SURVIVAL OUTCOMES IN EARLY GLOTTIC CARCINOMA; A SINGLE INSTITUTION EXPERIENCE

Muhammad Atif Munawar¹, Kamran Saeed¹, Tabinda Sadaf¹, Irfan Haider, Arif Jamshed¹
Department of Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.
Received: 2 June 2015 / Accepted: 20 December 2016

Abstract

Purpose: Laryngeal cancers are among the most common cancers affecting head and neck region. In this study, we analyze the overall survival following hypofractionated radiotherapy in early stage glottic carcinoma treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore.

Methods: Between October 2003 to June 2009, 87 patients with early stage glottic carcinoma were treated with hypofractionated radiotherapy. All patients were included in the study. Male 94% : Female 6%. Mean age was 62 years (range 31-83 years). 66% of the patients were smokers. AJCC stage was T1a in 76%, T1b 20% and T2 in 4% of the patients. Histological distribution; Squamous cell carcinoma 97%, Verrucous carcinoma 2%, squamous cell spindle variant 1%. Median follow up time was 59 months (range 4-122 months). Radiotherapy dose was 55 Gy in 20 fractions over a period of 4 weeks. Median radiotherapy treatment time was 28 days (range 23-35 days). Patients that lost to follow up were contacted via telephone.

Results: The 10 years overall survival (OS) was 83%. Patterns of failure; 7 local, 1 distant while 1 patient had persistent disease. 15 patients were dead at the time of study. Cause of death; 13 patients due to Ischemic heart disease and 2 due to primary disease.

Conclusion: Hypofractionated radiotherapy 55 Gy in 20 fractions seems to achieve good overall survival while offering potential for optimizing resources usage.

Key words: Hypofractionated, radiotherapy, overall survival, glottic carcinoma

Introduction:
Larynx or voice box is divided into three regions, supraglottis, glottis and subglottis. Among them glottic cancers comprises 60-65% [1]. Main histology is the squamous cell carcinoma and almost 40% of the patients have Stage III and IV disease at the time of presentation [2]. Patients with early squamous cell carcinoma of the laryngeal glottis are generally considered to have good prognosis [3,4]. The aims of treatment for early glottis cancer is cure, laryngeal voice preservation, optimal voice quality with minimal morbidity, expense, and inconvenience [5]. Both treatment modalities including surgery and radiation therapy are fairly successful in the management of early glottis cancers, the treatment of choice remains controversial as the evidence for most decisions is derived from non-randomized studies [6]. Radiation therapy has comparable cure rates for selected T1 and T2 early stage glottis cancers with laser excision, cordectomy and hemilaryngectomy. Radiation therapy is preferred over surgery due to its less selection criteria, good quality of voice and comparable local control and survival rates.³ Local control rates have ranged from 80-95% for T1 and from 50-80% for T2 early glottic cancers treated with radiotherapy. There is a range of radiation fractionation policies for the treatment of early laryngeal cancer worldwide. While most centers have adopted conventional 2Gy fractionation for 6-7
weeks, others use hypofractionated regimens with shorter overall time [7,8,9].

The traditional approach to treatment of stage I vocal cord cancer has been to deliver 66–70 Gy in two Gy daily fractions. A Japanese randomized trial compared hypofractionated radiotherapy (RT) at 2.25 Gy daily with 56.25 Gy for “minimal” T1 and between 63 Gy for larger T1 tumors with 60–66 Gy in 2-Gy fractions. Local control was superior with hypofractionation, and toxicity was reported as extremely low in both arms, leading to widespread adoption of the hypofractionated regimen.

The use of hypofractionation to minimize potential for tumor repopulation during radiotherapy is particularly important for early larynx in view of small field sizes, potentially allowing larger doses per fraction without excessive late morbidity [9]. There is only limited published data documenting the efficacy of the more hypofractionated schedules. Importantly, these is little data available to support the use of similar schedules for the treatment of T2 glottic carcinoma, with the two main series reporting the use of hypofractionated schedules with fraction sizes >2.5Gy included only T1 disease [11,12].

A study published in 2011 in International Journal of Head and Neck Surgery showed 5 years OS of 86% [13]. Those patients were followed for another 5 years and here we report our 10 year experience of treating T1 and T2 glottic carcinoma with 55Gy in 20 fractions over a period of 4 weeks.

