Definitive Radiation Therapy for Moderately Advanced Laryngeal Cancer: Effects of Accelerated Hyperfractionation

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Objective: The purpose of this retrospective study was to analyze the results of accelerated hyperfractionation for patients with moderately advanced (T2 and T3) laryngeal cancer.

Methods: Between 1998 and 2007, 9 supraglottic carcinomas (6 T2N0M0, 2 T2N2M0, 1 T3N0M0), 30 glottic carcinomas (25 T2N0M0, 5 T3N0M0), and 1 T2N0M0 subglottic carcinoma were treated with definitive radiotherapy using accelerated hyperfractionation without concurrent chemotherapy. The dose-fractionation for 35 patients was 72.8 Gy/56 fractions/5.6 weeks, and that for four patients treated between 1998 and 2001 was 72 Gy/60 fractions/6 weeks. One patient who had been treated with steroid therapy for systemic lupus erythematosus was treated by 67.8 Gy/44 fractions/4.4 weeks.

Results: The local control and overall survival probabilities at 5 years for supraglottic carcinomas were 75% and 86%, respectively. Those for glottic carcinomas were 80% and 92%, respectively. The 5-year local control probabilities for T2 and T3 tumors were 85% and 56%, respectively. This excellent local control rate especially for T2 laryngeal carcinomas may be attributable to the effect of accelerated hyperfractionation. No late toxicities of grade 2 or more was noted among the 39 patients treated with 72.8 Gy/56 fractions or 72 Gy/60 fractions.

Conclusion: Accelerated hyperfractionation of 72.8 Gy/56 fractions/5.6 weeks using 1.3 Gy/fraction seems a safe and effective dose-fractionation for patients with moderately advanced laryngeal carcinomas.

Key words: accelerated hyperfractionated radiotherapy – laryngeal cancer – radiation therapy

INTRODUCTION

Radiotherapy (RT) is a well-established treatment method for patients with early laryngeal carcinomas, although laser therapy and partial laryngectomy can also treat early laryngeal carcinomas definitively (1–3). The goals of treatment are cure of the cancer, preservation of the vocal cord with acceptable voice quality and minimal treat-related mobility. Definitive RT can achieve all these goals for most of patients with early laryngeal carcinomas. In addition, salvage laryngectomy can be performed for patients with relapse after definitive RT, effectively. The ultimate local control late for the patients with salvage laryngectomy for recurrences after initial RT has been reported to be in the range 90–100% for early laryngeal carcinomas (4–9).

The local control rates for laryngeal cancers treated with conventional fractionation (CF) are from 80% to 90% for T1 glottic lesions and approximately 70% for T2 glottic lesions (8,10–12). Thus, although conventional RT alone yields an
adequate local control rate for T1 glottic lesions, the local control for T2 lesions has much scope for improvement. Several approaches have been employed to improve control rate for T2 glottic and supraglottic laryngeal cancer, including hyperfractionated RT, combined chemotherapy with RT and induction chemotherapy after partial laryngectomy. Garden et al. (13) reported that hyperfractionated RT improved the local control rate for patients with T2 glottic cancer as compared with CF.

Consistent radiobiological and clinical data suggest that increasing the overall treatment time (OTT) is detrimental to locoregional control as it enhances tumor repopulation during treatment (14–16). The importance of OTT on tumor control for T3–4 laryngeal cancers was first noted in 1983 by Maciejewski et al. (17). Nishimura et al. (11) demonstrated that 1 week prolongation of treatment time reduces the 5-year local control rate for patient with early laryngeal cancer from 89% to 74%. Accelerated hyperfractionation (AHF) is defined as a scheme with a significant reduction of OTT compared with CF. At our hospital, hyperfractionated RT of 72 Gy/60 fractions/6 weeks was given for moderately advanced laryngeal cancer since 1998, and this institutional protocol was changed to more accelerated scheme of RT using 1.3 Gy/fraction two fractions daily to a total dose of 72.8 Gy in 2001 because of the mild acute toxicities of the former fractionation. The present study is a retrospective analysis of the results of accelerated hyperfractionated RT for patients with moderately advanced laryngeal cancer at Kinki University Hospital.

PATIENTS AND METHODS

PATIENTS

Between 1998 and 2007, 44 consecutive patients with moderately advanced (T2 and T3) squamous cell carcinomas of the larynx were treated with definitive RT at Kinki University Hospital. This retrospective analysis included 40 of the 44 patients treated with hyperfractionated RT without concurrent chemotherapy. Characteristics of the 40 patients are shown in Table 1. Patient’s stage was defined according to the 2002 TNM classification (6th edition, International Union Against Cancer). The average age of the patients was 63 years (range; 49–83 years). Performance status (PS) for most patients was PS0 or PS1. The distribution of the primary site was follows; glottis in 30 patients; supraglottis in 9; subglottis in 1. All patients with glottic or subglottic carcinomas had no clinical neck metastasis. Two patients with supraglottic carcinomas had lymph node metastasis, and those patients were treated with neck dissection before definitive RT for primary tumors. Nine patients (23%) had double cancers; one head and neck cancer, three gastric cancers, one esophageal cancer, two liver tumors, one prostate cancer and one colon cancer. The median follow-up duration of the patients was 54 months (range; 7–95 months). Only one patient was lost with follow-up at 7 months.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Supraglottic carcinoma</th>
<th>Glottic carcinoma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Median ages (years)</td>
<td>64 (54–80)</td>
<td>62 (49–83)</td>
</tr>
<tr>
<td>Performance status (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
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<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>T stage (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>8</td>
<td>26*</td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>N stage (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>N1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Clinical stage (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>26*</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>IVA</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*One patient with subglottic carcinoma was included.

