Accelerated Radiotherapy and Larynx Preservation in Favorable-risk Patients with T2 or Worse Hypopharyngeal Cancer

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Objective: To evaluate the advantage of accelerated fractionation radiotherapy for patients with hypopharyngeal cancer requiring total laryngectomy.

Methods: Seventy patients with previously untreated, technically resectable hypopharyngeal cancer who received larynx-preserving treatment with radiotherapy between April 1992 and June 2004 were analyzed. No patients had previous history of other malignancy or poor performance status that would possibly affect the outcomes. A total RT dose of ≥60 Gy/6 weeks was determined depending on the tumor clearance during treatment before December 1998, and fixed to 70 Gy in all patients thereafter. Accelerated fractionation (70 Gy/49 days) was completed in 35 patients during the latter period. Concomitant platinum-based chemotherapy was used in 41 patients after May 1998.

Results: Local control rates at 2 years were 72 and 68% for patients with T2 and T3/T4 disease, respectively. Patients who had received 70 Gy/49 days achieved a better local control rate than those who had received other, more conservative total dose/overall treatment time with statistical significance (91% versus 50% at 2 years, P < 0.001). Multivariate analysis involving 70 Gy/49 days of radiotherapy, T-classification (T2 versus T3/4), and use of chemotherapy revealed that administering 70 Gy/49 days was the only independent prognostic factor (P = 0.007) for better local control.

Conclusions: Our experience in radiotherapy for hypopharyngeal cancer mirrored the results of previously conducted large randomized trials for various head and neck cancers. Encouraging local control in this study warrants prospective study to test the long-term oncological and functional outcome of larynx-preserving treatment in patients with advanced but resectable volume of this disease.

Key words: hypopharyngeal cancer – radiotherapy – overall treatment time

INTRODUCTION

Hypopharyngeal cancer often presents with advanced primary tumor and is associated with early nodal and systemic dissemination in patients who have multiple co-morbid conditions and a high risk of second malignancy. Approximately 30–40% of overall survival at 5 years has been reported after standard treatment, i.e. surgery with post-operative radiotherapy (1–7). Although no clear difference in survival after surgery and definitive radiotherapy (RT) has been observed (5,8,9), the reported results of RT vary considerably. This is partly because of patient selection and various RT doses administered, ranging from 50 Gy/4 weeks to 75+ Gy/7+ weeks with or without chemotherapy (10–22). Altered fractionation or concomitant chemoradiation therapy has repeatedly demonstrated improvement of locoregional control and/or overall survival compared...
to conventional RT alone in large randomized trials (23–33). These developments have been changing patterns of practice in advanced head and neck cancer, however, the percentage of patients with hypopharyngeal cancer involved in these studies is limited, ranging from 0 to 36%. Unlike oropharyngeal and supraglottic laryngeal cancer, data are still incomplete regarding the dose–response relationship in RT for this relatively rare head and neck cancer (10,34).

RT for hypopharyngeal cancer has specific problems because of its tendency to cause pharyngeal stenosis, cartilage necrosis and mis-swallowing even after tumor cure. Therefore toxicity management to minimize treatment-induced serious mucosal injury has particular importance (35). RT alone has been preferred for patients who have tumors with favorable morphology, i.e. small and/or exophytic disease (18,21). Intensive local treatment for more advanced disease requires a meticulous, labor-intensive and multi-disciplinary approach regarding patient selection and safety conduction of treatment. In Japan, the attitude toward the application of RT for resectable hypopharyngeal cancer is still conservative, and RT with modest dose/fractionation according to the tumor clearance during RT has been mainly used to maintain the safety of possible salvage surgery (36–38). In our institution, policy was changed from this concept to a standard approach in which RT is delivered at 70 Gy/≤7 weeks concomitant with chemotherapy, based on compelling positive data from large randomized trials. The results of this changed policy are reviewed in this report.

PATIENTS AND METHODS

PATIENT POPULATION

All patients underwent computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck as part of the pretreatment evaluation. Diseases were re-staged according to the American Joint Committee on Cancer Staging Manual 6th edition (39). Technically unresectable disease was defined as a tumor with fixation to the prevertebral muscles, encasing the carotid artery, and/or invading the bony structures at the skull base or cervical spine on CT and/or MRI. A primary tumor with massive extension to the oropharynx that precluded functional reconstruction was also defined as unresectable. Selection of treatment was done in multi-disciplinary conference. Patients were generally considered as contraindication to an organ-preserving approach if they were with resectable primary tumors showing endophytic and ulcerative growth patterns associated with marked destruction of thyroid cartilage and/or airway stenosis requiring tracheostomy, unless they refused mutilating surgery.

