Objective: The purpose of this study is to clarify the efficacy and toxicity of hyperfractionated radiation therapy (RT) for patients with nasopharyngeal cancer (NPC).

Methods: Twenty-two patients with NPC treated at our hospital between April 1994 and December 2002 were the subjects of this study. They received hyperfractionated RT with a fraction size of 1.2 Gy, with a median tumor dose of 72 Gy (range 64.8–80.4). During this study period, our institutional strategy for locoregionally advanced NPC included neoadjuvant or concurrent chemotherapy combined with hyperfractionated RT, and 17 patients received some forms of cisplatin-containing chemotherapy.

Results: With a median follow-up of 59 months, the estimated 5-year disease-free survival rate and overall survival rate were 72.7 and 85.2%, respectively. Acute hematological toxicities were acceptable and manageable. However, >50% of patients required nutritional support, and experienced severe pharyngitis, skin reaction and body weight loss. With regard to late sequelae, one patient developed grade 3 osteomyelitis, and one patient each developed grade 4 passage disturbance and laryngeal edema. No patients experienced any grades of optic nerve injury or temporal lobe necrosis.

Conclusions: Hyperfractionated RT using 1.2 Gy per fraction, for a total dose of 72 Gy, produces a comparable treatment outcome. Although deleterious neurological sequelae were not observed in this study, caution should be exercised regarding other late sequelae, such as osteomyelitis and passage disturbance.

Key words: nasopharyngeal cancer (NPC) – hyperfractionation – altered fractionation – late effect

INTRODUCTION

Radiation therapy (RT) has long been a primary treatment of choice for patients with non-metastatic nasopharyngeal carcinoma (NPC). However, significant numbers of patients with locoregionally advanced disease develop recurrence above the clavicle and distant metastasis. As NPC is not only a radiosensitive tumor but also a chemosensitive one, several investigators have incorporated chemotherapy into the management of NPC in an attempt to improve both the local control rate and survival probability (1–4). As a result, concurrent chemoradiotherapy with adjuvant chemotherapy improved survival, but randomized studies have not supported the use of neoadjuvant or adjuvant chemotherapy (1–6).

In contrast, several researchers have tried to deliver a higher radiation dose, without increasing late complications, to improve the local control rate and survival probability. One of these contrivances is the application of a hyperfractionated RT schedule. The rationale for hyperfractionation is based on exploiting differences in the radiobiology of the tumor and late responding tissues (7). The observations that late responding normal tissues show greater repair of non-lethal injury between dose fractions than do tumor cells, and tumor cells in the radioresistant phase of the cell cycle are redistributed into the more radiosensitive phase between dose fractions, enabled the increase of the relative biological dose to the tumor. The recent large RTOG (Radiation Therapy Oncology Group) randomized controlled trial demonstrated that both hyperfractionation and accelerated fractionation with the concomitant boost technique were superior to standard fractionation in terms of locoregional control and disease-free survival (8). Although NPC shows a somewhat different clinical behavior from other head and neck cancers and is usually dealt with...
separately, a similar strategy has been applied for locoregionally advanced NPC, increasing the total dose to the tumor without increasing late complications, through hyperfractionation (9–16). Here we report our experience with hyperfractionated RT for patients with NPC.

PATIENTS AND METHODS

PATIENT CHARACTERISTICS

Between April 1994 and December 2000, 22 consecutive patients with locoregionally advanced NPC treated at our hospital by hyperfractionation were the subjects of this study. There were 17 males and five females, of ages ranging from 35 to 78 years with a median age of 54 years. Histological examinations according to the World Health Organization (WHO) classification revealed that nine cases were WHO II, and 12 were WHO III. Detailed patient characteristics are listed in Table 1. Pre-treatment evaluation included a complete history and physical examination with fiberoptic endoscopy, chest radiographs, computed tomography (CT) of the head and neck, chest and abdomen, magnetic resonance imaging (MRI) of the nasopharynx and base of the skull, and bone scintigraphy. All patients had a biopsy from the nasopharynx to confirm the diagnosis. Laboratory studies included complete blood counts, blood chemistry with hepatic and renal function tests, and urinalysis. Patients receiving chemotherapy also had three consecutive days of 24 h creatinine clearance. All patients were restaged using the 1997 UICC-TNM staging system, and their stage distributions are indicated in Table 1. All but one patient had stage IIIB or more advanced disease.

TREATMENT

RT therapy was delivered with a combination of 4 and 10 MV photons to achieve dose homogeneity. An appropriate energy of the electron field was also applied to treat the posterior neck node after sparing the spinal cord. The treatment volume included the primary tumor site and the neck nodes above the clavicle. The nasopharynx and the upper neck were treated with two opposed lateral fields. A separate anterior supraclavicular field was used to irradiate the lower neck and supraclavicular fossa. The fractional dose was 1.2 Gy, two fractions per day, and at least a 6 h interval between dose fractions with a planned dose of 72 Gy. The typical irradiation fields and dose distributions are shown in Fig. 1.

The median tumor dose was 72 Gy (range 64.8–80.4). Seventeen patients (77%) received 72 Gy in 60 fractions of RT, three received <70 Gy, and the remaining two received 75.6 and 80.4 Gy, respectively. The median total treatment time during RT was 45 days (range 39–54).

During this study period, our institutional strategies in the management of NPC included neoadjuvant and/or concurrent chemotherapy; however, the decision regarding whether chemotherapy would be given depended solely on the discretion of the treating physician. Although five patients did not receive any form of chemotherapy, 11 received chemotherapy concurrently with RT (CRT group). Of these 11 patients, three also received neoadjuvant chemotherapy. Of the remaining six patients, two received both neoadjuvant and adjuvant chemotherapy, and four received neoadjuvant chemotherapy exclusively. Adjuvant or neoadjuvant chemotherapy consisted of a combination of 100 mg/m² of cisplatin (CDDP) and 1500 mg/m² of 5-fluorouracil for 5 days. In a concurrent setting, five patients received 70–100 mg/m² of CDDP in a tri-weekly schedule, three received 5 or 6 mg/m² of daily CDDP administration, and the remaining three received 100 mg/m² of weekly carboplatin (CBDCA).

Acute toxicities were graded according to the National Cancer Institute common toxicity criteria version 2.0. Late toxicities were recorded according to the RTOG scale as long as this was feasible. The Kaplan–Meier method was used to calculate survival probability (17). Informed consent was provided according to the Declaration of Helsinki.

RESULTS

At the time of this analysis, 17 patients were alive with a median follow-up of 59 months (range 34–106). The estimated 5-year locoregional control rate (LCR), disease-free survival and overall survival rates were 80.2% [95% confidence interval (CI), 62.8–97.6], 72.7% (95% CI, 54.1–91.3) and 85.2% (95% CI, 69.6–100), respectively (Fig. 2). The 5-year LCR in the CRT group was 80% (95% CI, 55–100). However, it was 81% (95% CI, 57–100) among patients who did not receive concurrent chemotherapy (non-CRT group). Four patients experienced in-field recurrence, two of whom died of their disease, and the remaining two were alive after salvage operations. Two patients with intercurrent disease and one patient who developed liver metastasis also died.

The acute toxicity profiles other than hematological adverse events are listed in Table 2. Two patients experienced grade 3 leukopenia, but no patients developed more than grade 2 anemia or thrombocytopenia. Nineteen patients suffered from grade 3 skin reaction and/or pharyngitis, and the median body weight loss was 11.8% (range 1.6–24.0). As shown in Table 2, the severity of acute adverse events was not related to the concurrent chemotherapy. With regard to late complications, grade 2 and 3 xerostomia occurred in 10 (45%) and three (14%) patients, respectively. Furthermore, three patients experienced more than grade 2 sequelae. One patient developed grade 3 osteomyelitis of the mandible.
one required gastrostomy for nutritional support (grade 4) and one underwent tracheostomy for persistent laryngeal edema (grade 4). These three patients received a total dose of 72, 72 and 75.6 Gy, respectively. No patients experienced optic

Table 2. Acute adverse events other than hematological toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis (grade 3 and 4)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Skin reaction (grade 3 and 4)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Nutrition (grade 3)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Body weight loss (grade 2 and 3)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Non-CRT</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis (grade 3 and 4)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Skin reaction (grade 3 and 4)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Nutrition (grade 3)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Body weight loss (grade 2 and 3)</td>
<td>4 (36)</td>
</tr>
</tbody>
</table>

CRT, chemoradiotherapy.
nerve injury, symptomatic temporal lobe necrosis or treatment-related death. The total dose to the temporal lobe ranged from 49.1 to 75.6 Gy with a mean dose of 70.7 Gy.

