DOI: 10.29409/ijcmg.v17i2.400

Cancer Research

Iraqi Journal of Cancer and Medical Genetics

10-Year Survival and Voice Preservation after Definitive Radiotherapy for T1--T2 Glottic Laryngeal Squamous Cell Carcinoma in a Region of Conflict: A Single Institution Retrospective Report

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Abstract

Background and purpose: Early-stage laryngeal cancer represents a large proportion of cancer patients treated with definitive radiotherapy (RT). This study aimed to evaluate the outcomes of radical RT for patients with T1-T2 cN0 laryngeal cancer at an institution in a developing country without adequate infrastructure and to address overall survival and voice preservation. Research has shown that radical RT should be performed as soon as possible after the diagnosis of early-stage laryngeal cancer if RT is selected as the main treatment. We evaluated the efficacy of this type of treatment despite the delay in its initiation.
Methods: We reviewed the medical records of patients who had cT1-cT2/cN0 squamous cell carcinoma of the larynx treated with definitive RT from June 2009 to June 2020 and who had not undergone previous surgical treatment or chemotherapy.
Results: The median age of the study population was 63 years, with a male predominance (94%). Histologically, all laryngeal cancers were confirmed to be squamous cell carcinomas, and 86% were glottic squamous cell carcinomas. The mean time from diagnosis until initiation of RT was 120 days (4 months). The median follow-up period was six years. Among the 53 patients enrolled, the 2-, 3- and 5-year survival rates were 83%, 71% and 66%, respectively, during the follow-up period. The majority of the surviving population (97%) had good voice preservation.
Conclusion: Despite these challenges, the results are promising. Definitive RT achieved an acceptable cure rate and voice preservation in patients with cT1-2 laryngeal carcinomas.

Keywords: *Delays in radiotherapy, developing countries, early-stage laryngeal cancer*

Introduction

Laryngeal squamous cell carcinoma, the most common histologic type, arises on true vocal cords and results in voice changes at an early stage of the disease, which has a low incidence of positive lymph nodes for T1--2 glottic cancer due to sparse lymphatic drainage [1]. Evidence from previous studies supports the use of larynx-preservation approaches for appropriately selected patients without compromising survival [2].
Radiotherapy (RT) and CO2 laser excision are the first-line treatments for early glottic cancer [3]. Oncological and functional results are considered comparable between the two treatments for ESLC; however, no direct comparisons exist for vigorous analysis [4]. In a radical RT setting for laryngeal cancers, a 19% absolute improvement in 5-year survival was observed, with a time to treatment initiation (TTI) of ≤ 30 days versus 40 days [5]. Notably, approximately one-quarter of all patients diagnosed with head and neck cancer who receive delayed treatment are associated with an increased mortality rate relative to a TTI of 46–52 days, which becomes most pronounced after 60 days [5].
This study was conducted at Zhianawa Cancer Center (ZCC), one of the few academic, high-volume, nonprivate, major centers of radiotherapy in Iraq, which provides access to effective, evidence-based and innovative and safe RT protocols. The RT team at the ZCC consists of radiation oncologists, radiologists, medical physicists, dosimetrists, radiology and radiotherapy technologists, nurses, supportive care personnel and engineers.
There are few population-based studies on cancer in general and laryngeal cancer, particularly in Eastern nations (includ-

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ing Iraq), that provide survival estimates by prognostic factors. Therefore, the aim of the present study was to evaluate long-term RT outcomes, including overall survival (OS), and to investigate the difference between these outcomes after a delay in the initiation of treatment after diagnosis because of the lengthy waiting list in comparison to RT results in other countries. In addition, we aimed to evaluate voice preservation and determine the independent factors affecting patient prognosis.

Methods

1. Patients

Patient data from archives of the ZCC were used after approval was obtained from the administration unit of the ZCC. For this purpose, seventy-one potentially eligible patients were initially enrolled in the present study, and seven were subsequently excluded because of previous chemotherapy application or surgery. Among the remaining 64 patients, 11 patients were lost to follow-up. The data of the remaining patients with T1-T2/N0 glottic laryngeal carcinoma who underwent radical RT between June 2009 and June 2020 according to the laryngeal carcinoma protocol were reviewed retrospectively.