Between April 1992 (the year our institute was established) and June 2004, 165 patients with previously untreated, biopsy-proven hypopharyngeal cancer without distant metastasis underwent RT with curative intent. Tumors that were judged as originating from the arytenoids or aryepiglottic folds were excluded. Eight patients were lost to follow-up within 2 years without evidence of disease recurrence. Of the remaining 157 patients, 48 had technically unresectable primary tumor and/or nodal disease and were excluded from this study. In addition, 39 patients were excluded because of the following reasons: 11 who had primary tumors that were staged as T1 disease; 11 who had poor Zubrod performance status (PS) of 2 or worse; seven who underwent pre-operative chemotheray that resulted in complete tumor resolution and, therefore, changed the treatment to RT instead of surgery; five who had a history of other malignancies within the past 5 years; five who had primary tumors that were amenable to partial laryngectomy as curative approaches but who refused surgery. Therefore 70 patients were the subjects of this study. Patient characteristics are listed in Table 1. All patients were followed for

Table 1. Characteristics of 70 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
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</tr>
<tr>
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<tr>
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<tr>
<td>IV</td>
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more than 2 years or until death. The median follow-up period for surviving patients was 36 months (24–89 months).

**Radiotherapy Technique**

All patients underwent CT-based treatment planning. Elective nodal irradiation encompassing bilateral jugular and retropharyngeal lymph nodes was performed at doses of 40–50 Gy. Anterior oblique wedged-pair beam arrangement with appropriate wedge filter was mainly used. RT portals were then shrunk to the gross tumor and involved nodes with adequate margins.

The total RT dose was determined depending on tumor clearance during treatment between April 1992 and December 1998, ranging from 60 to 72 Gy, and fixed at 70 Gy in January 1999 regardless of tumor clearance. Conventional fractionation (CF) using 1.8–2.0 Gy once-daily fractionation was always used before January 1999. After that, accelerated fractionation (AF) was mainly used. AF was planned to deliver 40–46 Gy/4–4.5 weeks with CF followed by 24–30 Gy/1.5–2 weeks using 1.5 Gy twice-daily fractionation with a minimum interfraction interval of 6 h to a total dose of 70 Gy. The maximum total dose to the spinal cord was restricted to 46 Gy. The RT dose was prescribed to the midplane along the beam axis. All treatments were done using 6 MV X-ray with 9 or 12 MeV electron beam for posterior neck boost as indicated.

**Chemotherapy**

In principle, patients with technically resectable disease received RT alone before May 1998, whereas all patients who had stage II–IV disease were considered as candidates for concomitant chemotherapy with RT thereafter. The FP regimen, which consisted of bolus infusion of cisplatin (80 mg/m²²) on day 1 combined with continuous 96 h infusion of 5-FU (400 mg/m²/day) on days 1–4, was used with individualized dose modifications. FP was administered only as one course during the last 2 weeks when combined with AF. CF was always used for patients receiving two courses of concomitant FP.

**Patient Follow-up and Statistical Considerations**

Follow-up visits were requested monthly until 2 years after completion of RT and at least once per 3–6 months thereafter. Radiological examinations including CT and/or MRI of the head and neck were done at least twice within 6 months immediately after treatment, and at regular intervals of 6–12 months thereafter. Local control, local recurrence-free survival, and overall survival rates from the start of RT were calculated using the Kaplan–Meier method. Recurrence of the primary tumor (local recurrence) was considered as an event for calculating the local control rate, and patients who died without this event were censored at the time of last follow-up examinations. Local recurrence or death from any cause was considered as an event in calculating local recurrence-free survival. Death from any cause was considered as an event in calculating overall survival rate.

Differences in actuarial incidences were tested using the log-rank test, and multivariate analysis was performed with Cox’s proportional hazards model. Treatment-related adverse events were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. All patients agreed to receive their individual treatment after informed consent. The institutional ethics committee in our institution approved this retrospective chart review.

**RESULTS**

**Radiotherapy Dose and Use of Chemotherapy**

The total dose for 18 patients who underwent RT between April 1992 and December 1998 ranged from 60 to 72 Gy (median 66 Gy), and eight (44%) received ≥70 Gy using CF. After that 45 (87%) of 52 patients received 70 Gy using AF. Ten of these 45 patients failed to complete 70 Gy within less than 49 days and underwent 49–69 days (median 53 days) of overall treatment time; two of them because of adverse events, and eight because of public holidays and/or unavailability of RT machine. Otherwise 35 patients completed their RT in less than 49 days (median 45 days, 43–48 days) using AF.

