results

Median follow-up was 51 months (range, 6-136). Overall 5-year survival were 55 months in all patients (Figure 1). Five year overall survival rates were 73.7 % in T1 and 81.8 % T2. Local control rate was 85.5 % in our patients. Five year local control rate was 71.4 % (Figure 2).

A total of 13 patients died, these deaths were due to secondary cancers or to intercurrent disease and no deaths were related to laryngeal cancer. The 5-year local control rates by initial radiotherapy were 71.4% in our patients. Local recurrences developed in 11 (14%) patients during the follow-up period. All recurrences were confirmed by biopsy. Among these patients, the initial T stage was T1a in 8 cases and T2 in 3 cases. Six patients were diagnosed with anterior commisur involvement and 4 patients with radiation doses under 66 Gy. Univariate analyses revealed that prognostic factors negatively influencing local control were patients age who were over 61, female gender. In multivariate analysis, no parameters were found to be of significant influence on recurrent disease. All the 11 patients who developed local recurrences underwent salvage surgery for local control. Total laryngectomy was performed in all patients. No reirradiation was proposed to the patients who developed recurrence. No deaths were related to laryngeal cancer. The ultimate larynx preservation rate was, therefore, 85.5 %.

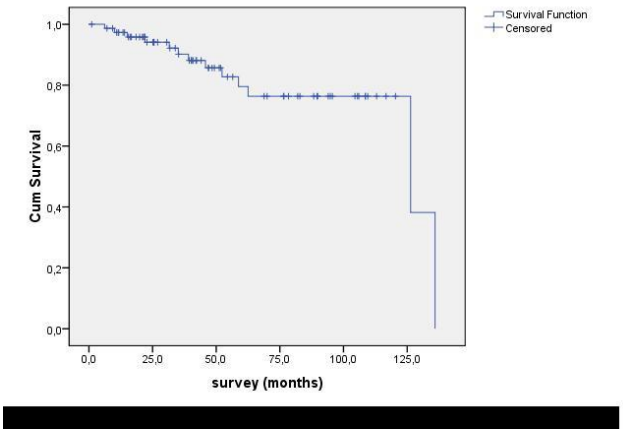

Figure 1. Overall Survivall

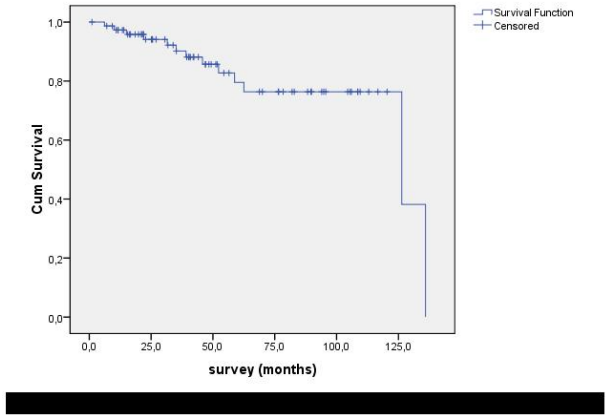

Figure 2. 5-year disease-free survivall

Acute adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0. Radiation mucositis was observed in 58 patients (Grade 1-2: 56, Grade 3: 2), and radiation dermatitis was observed in 50 patients (Grade 1-2: 49, Grade 3: 1), edema was observed in 56 patients (Grade 1-2: 52, Grade 3: 4). One patient treatment was interrupted because of edema. No significant late toxicity was observed. During a median period of 51 months (range: 6–136 months) 4 patients developed a second cancer. Three patients developed lung cancer and 1 patient cholangiocarcinoma. Salvage treatment for those patients is composed of surgery in 2, curative RT in 2 and chemotherapy in 3 patients.

Discussion

RT is generally used as a primary method in the treatment of early glottic carcinoma. Both RT and conservative surgery (cordectomy, laser microsurgery or partial laryngectomy) seem to be equally effective methods with

regard to local control and survival although not confirmed by any randomized comparison [10-12]. However, voice quality, preservation organ function and structure is presented to be better after RT. This superiority is usually observed by the patient himself, by the family, and by the physician. In our instituion patients with early stage laryngeal cancers generally prefer RT because of the voice quality.

Five and 10 years local control rates are similar with RT and surgery in the literature. Generally, local control rates after RT is about 80-93% for T1 tumors and 52-88% for T2 tumors [13-15]. In our study, 5 years local control rate is 71.4%.

Numerous reports regarding the treatment of early stage glottic cancer have evaluated some prognostic factors, i.e., tumor volume, stage, tumor kinetics including p53 status, histological differentiation, intrinsic radiosensitivity, continued smoking during and after RT and hypoxia, low hemoglobin levels, poorly differentiated tumors, dose per fraction, total dose, overall treatment time, field size, beam energy, radiation technique, and anterior commissure involvement [3,16-25]. These factors were not constantly presented to have a prognostic influence by all authors. At the moment, no systematic review or meta-analysis of these data has been reported.

Previous studies reported anterior commisure involvement as one of the poorest independent prognostic factors, as determined using multivariate analysis. They concluded that anterior commisure involvement is a predictor of poor response to RT in terms of local control, possibly because the treatment strategy was underpowered [7,26-27].

It was showed that local-regional control increased when the total radiation dose was given in higher fractions and thus a shorter time. Similar outcomes were confirmed in the prospective, randomized trials. In two randomized studies, it was claimed that overall treatment time was the determinant factor in the time-dose relationship and both recommend the use of fraction sizes higher than that of the conventional 2 Gy to reduce overall treatment time. Yamazaki et al. argued that use of 2.25 Gy fractions with a shorter overall treatment time for early stage larynx cancer showed superior local control compared with conventional use of 2 Gy fractions without adverse reactions from the greater fraction [28,29].

T-classification is a well-known prognostic factor in glottic cancer, and in all series T1 tumors do better than T2 in terms of local control: at 5 years it ranges between 80–95% for T1, and 60–80% for T2 [16]. In the present study, the 5-year local control was 75%, and 0% for T1, and T2 tumors, respectively. Our patients who had T2 tumors did not survive to 5 years, so our T2 patients 5-year local control was 0%.

The fact that age was not prognostic for overall survival, although the expected trend was seen for older age groups, was probably due to the relatively poor survival of the youngest age group (<50 years). This is also indicated by the fact that age, on the basis of the youngest age group, was a significant factor for decreased disease-specific survival in univariate analysis [4]. In this study, univariate analysis showed only patients under 61 years to be predictive of disease-free survivall.

Gender was reported by some to have an impact on local control, while others did not find it to be a significant factor whether in glottic cancer or in other tumors of the head and neck region. There is no clear-cut explanation for this finding [30]. In present study, female gender had better local control, but we think this is not important, because there was only 2 female in our series.

In order to ameliorate the local control especially in T2 tumors, either altered fractionation or increased total dose was proposed. Le et al. reported that local control was influenced by increasing the total dose only in T2 and not in T1 tumors [31,32].

In conclusion, this study was a retrospective analysis performed in 76 consecutive patients with early glottic cancer treated with definitive RT. In multivariate analysis, we found no factor prognostic for disease-specific survival, and only age was prognostic for overall survival. The size of our series may justify these results. In spite of this, we can conclude that, for early-stage glottic cancer, RT alone gives an excellent outcome with accepted good voice quality.

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