All the patients with laryngeal cancer included in this study were histopathologically confirmed to have squamous cell carcinoma. The median follow-up period of the surviving patients was six years (range: 3–14 years). The American Joint Committee on Cancer (AJCC) staging system, 7th edition, was used in this study for staging. A physical examination with laryngoscopy and/or CT scan was used for the staging procedure.

As a standard treatment for patients with laryngeal cancer, all patients were treated in the supine position; the head of each patient was noninvasively immobilized with a thermoplastic head–neck or head–neck–shoulder mask and subjected to noncontrast-enhanced CT. CT images were acquired at a slice thickness of 3–5 mm and imported to the Monaco treatment planning system. All patients received a continuous course of RT with once-daily fractionation, 5 fractions per week. All fields were equally weighted and treated in each fraction. All patients were treated exclusively with 6-MV photons. Appropriate wedge filters were used to improve the dose homogeneity. In some patients, wax boluses are used for diseases involving the anterior commissure (AC). The median total RT dose was 65.25 Gy, with daily fraction sizes of 2 Gy in 17% of patients and 2.25 Gy in 83% of patients. The RT dose was administered via three-dimensional conformal radiation therapy (3D CRT), with the RT field extending from the hyoid bone superiorly to the cricoid cartilage inferiorly.

The medical data from the identified patients with early-stage laryngeal cancer, including history, histopathology, and RT treatment charts, were entered into the Microsoft Excel program. Follow-up with the patients or their relatives was conducted by phone. After providing informed consent for their participation in the study, the patient or their relative was asked in detail about the post-RT performance status, the need for further treatment modalities after finishing RT, short- and long-term side effects if present, smoking status, and finally, the cause and timing of death in patients who were dead by the time of the communication.

2. Statistical analysis

MedCalc® Statistical Software version 22.021 was used to perform the statistical analyses. The parameters that were studied included age group, tumor grade (well vs. moderate vs. poorly differentiated squamous cell carcinoma), T stage (T1 versus T2) and gender. The RT parameters included the daily dose (2.0 Gy vs. 2.5 Gy) and time from diagnosis until RT initiation.

The Kaplan–Meier method was used to estimate the survival proportion, which was defined as the proportion of patients who survived at the last follow-up. Only factors with a level of significance less than 0.05 in the univariate analysis were further analyzed in the multivariate analysis. Differences with p values <0.05 were considered statistically significant.

Results

The median age of the patients was 63 years (37-91 years), and the vast majority (94%) of them were men (four females and 49 males). Clinical T1 disease was detected in 37 (58%) patients, whereas 27 patients (42%) had T2 disease. With respect to smoking status, 29 of the remaining 24 patients were smokers for whom no information regarding smoking status was available (Table 1).

Table .1 Patient-tumor characteristics, demographics and radiation technique.

Sex	Male: 60	94%
	Female: 4	6%
Age	Range 37-91 (median age: 63 years)	
Grade	GI: 23	36%
	GII: 37	58%
	GIII: 2	3%
	Unknown: 2	3%
Diagnosis	Supraglottic: 7	11%
	Glottic: 55	86%
	Infraglottic: 2	3%
T-stage	T1 N0: 37	58%
	T2 N0: 27	42%
Target volume	Without LN: 53	83%
	With LN: 11	17%
Dose	63Gy: 27	42%
	65Gy: 3	5%
	65.25Gy: 23	40%
	70Gy: 11	17%
Time from diagnosis till radiotherapy	Range (1-12) months	
	Mean 4.25 months	
Current status	Alive: 33	62%
	Death related to cancer: 12	60%
	Other causes: 8	40%
	Lost to FU: 11	
Technique	3DCRT: 64	100%
Status of voice	Preserved: 35	66%
	Absent: 2	4%
	Unknown:18	34%
	Preserved in the survived population: 32	97%

T-stage: tumor-stage, 3DCRT: 3D conformal plan

The median follow-up period for the surviving population was 6 years. With respect to survival, at the last follow-up, 20 (38%) patients had died: 12 from glottic carcinomas and 8 from intercurrent disease. A comparison of survival curves via the log-rank test revealed a statistically significant influence of age (p=0.027) (Figure. 1).