Of 55 patients who started their RT after May 1998, eight (15%) received two courses of FP, and six who started RT after January 1999 received 70 Gy using CF according to the patients’ preference. However, 13 (24%) patients underwent RT alone based on the physician’s judgment because of past history of cardiovascular and/or hepatic co-morbidities in six, high age (≥75 years) in four and patients’ refusal in three. Nine of the 13 patients completed receiving 70 Gy within less than 49 days. An additional patient could not receive AF because of logistical problems and underwent 70 Gy/53 days of RT alone using CF. The background of patients relating to total RT dose received, overall treatment time and use of chemotherapy is summarized in Table 2.

**Local Control**

Twenty patients experienced local recurrences or persistence, all of which occurred within 24 months. Local control rate at 2 years for all 70 patients was 70% (95% confidence interval, 59–81%), and it was 72% (58–86%), 61% (40–82%) and 86% (60–100%), for T2, T3 and T4 disease, respectively. Univariate analyses for local control involving various factors as listed in Table 3 showed that use of AF, uninterrupted administration of 70 Gy/≤49 days, use of concomitant FP, and study period had statistically significant influence on local control (P < 0.050). T classification had no influence on local control. Of 35 patients who completed 70 Gy/≤49 days of RT, three experienced local recurrence
and two of them received a single course of concomitant FP. The local control rate at 2 years for the 35 patients was 91% (95% CI, 81–100%). This was better than for those patients who received other total doses and/or overall treatment time during the entire study period (n = 35), after January 1999 (n = 17), or patients who received 70 Gy/C21 49 days using AF (n = 10) with statistical significance. Those three groups of patients achieved a local control rate at 2 years of 50% (95% CI, 33–67%, P = 0.001), 52% (28–76%, P = 0.002), and 50% (19–81%, P = 0.002), respectively. No statistically significant difference of local control rate at 2 years was observed between patients who received 70 Gy/C21 49 days after January 1999 using AF and CF (50 and 54%, P = 0.761).

Multivariate analysis involving three factors, i.e. 70 Gy/C21 49 days (yes or no), use of chemotherapy (yes or no), and T-classification (T2 versus T3/4) revealed that 70 Gy/C21 49 days was the only independent and statistically significant prognostic factor (P = 0.007) as shown in Table 3.

**Local Recurrence-Free Survival (LRFS)**

Adding to 20 local recurrences, eight patients died within 2 years (median 15 months, 2–23 months) without clinical evidence of local recurrence because of distant metastasis in five, uncontrolled nodal recurrence in two, and treatment-related cause in one. LRFS for all 70 patients was 61% (95% CI, 50–73%), and it was 63% (95% CI, 49–78%), 52% (31–74%), and 75% (45–100%), for T2, T3 and T4 disease, respectively.

**Table 3. Uni- and multi-variate analyses for local control**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of patients</th>
<th>Local control at 2 years (%)</th>
<th>Univariate P</th>
<th>Multivariate P</th>
<th>Hazard ratio for worse prognostic group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 70 years</td>
<td>Yes 51, No 19</td>
<td>Yes 70, No 72</td>
<td>0.940</td>
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<tr>
<td>T2</td>
<td>Yes 41, No 29</td>
<td>Yes 72, No 68</td>
<td>0.555</td>
<td>0.219</td>
<td>1.9 (0.7–4.9)</td>
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<tr>
<td>Total RT dose ≥ 70 Gy</td>
<td>Yes 60, No 10</td>
<td>Yes 62, No 47</td>
<td>0.119</td>
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<td></td>
</tr>
<tr>
<td>Use of accelerated fractionation</td>
<td>Yes 46, No 24</td>
<td>Yes 80, No 51</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70 Gy/C21 49 days</td>
<td>Yes 35, No 35</td>
<td>Yes 91, No 50</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>5.2 (1.5–18.9)</td>
</tr>
<tr>
<td>RT started after January 1999</td>
<td>Yes 52, No 18</td>
<td>Yes 78, No 48</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant administration of cisplatin and 5-FU</td>
<td>Yes 41, No 29</td>
<td>Yes 80, No 61</td>
<td>0.039</td>
<td>0.193</td>
<td>2.3 (0.9–5.9)</td>
</tr>
<tr>
<td>Pyriform sinus origin</td>
<td>Yes 62, No 8</td>
<td>Yes 70, No 73</td>
<td>0.802</td>
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</table>
overall treatment times during the entire study period, after January 1999, or those who received 70 Gy/≥49 days using AF with statistical significance; those patients achieved LRFS at 2 years of 43% (95% CI, 26–59%, P = 0.004), 47% (23–71%, P = 0.013) and 50% (19–81%, P = 0.041), respectively. LRFS for patients who received 70 Gy/<49 days and others is shown in Fig. 1.