Methods

The time duration for this retrospective study was between October 2003 and December 2014. The records of total 87 patients with early stage glottic carcinoma who have been treated with hypofractionated radiotherapy were identified via the head and neck database as well as the online information system. Hypofractionated radiotherapy was defined as the delivery of a smaller total radiotherapy dose in a few larger fractions. All patients were included in the study. 94% of the patients were male and 6% were females. 78% belonged to Punjab while 16% were from KPK province.

The mean age of the patients was 62 years (range 31-83 years). 66% of patients were smokers. AJCC stage wise distribution is shown in the table 1 and histologic distribution is shown in the table 2 respectively.

<table>
<thead>
<tr>
<th>AJCC stage</th>
<th>Number of patients (%)</th>
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<tbody>
<tr>
<td>T1a</td>
<td>66 (76)</td>
</tr>
<tr>
<td>T1b</td>
<td>18 (20)</td>
</tr>
<tr>
<td>T2</td>
<td>3 (4)</td>
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</table>

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>84 (97)</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Squamous cell spindle</td>
<td>1 (1)</td>
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</tbody>
</table>

Median follow up duration was 59 months with a range of 4-122 months. Radiotherapy dose was 55 Gy in 20 fractions over a period of 4 weeks. Radiotherapy was given 5 days a week. 21% of the patients were treated on Cobalt 60 and 79% of the patients were treated on linear accelerator. Energy used was 6 MV photons. The median radiotherapy treatment time was 28 days (range 23-35 days). Patients who lost to follow up for more than 2 years were contacted via telephone to assess the disease status. Overall survival was defined as the time duration between the start of treatment to the time till death.

Results

The 10 years overall survival (OS) as determined by the Kaplan Meir method was 83%. (Figure 1)
Fig 1. Patterns of failure; Local 7, distant 1 while persistent disease in 1 patient respectively. 15 patients were dead at the time of study. Cause of death; 13 patients due to Ischemic heart disease and 2 due to primary disease. Voice quality was assessed via telephonic interview with patients having intact larynx. About two third of the patients were satisfied with their voice quality.

Table 3: Patterns of failure

<table>
<thead>
<tr>
<th>Patterns of failure</th>
<th>Number of patients (%)</th>
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<tbody>
<tr>
<td>Local</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Distant</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Persistent</td>
<td>1 (1%)</td>
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Discussion