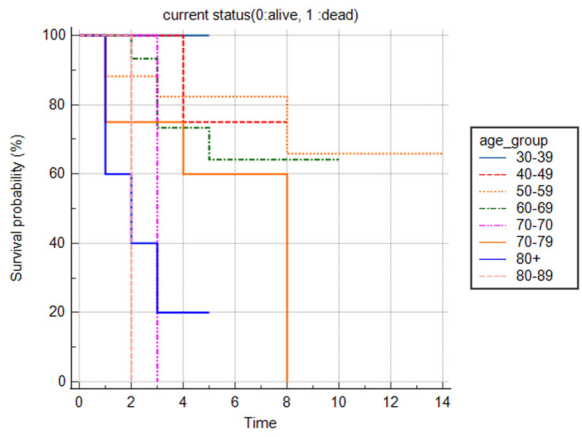

Figure 1: Survival probability according to age group.

and tumor grade, p=0.057, with respect to survival time (Figure. 2).

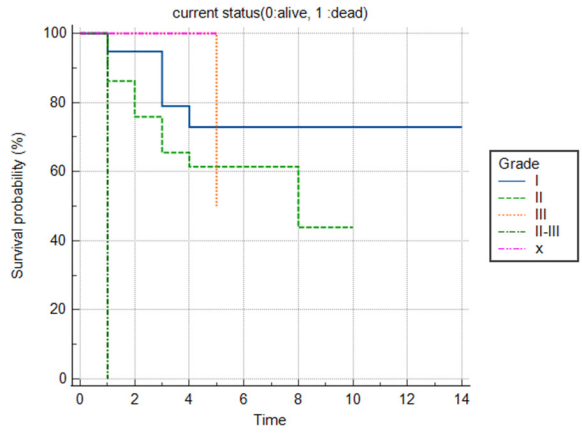

Figure 2: Survival probability according to tumor grade.

There was no difference in T stage according to age (p=0.27), T stage and gender (p=0.66), gender and survival (p=0.60). Surprisingly, there was no statistically significant difference in survival according to T stage (p=0.53), as shown in Figure 3.

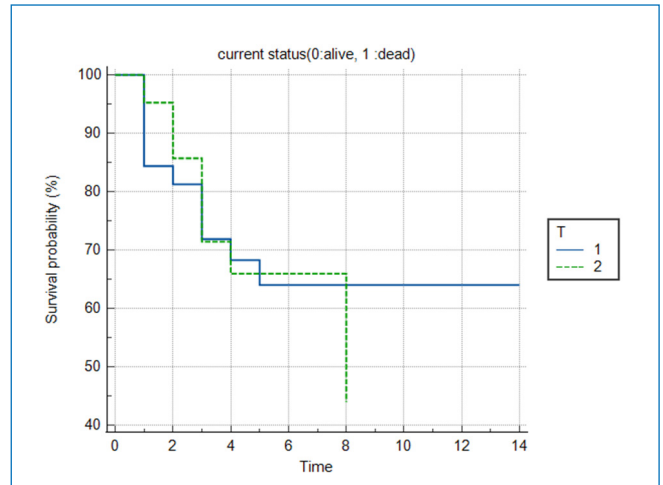

Figure 3: Survival probability according to tumor stage.

Discussion

In this retrospective cohort, we assessed the 10-year clinical outcomes of definitive RT for T1-T2/N0 glottic laryngeal squamous cell carcinoma in an emerging country with limited income and infrastructure. In line with the higher incidence of laryngeal cancer in men [6], the majority of the patients were male. Laryngeal cancer is more common in individuals older than 60 years of age [7] ; accordingly, the median age of the study population was 63 years.