**SALVAGE TREATMENT**

Of 20 patients who experienced local recurrence or persistence, 12 underwent surgical salvage with total laryngectomy with partial pharyngoesophagectomy. No surgical mortality or second recurrence at the primary sites was observed, however, three patients died from uncontrolled nodal failure at 6, 10 and 41 months after surgery. The overall survival rate at 2 years after salvage for these 12 patients was 83% (95% CI, 60–100%). Of six patients who experienced nodal recurrence without local failure, four underwent salvage neck dissection. One died at 4 months from uncontrolled nodal recurrence, whereas three were alive and disease-free at 14, 21 and 36 months subsequently. The median survival time after unresectable local, nodal or distant failure (n = 17) was 6 months.

**DENovo MALIGNANCY**

A total of 12 patients experienced newly developed malignancy, five at the esophagus (two with additional head and neck cancer), three in the lung, one in the oral cavity and oropharynx, one in thyroid, one in prostate and one in bladder. One additional patient developed malignant lymphoma. The actuarial incidence of second malignancies was 12% (95% CI, 4–20%) and 36% (13–58%) at 3 and 5 years, respectively (Fig. 2).

**OVERALL SURVIVAL**

A total of 21 patients died from cause-specific reasons because of local (n = 10), nodal (4), distant failure (6), or treatment-related causes (1). One patient died at 97 months because of malignant lymphoma without evidence of recurrence of hypopharyngeal cancer. Five patients were alive and receiving treatment for other malignancies at the time of last follow-up without evidence of recurrence of hypopharyngeal cancer, and six were alive and disease-free after successful treatment for their second malignancy. Overall survival rates (OAS) at 3 and 5 years for all 70 patients were 74% (95% CI, 64–85%) and 61% (44–78%), respectively.

OAS at 3 years in patients who received 70 Gy/<49 days of RT was 83% (95% CI, 70–95%). This was not statistically significantly different from that of patients who received other total dose or overall treatment time during the entire study period, after January 1999, or those who received 70 Gy/49 days using AF; those patients achieved OAS at 3 years of 66% (95% CI, 50–81%, P = 0.179), 71% (49–92%, P = 0.457) and 80% (55–100%, P = 0.940), respectively. OAS for patients who received 70 Gy/<49 days and others is shown in Fig. 3.

**FUNCTIONAL OUTCOME OF PRESERVED PHARYNGOLARYNX**

Of 50 patients who did not experience local recurrence after RT, one developed dysphagia requiring permanent tube feeding and tracheostomy at 3 months. This patient suffered from serious mucositis of grade 4 during RT of 70 Gy/47 days using AF concomitant with chemotherapy. Another patient experienced grade 3 chondronecrosis at 9 months after 70 Gy/44 days of RT with FP that was spontaneously resolved. He was alive and disease-free with normalcy of diet at 38 months. Otherwise no adverse events of grade 3 or worse were observed after completion of RT. The actuarial

Figure 1. Local recurrence-free survival (LRFS) in patients who completed 70 Gy/<49 days of radiotherapy in comparison with others.
incidence of grade 3 or worse pharyngolaryngeal adverse events at 2 years was 6% (95% CI, 0–14%) in patients receiving 70 Gy/<49 days. This was not statistically significantly different from that of 0% for patients receiving other total dose/overall treatment time ($P = 0.145$).

**DISCUSSION**

In retrospective studies of radiotherapy for hypopharyngeal cancer, a remarkable heterogeneity of patient backgrounds was inevitably present in the literature because of the rarity of the disease, its association with multiple co-morbidities and different processes for patient selection. We focused on patients with resectable disease that required total laryngectomy, good performance status, no previous malignancy and no induction chemotherapy. Because a study period that lasted more than a decade also possibly could influence the outcome, we stratified patients in relation to two study periods for which different policies of RT were adopted. Currently, in our institution, the patients presenting with the above features are mainly treated with larynx-preserving treatment. To the best of our knowledge, this is the largest, hypopharyngeal cancer-specific study reported regarding overall RT treatment time in patients of uniform background who received this treatment despite being good candidates for total laryngectomy.