RADIATION TREATMENT

The standard RT technique was parallel opposing lateral fields using 60Co γ-ray in 5 patients (12%) between 1998 and 2000, or high energy photons of 4–6 mV X-ray in 35 patients (88%). A telecobalt unit was replaced to a 4 MV linear accelerator in 2000. During the period of its installation, two patients were treated with 6 mV X-ray. Patients were immobilized using a bite block and/or shell in the supine position. All patients received continuous-course irradiation using twice-a-day fractionation.

The details of RT methods and dose-fractionation are shown in Table 2. Irradiation for T2 glottic tumors was delivered by local portals (mostly 5–6 × 5–6 cm) covering only the primary lesion. The cervical lymph node chain was not electively treated. For T3 glottic tumors, larger portals (mostly 6–8 × 6–8 cm) which included the primary lesion and upper and middle jugular lymph nodes were used. The dose-fractionation for 28 of 31 patients (90%) with glottic carcinomas was AHF of 72.8 Gy/56 fractions/5.6 weeks, and that for the remaining 3 patients (10%) with glottic carcinomas treated between 1998 to 2001 was 72 Gy/60 fractions/6 weeks.

For patients with supraglottic carcinomas, RT field included upper and middle jugular lymph nodes. Supraclavicular lymph nodes were irradiated in separate low-neck portals for two patients with lymph node
metastasis. Initial portals were reduced after 45–46 Gy to exclude the spinal cord, and boost RT was given to the primary lesion. The dose and fractionation for seven patients of nine (78%) with supraglottic carcinomas was AHF of 72.8 Gy/56 fractions/5.6 weeks, and that for one patient treated at 1998 was 72 Gy/60 fractions/6 weeks. The remaining one patient who had been treated with steroid therapy for systemic lupus erythematosus (SLE) was irradiated by AHF using concomitant boost (1.2 Gy and 1.8 Gy/fraction) with total dose of 67.8 Gy/44 fractions/44 days.

EVALUATION OF THE LOCAL RESPONSE AND TOXICITY

Local response was estimated by laryngoscope 1 month after the completion of RT. Local failure or recurrence was considered to have occurred when local recurrence developed after initial complete response (CR). In evaluating acute or late effect, toxicity criteria of the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) were used.

STATISTICAL EVALUATION

The endpoints were local control and overall survival, which were calculated from the first date of RT. All patients whose primary lesions failed but were successfully salvaged by surgery were counted as local failure of RT. For overall survival, all the causes of death were considered as events. Survival was plotted using the Kaplan–Meier method, with statistical significance assessed by using log-rank test.

RESULTS

LOCAL CONTROL AND OVERALL SURVIVAL

Local control and overall survival curves for supraglottic and glottic carcinomas are shown in Figs 1 and 2. Local control probabilities at 5 years for supraglottic and glottic carcinoma were 75% and 80%, respectively (Fig. 1). The difference of local control probability between supraglottic and glottic carcinomas was not statistically significant ($P = 0.850$). Overall survival probabilities at 5 years for supraglottic and glottic carcinomas were 86% and 92%, respectively, without significant difference ($P = 0.541$; Fig. 2).

Figure 3 shows the local control probabilities for T2 and T3 supraglottic and glottic tumors. The 5-year local control probabilities for T2 and T3 tumors were 85% and 56%, respectively.
respectively. No significant difference in local control probabilities was observed between T2 and T3 tumors ($P = 0.300$).

**Salvage Treatment**

Four local recurrences were noted and total or hemilaryngectomy was performed for them, and surgical salvage was successful for three of the patients (Table 3). The voice was preserved in one patient successfully salvaged by hemi-laryngectomy.

**Complications**

Table 4 shows the acute and late complications of RT. Eight (20%) of the 40 patients had grade 2 acute dermatitis. Although six patients (15%) showed grade 3 acute mucositis, no patient showed grade 4 or more acute toxicities (Table 4).

Severe late complications were noted in one of the 40 patients (Table 4). The patient with T2N2bM0 supraglottic carcinoma was treated with AHF of 67.8 Gy/44 fractions/44 days without concurrent chemotherapy. The patient had used steroid therapy for SLE. This patient needed laryngectomy 9 months after RT due to laryngeal necrosis (grade 4), and skin ulcer (grade 4) developed 14 months after RT.