Laryngeal cancers account for one-third of all head and neck cancers and may arise from any anatomical location of the larynx: the supraglottis, glottis or subglottis, with squamous cell carcinoma being the most common histologic type [7]. Histopathological results confirmed that all the patients included in this study had squamous cell carcinoma.

Surgical expertise in endoscopic laryngeal management is lacking in our country; therefore, nearly all patients with early-stage disease must undergo RT, and in cases of recurrent disease, salvage laryngectomy should be performed. The majority of patients have glottic squamous cell carcinoma, which is associated with a lower incidence of positive lymph nodes and better outcomes than other types of laryngeal cancer [1].

The proportion of IMRT used for the treatment of head and neck cancers in general has increased over the last few decades [8]. Although there has been no difference in results between patients receiving IMRT and those receiving 3D conformal planning (3DCRT) in many retrospective studies [8,9], IMRT provides a more homogenous dose distribution than does 3DCRT in terms of the mean carotid artery dose [10], but this approach is more applicable if the GTV location is obvious at the time of contouring. Because of the availability, ease of the 3DCRT technique, small volume of irradiated planning tumor volume in T1-T2 laryngeal cancer, uncertainty regarding the exact location of the tumor and relative applicability of adequate normal tissue preservation (for example, the parotids), we used 3DCRT in all patients.

Compared with conventional fractionation, moderate hypofractionation in laryngeal cancer is associated with enhanced local control [11]. Therefore, moderate hypofractionation with a daily fraction size of 2.25 Gy was used in the majority of our plans, which is suggested to be the standard RT fractionation method for T1-T2 laryngeal cancer. To eliminate bias, we excluded all patients who were treated with surgery prior to RT or who received (not according to guidelines) chemotherapy.

Many factors are strongly associated with worse outcomes in treating laryngeal cancer, among which the time from diagnosis until the start of treatment is one of the clearest examples [12]. Another known contributing factor to lower OS is patients living in a low socioeconomic area [13]. The median time from diagnosis to the start of RT was approximately 4 months, which is longer than the recommended timeframe in the literature [12]. This delay in treatment initiation was due mainly to the long waiting time because of the large number of patients seeking treatment at the ZCC because of inadequate RT centers throughout Iraq in general, particularly in the Kurdistan region of Iraq, and lower socioeconomic status. The problems of the inaccessibility of facilities, scarcity of human resources, and diagnostic and therapeutic tools are well known and were recently declared in a publication highlighting the access barrier and framework for the barriers to cancer care during conflicts in a war-torn country: Iraq [14].

Early-stage laryngeal cancer is known to have favorable results if it is treated with RT. Five-year overall survival rates range from 65–84% for T1–T2 tumors [15,16], with particularly higher local control for T1 tumors at 93–94% and less for T2 disease at 70–80% [15]. The results of this study revealed that the 2-, 3- and 5-year survival rates of the study population were 83%, 71% and 66%, respectively, which are lower than those reported in previous studies in other developed countries but still promising. In terms of voice preservation, this study demonstrated excellent voice preservation in surviving patients (97%), which is comparable with the findings of previous reports [17].

The limitations of our study include its small sample size and single institutional review. In addition, the follow-up was performed by phone, which may provide inadequate information from a relative's history regarding the cause of death, exact date and time of death, smoking status and any possible side effects.

Conclusion

The results of this study demonstrate that definitive radiotherapy is an effective treatment modality for T1–T2 glottic laryngeal squamous cell carcinoma in a developing country. Despite the challenges, including delays in treatment initiation and limited resources, acceptable survival rates and good voice preservation outcomes have been achieved.

Acknowledgment

We are grateful to Dr. Akhtar Najmadeen for her scientific support and continuous encouragement.

Author contributions:

Lana H. Baba Haji collected the data, designed the study, interpreted the data, and discussed and supervised the workflow. Shwan A. Mohammed designed the study, interpreted the data and provided technical support. Ariwan O. Saeed analysis of data. Bamo M. Muhsin: data collection.

Conflict of interest: The authors declare that there is no any conflict of interest to disclose.

Ethical approval: The study was approved by the Ethics Committee of the Zhianawa Cancer Center.

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