This retrospective study could not provide enough power to detect a difference in the outcomes in relation to RT fractionation, or use of chemotherapy, in a subgroup of patients.

**Figure 2.** Actuarial incidence of newly developed malignancy. Patients who did not experience second malignancy were censored at the time of death or last follow-up visit. Error bars indicate 95% confidence interval.

**Figure 3.** Overall survival (OAS) in patients who completed 70 Gy/<49 days of radiotherapy in comparison with others.
with T3/4 disease. However, there was no apparent differences in local control and LRFS between these patients and those who had T2 disease. This was in agreement with our previous finding that tumor volume, rather than T-classification, was more important for predicting local cure (40). The reported local control rates for T2 or T3 hypopharyngeal cancer ranged from 41 to 60% or 15 to 50%, respectively, after conventional fractionation RT with or without chemotherapy (5, 8, 12, 14, 15, 17, 19, 20). In this study, a local control rate of approximately 50% was almost uniform during the entire study periods for patients receiving RT other than 70 Gy/49 days regardless of RT dose/fractionation and use of chemotherapy. Furthermore, the local control or LRFS in selected patients with T4 disease was, at least, 75%. Therefore it is unlikely that an imbalanced distribution of patients according to T-classification among the different study periods and administered dose/overall treatment time (Table 2) significantly affected the outcomes.

Overall treatment time, rather than the method of RT fractionation or changed policy itself, had a significant influence on local control in this series of patients. This mirrored the concept of radiation biology in head and neck cancer, which emphasizes the importance of overwhelming and accelerated repopulation of cancer cells; this concept was supported in clinical trials (23, 25). Multivariate analyses for local control (Table 3) showed that uninterrupted administration of 70 Gy/49 days had statistical significance, whereas the use of concomitant chemotherapy and T-classifications did not. This suggested that inappropriate dosing and overall treatment time of RT might obscure the effect of chemotherapy. The chemotherapy regimen used in our practice was relatively less intense than that reported in previous clinical trials. This was because in these moderately advanced diseases in order to minimize serious mucosal injury we used chemotherapy as a radiosensitizer, rather than expecting a tumoricidal effect of chemotherapy itself. In randomized trials, Staar et al. (32) and Bensadoun et al. (41) in their subgroup analyses failed to demonstrate the advantages of chemotherapy in terms of overall survival and locoregional cure when combined with altered fractionation RT in patients with unresectable hypopharyngeal cancer. Although the effect of chemotherapy on unresectable hypopharyngeal cancer per se is still controversial in combination with this fractionation RT, accumulating evidence clearly demonstrates that concomitant chemotherapy enhances locoregional tumor cure (24, 28–31, 42, 43) in head and neck squamous cell carcinomas. Therefore, the role of combined modality therapy in patients with advanced but resectable volume of hypopharyngeal cancer should be further pursued focusing on the safety and long-term oncological and functional outcomes. We could not obtain any conclusive data regarding the benefit of accelerated fractionation according to the histological grade (well/moderately versus poorly differentiated tumors) in this limited number of patients (25). However, based on the encouraging results in this study, maintaining a safe administration of RT of 70 Gy/49 days should be of high priority in designing larynx-preservation trials and administering total RT doses of less than 70 Gy or 70 Gy/49 days should be avoided whenever possible outside of the clinical trials. Intensity-modulated radiotherapy (IMRT) with simultaneous integrated boost technique also permits administration of 70 Gy in 6 weeks (44). Considering the fact that xerostomia in long-term survivors after RT has a tremendous negative impact on deglutition, which has been a particular problem in patients with this disease who have received larynx-preserving treatment, the benefit of IMRT should be scrutinized (45). The safety of salvage surgery should be carefully considered and meticulous surveys for de novo malignancies, especially in the upper aerodigestive tract, are also warranted. Both of these factors are important for improving overall survival even in selected patients with this devastating disease.

In conclusion, RT of at least 70 Gy within an overall treatment time of less than 49 days is preferable in larynx-preserving treatment for patients with favorable risks. This concept should be tested in future trials because this retrospective comparison in a small number of patients may be rather biased in order to provide a definitive conclusion. RT using accelerated fractionation, or IMRT using simultaneous integrated boost technique should be considered positively in this setting. The effect of combined modality treatment should be tested in combination with these RT techniques, with special attention to the long-term functional outcomes. To accomplish these clinical studies, meticulous quality control of radiotherapy, as well as toxicity management and adequate surgical salvage by a multi-disciplinary team, is mandatory.

Conflict of interest statement
None declared.

References