**DISCUSSION**

In the present study, local control probabilities at 5 years for T2–3 supraglottic and glottic carcinomas were 75% and 80%, respectively. These results are better than other reports on the result of RT using CF (approximately 70%) (12,13,21), and consistent with other reports on the result of RT using hyperfractionated RT for laryngeal cancers (11,13,18,19,21). Literatures for supraglottic carcinomas treated by definitive RT are relatively limited compared with glottic carcinomas (19–18). Mendenhall et al. (19) reported an overall local control rate of 83% for supraglottic carcinomas treated with RT using CF (60 to 75 Gy, 1.8 to 2.0 Gy/fraction) or HF (74.4 to 79.2 Gy, 1.2 Gy/fraction). The other investigator reported that the local control rate for the primary site of patients with supraglottic carcinomas irradiated using CF was 57% (18). Thus, the 5-year local control rate of 75% at our hospital is quite consistent with the literatures using CF or HF (18–20).

The 5-year local control probability for T2 supraglottic and glottic tumors was 85% in the present study (Fig. 3). This excellent result may be attributable to AHF. When a fraction size of 1.1–1.2 Gy is adopted as a pure hyperfractionation schema, a total RT dose can be increased approximately 10% without shortening of OTT (13,21). Garden et al. (13) reported that a 79% local control rate for patients treated with hyperfractionation RT (1.2 Gy/fraction, a total of 74–80 Gy) compared with 68% for patients treated with CF (70 Gy/35 fractions; $P = 0.06$) in a series of 230 patients with T2 glottic carcinomas. In a randomized trial for patients with T2 glottic carcinomas, Trotti et al. (21). showed a higher local control rate of 79% by hyperfractionated RT of 79.2 Gy/66 fractions (1.2 Gy/fraction) compared with that of 70% by CF (70 Gy/35 fractions). Although there was no significant difference in local control rate between the two arms, there was a trend for improvement in disease-free survival with hyperfractionated RT ($P = 0.07$).

Although there are many papers on pure hyperfractionated RT using a fraction size of 1.1–1.2 Gy for laryngeal cancer, no literature using a fraction size of 1.3 Gy to a total of 72.8 Gy has been reported for laryngeal cancer. At the start of this series, hyperfractionated RT of 72 Gy/60 fractions (1.2 Gy/fraction)/6 weeks was adopted for four patients. As the acute toxicities for the patients were so mild, we increased a fraction size to 1.3 Gy with a total RT dose of 72.8 Gy. Using a fraction size of 1.3 Gy, OTT could be shortened several days compared with a pure hyperfractionation schema. Another reason for the increasing fractional size was convenience of patients and to reduce the labor of RT unit. By increasing a fraction size, total number of fractions could be reduced four times. Although a total RT dose of 72.8 Gy in the present series is lower than those of pure hyperfractionation (74–79.2 Gy), the local control rate in the present study is as high as those of pure hyperfractionation. As our fractionation is slightly an accelerated fractionation,

Table 3. Salvage treatments and its results for four patients with local recurrence

<table>
<thead>
<tr>
<th>Salvage treatments</th>
<th>Clinical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemi-laryngectomy</td>
<td>NED 3</td>
</tr>
<tr>
<td>Total laryngectomy</td>
<td>DOD 1</td>
</tr>
</tbody>
</table>

NED, no evidence of disease; DOD, died of the disease.

Table 4. Acute and late toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute toxicities</th>
<th>Late toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Esophagitis</td>
<td>Laryngeal edema</td>
</tr>
<tr>
<td>0 or 1</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1*</td>
</tr>
</tbody>
</table>

Dermatitis | 32 | 8 | 0 | 0 |
Mucositis  | 28 | 6 | 6 | 0 |

Late toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute toxicities</th>
<th>Late toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1*</td>
</tr>
</tbody>
</table>

Skin | 39 | 0 | 0 | 1* |
Spinal cord | 40 | 0 | 0 | 0 |

*Occurred in the same patient.
this result indicates the importance of OTT for local control of laryngeal cancer.

AHF could be completed within a planned OTT without treatment interruptions (Table 2), although the incidence and degree of acute toxicities of AHF were slightly high (Table 4). Incidence of severe late toxicities (grade 3–4) was rare, and one patient (3%) showed grade-4 toxicity (Table 4). As one of the patients was treated with steroid therapy for SLE, altered fractionation or concurrent chemo-radiotherapy may be contraindicated for patients with the collagen disease. No late toxicities of grade 2 or more was noted for the 39 patients treated with 72.8 Gy/56 fractions or 72 Gy/60 fractions.

In conclusion, we have demonstrated that definitive RT gives patients with moderately advanced laryngeal carcinomas high cure rates with maintaining the quality of life. AHF of 72.8 Gy/56 fractions/5.6 weeks using 1.3 Gy/fraction seems a safe and effective dose-fractionation for patients with T2–3 laryngeal carcinomas.

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Conflict of interest statement

None declared.

References