There are certain number of factors that affect the outcome of early glottic cancers which are related to patient, tumor and treatment offered. Females have same prognosis or even better than males in head and neck cancers. The reason for this observation is unknown. In our series none of the five women failed treatment. Higher T stage adversely impacted local control. AJCC staging system sub classifies T1 glottis cancers into two types, T1a tumor limited to one vocal cord (may involve anterior or posterior commissure) and T1b tumor involvement of both the vocal cords. The incidence of regional nodal metastasis in T1 glottic cancers ranges from 0-2% while it is 10-15% in T2 and T3 respectively [11]. Local control rates for T1 glottis cancer treated with radiation vary between 80 - 95% and with surgical salvage ultimate local control rates are between 90 - 100%. Patients with stage T1b lesions are considered to have a lower local control rates compared with T1a tumors [12,14,15]. In a series covering 449 patients local control rates for T1a and T1b was 91% and 82% respectively [12]. However, other authors have failed to show such difference in loco regional control for T1 lesions [5-9]. The management plans for T2 carcinoma of the glottis cancers remain controversial and have wide variations. In general T2 lesions have poor cure rates then T1 lesions. The local control rates for T2 squamous cell carcinoma of the glottis with conventional radiotherapy is approximately 71 – 85% and salvage rate for local radiation failure is 88 -95%.[7]. In our study total number of patients with T2 tumor were four. They were treated with conventional fractionation encompassing the primary site & upper neck with radiation treatment portals. Among the 4 patients with T2 tumors, 2 had local failure at 9 and 14 months following treatment that were salvaged with laryngectomy. Anterior commissure involvement has been reported by some authors to be associated with poor local control however it is controversial. A review of approximately 2200 Stage I patients with glottic carcinoma showed no increase in local failure with anterior commissure involvement [16]. Other studies indicate that anterior commissure involvement is a poor prognostic variable for local control with both radiotherapy and surgery [4-9]. Other factors associated with poor outcome in early glottic cancers include total dose (<65 Gy) [19]; overall treatment time (> 41 days); poorly differentiated histology [20]; smaller fraction sizes (< 2Gy vs > 2 Gy [21]; subglottic extension; treatment delay (> 3 days) [22]; treatment interruptions; age and smaller field size [22]. Smokers particularly those who continue to smoke after treatment are considered to have a worse loco-regional control. 10. The potential risk of prolonged overall radiotherapy treatment time in head and neck cancer is
well documented. Prolonged overall radiotherapy treatment time has a negative impact on LRC and survival [23]. Rudoltz et al. reported 100% local control when radiotherapy was completed within 42 days, in contrast to 50% local control when treatment lasted from 55 – 66 days [24]. Fein et al. in his study reported a lower local control rate when radiation was extended for more than 50 days in the management of T1 – T2 glottic carcinoma.16 Machine breakdown, holidays and patient related factors are major causes for treatment interruptions. An audit by Royal College of Radiologists of radical radiotherapy for head and neck cancer showed 81% of treatment interruptions were due to machine breakdown or servicing [25]. Local control rate may be affected by size of the fraction. Many studies have demonstrated better local control rates if fraction size is ≥ 2 Gy [26, 27, 28, 29, 30]. Short et al reported 95% locoregional control with accelerated hypofractionated regimen 52.5 – 55 Gy over 4 weeks compared with 75% when treating with 60 – 66 Gy over 6-6.5 weeks (p=0.002).25 In another study covering 171 patients control rate was significantly improved using 2 Gy than 1.8 Gy per fraction [27]. Patients treated with higher fraction size > 3 Gy have a higher risk of developing late complications and this is in contrast to the findings of the BIR trial [10, 29]. In our study, only 7 out of 87 patients (8%) failed locally which accounts for 82% local control rate that is in contrast with published international literature.

The optimum beam energy advocated for the management of early glottic carcinoma is cobalt-60 or 4-MV photons.17 The rationale for using lower beam energy is the fact that high energy photons has increased penetrating power that causes inadequate build up in the anterior commissure due to thin wedge shape of the midline of the neck that allow underdose of tumor. Dosimetry studies to calculate the degree of under dosage have yielded conflicting results. The dose absorbed in the anterior commissure decreased by 12% with 6-MV photons and 18% with 10-MV photons when compared with cobalt-60 [31]. Akaine et al reported on 154 patients with stage T1 tumors treated with 6 – MV; the 5-year local control rate with and without anterior commissure involvement was 81% (27 patients) and 91% (127 patients) respectively. While the result did not reach statistical significance it does invoke clinical concern [32]. Conversely data from other retrospective studies suggest that the estimated 5-year local control rates with 6-, 8-, 10- MV photons may be similar to those achieved with cobalt-60 [28].

Various studies have indicated that endoscopic laser excision produces oncologic outcome and voice quality comparable to radiotherapy treatment [33]. While radiation is often favored as it appears to be associated with reduced impairment of voice quality, but qualitative studies about vocal function in post-irradiated patients have been inconclusive and not uniform [34-36]. Dinapoli et al reported on 143 patients with T1 glottis cancer; 73 underwent surgery and 70 underwent radiotherapy. No statistically significant differences were found between the two groups in terms of overall survival and disease-free survival and better scores for voice quality were found for patients receiving radiotherapy compared to surgery [38]. In our study there was no formal assessment of voice. Telephonic interview was done with patients having intact larynx. About two third of the patients were satisfied with their voice quality.

There are several limitations for this study. First, our study is a single institutional retrospective review spanning over one decade. Second limitation includes availability of only subjective measurement of patient and physician reported voice quality measures. Lastly, as all of our patients received treatment with 2D planning system, tumor volume and tumor volume dosimetry is better captured in modern 3D treatment techniques.

Conclusion

Hypofractionated radiotherapy 55Gy in 20 Fractions seems to achieve good overall survival for T1-T2 N0 glottis squamous cell carcinoma with good voice preservation.
References:


