Early Stage Nasopharyngeal Carcinoma: Radiotherapy Dose and Time Factors in Tumor Control

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Objective: To evaluate radiotherapy dose and length of treatment in the control of early stage nasopharyngeal carcinoma (NPC) treated with a combination of external radiotherapy and brachytherapy,

Materials & Methods: We reviewed the records of 133 patients with early stage nasopharyngeal carcinoma (stage I or II, AJC/UICC staging system) who received definitive radiotherapy in Chang Gung Memorial Hospital from 1979 to 1991. The median follow-up time was 7.1 years with a minimum of 2 years. All patients were treated with megavoltage external radiotherapy to the nasopharynx area (63–72 Gy) followed by high dose rate intracavitary brachytherapy (5–16.5 Gy in one to three fractions, spaced 1–2 weeks apart). The median total dose and time of irradiation was 75 Gy (69.8–81.4 Gy) and 11.6 weeks (7.8–20 weeks) respectively. Survival analysis was used to examine the effect of several variables on prognosis.

Results: The 5-year rates were 86.4% for local control, 84.7% for disease free survival, 88.5% for actuarial survival and 84.2% for overall survival. The treatment group (combination of time and dose of irradiation) was the most important prognostic factor according to Cox's proportional hazard model. Patients receiving radiation at a total dose of ≤75 Gy completed in <12 weeks showed the best prognosis.

Conclusion: Treatment time and total treatment dose are both important factors in treating early stage NPC. Decreasing the total radiation time to <12 weeks and not exceeding a radiation dose of 75 Gy gave the best results.

Key words: treatment time – total radiation dose – early stage nasopharyngeal carcinoma – intracavitary brachytherapy

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is rare in most parts of the world (1), but it is relatively common in Southeast Asia. Chinese populations, living either in mainland China or elsewhere, have the highest incidence of this tumor worldwide (2). It is estimated that the prevalence of NPC in Taiwan is 6.9 and 3.4 per 100,000 per year for males and females respectively (3). The overall 5-year survival rates range between 60 and 85% for patients with stage I or II NPC but drop to about 30% for those with stage III or stage IV disease (4).

The major treatment modality for NPC is radiation therapy (RT) (5). The effect of RT dosage on this tumor has been investigated extensively, but controversy remains. Some studies (6-8) have reported benefit from elevating the radiation dose in NPC, but others have found no association (9-11). Few of these studies focused on early stages of the tumor, treated with the conventional radiotherapy strategy of five fractions per week, at 1.8–2 Gy per fraction. The role of total irradiation time in local regional control of other cancers has been emphasized recently (12-15), but again, there have been conflicting results with regard to NPC (16-18). Moreover, how the interaction of dose and total RT time influence the prognosis of NPC has never been studied. Unlike other factors such as age, gender and stage of the tumor, dosage and length of RT are two components which physicians can easily manipulate to control the disease. From the clinical point of view, understanding the effects of these two controllable factors is essential for developing optimum treatment strategies for NPC.
As a starting point in evaluating these factors, we retrospectively reviewed NPC patients treated at the Chang Gung Memorial Hospital-Linkou from 1979 to 1991. In order to limit possible confounding factors, we restricted the study subjects to patients with early NPC (stage I or II) who were treated with combined external radiotherapy and brachytherapy.

PATIENTS AND METHODS

PATIENT CHARACTERISTICS

From 1979 to 1991, 2270 patients with NPC were treated at the Department of Radiation Oncology of CGMH at Linkou. A total of 194 patients had histologically proven stage I or II NPC (AJCC/UICC staging system). Sixty-one patients were excluded from this study, comprising 11 patients who did not complete the planned treatment or whose total treatment time was longer than 6 months, and 50 patients who received external RT alone. The rationale for excluding the latter was that RT dose calculation differs considerably between external RT and intracavitary brachytherapy (ICBT). In addition, RT plus brachytherapy has different biological effects than external RT alone. We have shown previously that the use of ICBT provided better tumor control than did external RT alone (19). The records of 133 patients treated by combined external RT and ICBT were thus analyzed for this study.

There were 93 males (70%) and 40 females (30%), with a median age of 46 years (range 24–77). The pathology of all the tumors was documented as undifferentiated or squamous cell carcinoma of the nasopharynx. (Lymphoepithelioma is considered a variant of undifferentiated carcinoma.)

CLINICAL STAGING

Tumor staging was based on routine oncological evaluation, including physical examination, anterior rhinoscopy, indirect with or without direct nasopharyngoscopy, blood biochemistry, chest X-ray, bone scan, skull X-ray and conventional tomography. Computerized tomography had only been performed for staging in 73 of the patients. The rest had not had it, either because of its unavailability in the early years of the study period or because of high cost. Patients with a complaint of headache were considered to have T4 lesions and were excluded from this study.

TREATMENT MODALITIES

Standard treatment methods have been described previously (20). The primary tumor and upper neck were treated with $^{60}$Co or a 6 Mv photon beam via bilateral opposing portals. The lower neck was treated at a prescribed depth of 3 cm. External radiotherapy was given in five fractions per week at 1.8 Gy per fraction. After 26 fractions, radiation to the primary tumor area (excluding the spinal cord) was boosted using a 10 Mv beam, providing 16.2–25.3 Gy in 9–14 fractions. The total external dose ranged from 63–72 Gy with a median of 64.8 Gy; 95 (74.5%) patients received the median dose. ICBT, using a 2 curie $^{60}$Co source, was administered with a remote-controlled afterloading system (RAL) providing $\pm$5.5 Gy, 2 cm from the source to the major tumor site. This was given in an area about to the midline of the pterygoid fossa, in one or two applications spaced 1–2 weeks apart. In 77 patients, an additional 10–14 Gy was given to the upper neck by electron beam. The median total irradiation dose was 75 Gy (69.8–81.4). The total treatment time ranged from 7.8 to 20 weeks with a median of 11.6 weeks. Interruptions of therapy were mainly due to acute toxicity, holidays, machinery breakdown, insufficient machines and the interval between external radiation and brachytherapy.

FOLLOW-UP AND STATISTICAL ANALYSIS

The majority of patients were followed regularly up to December 1993. For those who did not return to the clinic, follow-up information was obtained from the patients themselves, their family, or the household registration office. Those who returned to the clinic regularly received a complete ENT examination, chest X-ray and period blood biochemical analysis. Bone and CT scans were performed for patients who had a relapse of symptoms or abnormal laboratory data. For the final 6 years of the study period, head and neck CT or MRI studies were performed periodically because most patients had insurance coverage or were able to afford them. Local recurrence was defined as a positive tissue biopsy or obvious recurrent tumor seen in the nasopharynx on CT or MRI and/or the presence of clinical symptoms. Metastasis was defined as new clinical symptoms or signs and compatible imaging or pathological findings in areas other than the nasopharynx.

To evaluate tumor behavior, we defined four outcomes: local recurrence, metastasis, death due to the tumor and death due to causes other than the tumor, and we analyzed the time from completion of treatment to occurrence of these outcomes. The Kaplan–Meier method was used to compute the rates of local control (endpoint: local or regional recurrence), disease free survival (endpoint: local and/or regional recurrence or metastasis), actuarial survival (death due to the tumor), and overall survival (death due to any cause). The effects of six possible prognostic factors (age, gender, initial CT scan, neck boost, irradiation dose and treatment time) were examined univariately using the log rank test (21) and multivariately using Cox’s proportional hazard model (22). The patients were stratified by age (≤40 and >40 years), as previous studies have shown a survival advantage in patients less than 40 years old (23). In general, $P \leq 0.05$ was accepted as indicating statistical significance. In pairwise comparisons, statistical significance was defined when the $P$ value was <0.05 divided by the number of pairwise comparisons.

RESULTS

Table 1. Final status by recurrence and metastasis of NPC

<table>
<thead>
<tr>
<th>Recur</th>
<th>Meta</th>
<th>Final status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lost F/U</td>
</tr>
<tr>
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<td>No</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
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</tr>
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<td>Yes</td>
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<td>Totals</td>
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</tbody>
</table>

Recur, recurrence; Meta, metastases; Loss F/U, lost to follow-up.
Table 2. Results of univariate analysis

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<th>Actuarial</th>
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<tr>
<td></td>
<td>n</td>
<td>No. events</td>
<td>5-yr rate (%)</td>
<td>No. events</td>
<td>5-yr rate (%)</td>
<td>No. events</td>
</tr>
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</tr>
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<td>13</td>
</tr>
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<td>13</td>
<td>15</td>
<td>0.0292</td>
<td>19</td>
<td>20</td>
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<td>9</td>
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<td>Female</td>
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<td>0.0021</td>
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<td>13</td>
</tr>
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<td></td>
<td></td>
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<td>II</td>
<td>III</td>
<td>IV</td>
<td>I</td>
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<td>5</td>
<td>7</td>
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<td></td>
<td></td>
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<td>5</td>
<td>5</td>
<td>12</td>
<td>97.7</td>
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</table>

*Treatment groups: I, ≤75Gy, <12wk; II, >75Gy, <12wk; III, ≤75Gy, ≥12wk; IV, >75Gy, ≥12wk.

The median follow-up time was 7.1 years with a range of 2–14.7 years. Five patients (3.8%) were lost to follow-up (Table 1). A total of 23 patients had a local relapse alone, five had metastases alone, and two had relapses both locally and distantly. Of those with local relapse alone, 10 tumors were confined to the nasopharynx area, three were intracranial or invading the base of the skull, and 10 were in the nasopharynx with intracranial or basilar skull extension. Metastases occurred in bone (four patients), liver (two patients) and lung (two patients), and two patients had metastases in two organs (bone and liver). Salvage radiotherapy with another 36–50 Gy was given to those with local or regional relapse, and cisplatin-based combination chemotherapy to those with metastases. The five-year rates were 86.4% for local control, 84.7% for disease free survival, 88.5% for actuarial survival and 84.2% for overall survival. The mean time at which the failure events occurred were 7.4 years (SD 0.20) for local recurrence, 7.5 years (SD 0.20) for local or distant recurrence, 10.7 years (SD 0.32) for deaths due to NPC and 10.2 years (SD 0.39) for overall deaths (Fig. 1).

Certain factors that were tumor-related were also examined to evaluate their effects on outcome (excluding overall survival). Underestimation of tumor stage might have occurred in patients who had not undergone a staging CT scan. We found no significant differences, however, in outcome between those with and without initial staging CT scan (Table 2), suggesting that incorrect staging was not a significant problem in the study. The effects of age and gender were also evaluated. Patients aged 40 or under had better rates of local control (P = 0.0292), disease free survival, disease free rate and local control rate are shown.
survival ($P = 0.0795$) and actuarial survival ($P = 0.0494$). Females had better prognosis in these rates but significance was not reached in any of these rates. Patients treated with electron boost to the neck were also found to have a better local control rate ($P = 0.0361$), disease free survival ($P = 0.0553$) and actuarial survival ($P = 0.0739$), suggesting that neck electron boost is beneficial in controlling the disease.

We are unaware of reports in the literature defining optimum RT dose or length of treatment for NPC. We therefore evaluated our data to determine appropriate cutoff points for these variables. We found that RT dose and treatment time were positively correlated (Pearson's correlation coefficient $r = 0.30, P = 0.0005$) and therefore chose to consider them together. Figure 2 displays a scatter plot of dose against treatment time for local recurrence. Similar results were seen for the other outcomes (details not shown). After evaluating various cutoff points, four treatment groups were defined: I, $\leq 75$ Gy and $<12$ weeks; II, $>75$ Gy and $<12$ weeks; III, $\leq 75$ Gy and $\geq 12$ weeks; IV, $>75$ Gy and $\geq 12$ weeks. Treatment group I had the best prognosis according to 5-year rates of local control (97.6%), disease free survival (97.7%) and actuarial survival (97.7%) (Table 2). These 5-year rates drop gradually, from 85.1-88.9% for treatment group II to 81.0-88.6% for treatment group III and to 65.9-73.1% for treatment group IV (Fig. 3). The effects of treatment group were highly significant for all three outcomes: local control ($P = 0.0021$), disease free survival ($P = 0.001$) and actuarial survival ($P = 0.0075$). Pairwise comparisons among the treatment group indicated that significant differences were only seen in the rates of local control, disease free survival and actuarial survival between treatment group I and treatment group IV ($P$ values were 0.0008, 0.0003 and 0.0002 respectively).

Table 3 shows the result of stepwise Cox's proportional hazard model. Only treatment group was included in the final model for any of the rates. Although the risks of local recurrence, local or distant recurrence, or death were higher than the tumor increased two to four times for treatment groups II and III compared to group I, these differences did not reach statistical significance (95% CIs included 1.00). Treatment group IV had a significantly higher risk of local recurrence (7.63), local or distant recurrence (8.35), or death due to the tumor (9.05), than did group I.

Most patients experienced some degree of minor complications, e.g. xerostomia, tinnitus, trismus or crusting of the nasopharynx. Twelve patients had major complications. One had NPC necrosis and 11 had soft palate or sphenoid floor perforation. None had temporal lobe radiation necrosis according to the available follow up CT scans.

Table 3. Results of Cox's proportional hazard model

<table>
<thead>
<tr>
<th>Group</th>
<th>Local recurrence</th>
<th>Local or distant recurrence</th>
<th>Death due to NPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>I</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
</tr>
<tr>
<td>II</td>
<td>2.26</td>
<td>0.68-11.96</td>
<td>2.86</td>
</tr>
<tr>
<td>III</td>
<td>3.28</td>
<td>0.99-14.91</td>
<td>3.85</td>
</tr>
</tbody>
</table>

* Treatment groups: I, $\leq 75$ Gy, $<12$ wk; II, $>75$ Gy, $<12$ wk; III, $\leq 75$ Gy, $\geq 12$ wk; IV, $>75$ Gy, $\geq 12$ wk; $^P < 0.05$. RR, relative risk.
DISCUSSION

In recent years, the role of total length of radiation treatment in treating cancer has attracted considerable attention, but it has not been extensively studied for NPC. Before conducting a lengthy and expensive prospective study, we believed it was wise to perform a retrospective analysis of our existing NPC records to provide practical treatment parameters on which to base such a prospective study.

To evaluate whether the results in our series are reasonable, several aspects were considered. First, use of three tumor-related outcomes allowed us to study the behavior of the tumor. The results of univariate and multivariate analysis of these three outcomes were consistent enough to give us confidence in our results. Our 5-year rates of local control (86.4%), disease-free survival (84.7%), actuarial survival (88.5%) and overall survival (84.2%) are similar to previous findings (23). Second, in agreement with other studies, we found that patients under 40 and those who had received an electron boost to the neck had a better prognosis. Multivariate analysis showed that the predictive power of age was less important than that of treatment group once the latter was entered into the model. Females seemed to have a better 5-year rate for local recurrence free survival, disease free survival and actuarial survival, but these differences essentially disappeared by 7 years, so a significant difference was not shown over the entire study period. Third, confounding effects from other variables were controlled for, either by limiting our study population or by multivariate statistical techniques. The present study only evaluated patients with early stage NPC (I: T1, N0, M0 or II: T2, N0, M0) who underwent similar treatment. It has been shown that combining these two tumor stages is reasonable, especially as distinguishing between them is difficult, similar treatment protocols are used for both stages, and their prognoses are similar (24). Further possible confounding factors (age, gender and electron boost to the neck) were also controlled for by multivariate statistical analysis. Fourth, we attempted to minimize understaging of the tumor by carefully reviewing skull X-rays and conventional tomography to detect basilar skull destruction for those patients who had not undergone initial CT scan. This, plus exclusion of patients with headache, may account for the fact that the use of CT scan in the initial work up did not strongly influence the results. Another study has suggested that use of a staging CT scan does not correlate with improvement in local recurrence free survival in T1 and T2 lesions (25).

However, RT dose and length of treatment were less well controlled, since this was a retrospective study. The overall treatment time was defined as the duration of combined external radiotherapy and brachytherapy, similar to study of cervical cancer conducted by Perez et al. (26) and Keane et al. (14). Girinsky et al. (27) treated 386 patients with cervical carcinoma using a very narrow range of RT dose (45–50 Gy, 90% receiving 50 Gy) and found a linear decrease in local control rate with prolongation of treatment time. A similar inverse relationship between length of treatment and local control rate was also found in a study by Keane et al. (14), treating tonsillar carcinoma (186 patients, total dose 50 Gy) and cervical cancer (621 patients, 45 Gy external beam and 40 Gy intracavitary). Our experience with a much wider range of RT doses (69.8–81.4 Gy) did not enable us to isolate the effect of treatment time from treatment dose as they were positively correlated. Our small number of patients (n = 133) also did not allow us to select only those who had received an RT dose within a narrow range, in order to separate out the effect of treatment time alone. The treatment period was also considerably longer for many patients in our series because this aspect was not well understood until recently.

We therefore needed to find an approach that would provide meaningful data by correlating dose and length of treatment. Neither discriminant analysis nor an ROC curve (in which occurrence time of the event was not accounted for) were helpful. We were able, however, to stratify patients into four different treatment groups (based on dose and time) by using simple scatter plots plus a series of log-rank tests based on different cutoff points.

Both univariate and multivariate analysis revealed that treatment I (≤ 75 Gy over <12 weeks) yielded the best prognosis, followed by II (> 75 Gy over <12 weeks) and III (≤ 75 Gy over ≥ 12 weeks). In fact, treatment groups II and III showed very similar behavior. Treatment group IV (> 75 Gy over ≥ 12 weeks) yielded the worst results, which differed significantly from treatment group I. Minimum RT doses have been recommended for treating NPC, but a maximum has not been suggested. Vikram et al. (17) and Lee et al. (28) suggested a minimum of 65 Gy. Perez et al. (29) found that a dose higher than 70 Gy gave 100% control in T1–3 NPC. Only two patients (1.5%) received the lowest dose of 69.8 Gy in our series; this data is insufficient to determine the lowest effective RT dose. However, our findings do suggest that a maximum of 75 Gy should not be exceeded when treating early stage NPC.

Withers et al. (12) suggested that accelerated proliferation of tumor clonogens during radiotherapy might explain the consistently observed decreases in local control with increasing overall treatment time. He postulated a possible onset of accelerated proliferation at about 4 weeks from the start of daily-fractionated radiotherapy. Keane et al. (14) supported this hypothesis, but they could not exclude the possibility that proliferation may commence at an earlier time in the context of more accelerated fractionated regimens. Overgard et al. (30) suggested that an increased dose of 11–12 Gy might compensate for prolongation of treatment time in laryngeal cancer. If this is so, it might explain why the results of treatments II and III were similar in our study.

Some authors (7, 17) have reported that increasing the radiation dose improves both tumor control and survival. In our study, we found better tumor control when the radiation dose was increased to 72.5–75 Gy but worsening results if it was pushed up to more than 75 Gy. After carefully reviewing the records again, we concluded the difference was not due to an increase in fatal complications caused by the higher irradiation dose. It is possible that higher doses were used for tumors that were bulkier or more radioresistant, but the available data did not allow us to analyze such a relationship. A recent prospective study (31) showed that an increase in the radiation dose gave a trend toward increased local control in head and neck cancer patients at 24 months but not...
in overall tumor control and survival. Murray et al. (32) suggested that moderate increases in the radiation dose gave the best results in quality-adjusted survival in malignant glioma patients. Cox et al. (33) reported similar benefit in patients with clinical N2 non-small-cell lung cancer by increasing the irradiation dose to 69.6 Gy by hyperfractionation. Doses greater than that resulted in poorer survival, in the absence of an increase in acute or late toxicities. These findings are consistent with our results in which tumor control did not improve with doses above 75 Gy.

The total radiation time for our NPC patients was much longer than that reported by other studies (25,34). Lee et al. (34) reported 7-year actuarial survival (85%) and local relapse free survival (62%) of early stage NPC, results that are similar to our findings. However, the median overall treatment time in Lee’s study (16) was 39 days (ranging from 38 to 75 days), much shorter than our median of 11.6 weeks. The median dose used in our study was 10 Gy higher than Lee’s. In addition, we gave a large fraction of radiotherapy by ICBT as the final stage of therapy. These differences in treatment strategy and techniques make a comparison between our study and Lee’s problematic. Nevertheless, this retrospective analysis does suggest a maximum treatment time which should not be exceeded when treating early stage NPC patients. Clearly a treatment time of 12 weeks is far above the current recommendation for treating NPC. Our retrospective study has in fact provided good guidelines for future prospective studies, as well as suggesting a better regimen until further research clarifies the optimum dose and length of RT. We have changed our treatment policy for patients with early stage NPC, increasing the external radiation dose from 68.4 to 70.2 Gy and decreasing the fraction size (2–2.5 Gy per fraction) and number (one to three) of treatments with ICBT. Our preliminary observations with this new combination treatment have not shown any major complications; even minor side effects such as crusts in the nasopharynx and foul odor from the nasal cavity are rarely seen. The analysis of local control and survival with this regimen requires longer follow-up.

In conclusion, our retrospective analysis indicates that early stage NPC patients treated with irradiation generally have a good prognosis. In our series, treatment with ≤75 Gy for <12 weeks was associated with the best prognosis. Further prospective studies should seek to establish optimum dose and treatment time below these maximum values.

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References