DISCUSSION

External beam RT is the standard treatment for patients with NPC; however, many patients with advanced disease suffer from local recurrence. As local control is prognostically important in NPC, various attempts have been made to improve local control probability by delivering higher radiation doses. These strategies include the addition of intracavitary brachytherapy, three-dimensional conformal RT, intensity modulated RT (IMRT) and hyperfractionated RT (9–16), which would enable us to administer higher doses without an apparent increase in late normal tissue sequelae. In a review with regard to altered fractionated RT for head and neck cancer (18), Nguyen and Ang concluded that the use of three fractions per day without total dose reduction produces a significantly higher frequency of late normal tissue complications; however, a modest acceleration of RT by 1 week without total dose reduction, a break in treatment by giving six fractions of 2 Gy per week or by a concomitant boost regimen, or an acceleration of RT by >3 weeks with total dose reduction of 6–7 Gy (10%) improved locoregional control without much increase in the late toxic effect. Moreover, they stated that hyperfractionated RT is better than standard fractionation for advanced head and neck carcinoma, and that reduction of the fraction size from 2 to 1.1–1.2 Gy permits a 7–17% escalation in total doses without leading to a detectable increase in late normal tissue injury.

Similar to other head and neck cancers, several investigators have applied hyperfractionated or accelerated hyperfractionated RT for the treatment of locoregionally advanced NPC to improve locoregional control probability. Jian et al. (16) evaluated the efficacy of hyperfractionated RT using 1.2 Gy per fraction for locally advanced NPC patients with base of skull or intracranial invasion. They administered a total dose of 74.4 Gy in 62 fractions concurrently with chemotherapy. They also gave adjuvant chemotherapy thereafter, and demonstrated a 3-year LCR of 93%. For T4 patients, the 3-year LCR was 91%, and they concluded that hyperfractionation achieved excellent local control and improved survival with acceptable and reversible toxicities. Jen et al. (15) also suggested that NPC patients can be safely treated using a 1.2 Gy twice daily program with a 6 h interval up to 80 Gy. The results of these two studies were well in accordance with those of our present study, which demonstrated that a 1.2 Gy hyperfractionated RT schedule for locoregionally advanced NPC produced promising outcomes without an increase in late normal tissue complications.

In contrast, a group from the Prince of Wales Hospital (PWH) first warned that accelerated hyperfractionation caused an unexpectedly high incidence of temporal lobe necrosis in patients with NPC (9). They reported that the incidence of temporal lobe injury was 35% at 2–3.5 years after hyperfractionated RT. They used a fraction size of 1.6 Gy to a total dose of 67.2 Gy, which was devised at Massachusetts General Hospital (MGH); however, the MGH group reported that no patient developed major neurological complications (13). In an update report in 1999 (10), the PWH group speculated that the discrepancy between the MGH group results and their experience was derived from the marked difference in delineating the target volume. In a final report from the PWH (11), they concluded that accelerated hyperfractionation when used in conjunction with a two-dimensional RT planning technique resulted in increased radiation damage to the central nervous system without significant improvement in efficacy. In response to a commentary from the PWH group, a Turkish group also abandoned hyperfractionated RT using the concomitant boost technique, because they also observed severe neural complications including temporal lobe necrosis and optic neuropathy (12). Jen et al. (14,15), who have accepted hyperfractionated RT using 1.2 Gy per fraction, also warned that an accelerated hyperfractionation schedule using 1.6 Gy per fraction led to a high incidence (27%) of temporal lobe necrosis. These reports suggest that accelerated hyperfractionation employing a fraction size of 1.6 Gy would result in a significant increase in late neurological toxicities.

No reports documented severe late sequelae other than damage to the central nervous system. Although we did not experience clinically detectable late optic nerve injury or temporal lobe necrosis, we encountered two patients who developed grade 4 late complications. As the PWH group have suggested, we have to seek to reduce the risk of late normal tissue toxicities by delineating the target volume carefully. The present study demonstrated that hyperfractionated RT using 1.2 Gy per fraction could produce a comparable outcome with acceptable and manageable acute toxicities, and we conclude that 1.2 Gy per fraction of hyperfractionated RT, for a total dose of 72 Gy, would be an acceptable treatment for locoregionally advanced NPC.

References


