Clinical Research Paper

Efficacy of accelerated fractionation versus conventional fractionation for nasopharyngeal carcinoma

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Key words: nasopharyngeal neoplasm, radiotherapy, accelerated fraction, conventional fraction, treatment efficacy

Background and Objective: Radiotherapy is an important treatment for nasopharyngeal carcinoma (NPC). The timing of radiotherapy itself has attracted more attention nowadays. This study assesses the efficacy of accelerated fractionation (six fractions per week) versus conventional fractionation (five fractions per week) on NPC, with the goal of improving treatment efficacy without increasing complications.

Methods: Three hundred and thirty-nine NPC patients treated with radiotherapy were retrospectively analyzed, including 181 patients in the accelerated fractionation group and 158 patients in the conventional fractionation group. All patients were irradiated using a 6MV X-ray beam, 2 Gy per fraction, once a day. A total dose (TD) of 64–72 Gy, divided into 32–36 fractions, were irradiated to the nasopharyngeal region; a TD of 62–68 Gy, divided into 31–34 fractions, were irradiated to the cervical region. The TD of prophylaxis was 50–52 Gy, divided into 25–26 fractions. All N3 patients received adjunct chemotherapy.

Results: The one, three and five year local control and survival rates of the accelerated fractionation group and the conventional fractionation group were (98.9% and 98.3%) vs. (98.1% and 96.8%), (95.5% and 91.2%) vs. (88.2% and 80.4%), (87.3% and 69.6%) vs. (76.6% and 51.3%), respectively. The three and five year local control and overall survival rates between the two groups were significantly different (p = 0.079 and p = 0.0011 vs. p = 0.09 and p = 0.0001). The incidence of acute reactions was higher in the accelerated fractionation group than in the conventional fractionation group (p = 0.002). The period was significantly longer in the accelerated fractionation group than in the conventional fractionation group (p = 0.002).

Conclusion: Compared with conventional fractionation, accelerated fractionation significantly improves the three and five year local control and overall survival rates, as well as the disease-free rate for NPC patients without increasing delayed toxicity.

Nasopharyngeal carcinoma is a common malignant tumor of the neck and head. Radiotherapy is an important treatment approach. According to the current research results in radiobiology, the increased proliferation of cloned tumor cells is the primary reason for failure in treatment. The factor of time and dosage dependency becomes a focus in the research for radiotherapy. However, the questions of best treatment time and best dosage fraction remain to be answered. The author used the regimen of six administrations per week of increased fractioned radiotherapy to treat patients of nasopharyngeal carcinoma to observe its therapeutic effect and toxic reactions. Also, the result was compared to the regimen of five administrations per week of increased fractioned radiotherapy. The retrospective analysis was then presented as follows.

Materials and Method

General data. Three hundred sixty-two cases of nasopharyngeal carcinoma were treated in the Therapeutic Radiology Department in People’s General Hospital of Hainan Province from February 1997 to February 1999. Three hundred thirty-nine cases were included in the study: 181 were in the group receiving six administrations per week and 158 were in the group receiving five administrations per week. Inclusion criteria were: (1) Pathological confirmation of poorly differentiated nasopharyngeal squamous cancer; (2) KPS score ≥70; (3) Ages were between 18- and 70-years-old; (4) Normal results in liver/kidneys function, chest x-ray and hepatic ultrasound; (5) No sign of remote metastasis was seen. Before treatment, examinations given included complete physical examination, CT/MRI of nasopharyngeal region, direct or indirect nasopharyngeal endoscopy, and an ECT scan of bones if necessary. According to the staging standard by Fuzhou in 1992, the composition charts of clinical data for the two groups are as shown in Table 1. The comparison of the data of the two groups presented no statistical significance and thus, they were comparable.
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Radiotherapy. Direct line accelerator 6MVX radiation was employed. At the neck, high energy electronic radiation was added, with 2.0 Gy per trial and once per day. Increased fractioned radiotherapy was performed six times per week, while the routine fractioned radiotherapy was only performed five times per week. The total dosages (TD) were listed in the followings: Nasopharyngeal part, TD64-72Gy/32-36fx; Neck, TD62-68Gy/31-34fx; Prevention, TD50-52Gy/25-26fx. The total treatment times for the group with six treatments per week and the group with five treatments per week were 37–42 days and 44–50 days, respectively. They were relatively shortened by seven to eight days. Patients in stage N3 all cooperated with designed radiotherapy.

Follow-ups. During treatment, examination was given once per week. After treatment, first re-examination was given at the end of the first month. Then, for the following one year, re-examination was given once per three months. Check-ups were given every six months for the next two to three years before the re-examination continued once every year. Besides routine examinations for the follow-up, check-ups included CT examination on a tentative schedule. The duration of follow-up started on the date at the end of radiotherapy and continued until February 20, 2006.

Statistical analysis. SAS 6.12 software was used for statistical analysis and the logrank method was used as a variance test. A chi-square test was used for comparison of composition. The survival rate and local control rate were calculated using the Kaplan-Meier method.

Results

Status at the completion of treatment and results of follow-ups. No cases were terminated due to acute reaction to radiation. The follow-up rate for the group was 100%. The medium follow-up time was 5.5 years (six months to eight years).

Local control rate and survival rate. The local control rate and survival rate for up to one year in the group with six treatments per week were 98.9% and 98.3%, respectively. The rates for the group with five treatments per week were 98.1% and 96.8%, respectively. They had p > 0.05, indicating no statistical significance. The local control rate and survival rate for up to three and five years in the group with six treatments per week were 95.3% and 88.4%, while the rates for the group with five treatments per week were 88.6% and 79.7%, respectively. The compared difference in the local control rates of the two groups had statistical significance (p < 0.05). The survival rates for up to three and five years in the group with six treatments per week were 91.2% and 69.6%, respectively. The rates for the control group were 80.4% and 51.3%. The compared difference in the survival rates had statistical significance (p < 0.05).

Reaction to radiation. The toxic reaction to radiotherapy was judged according to the RTOG standard by American Society for Therapeutic Radiology and Oncology. In the aspect of early reactions, were the following: The appearance rates for grade III reaction in the epidermis and mucous membrane in the group with six treatments per week were 5.2% and 14.8% and there were five cases with reactions of grade IV. The appearance rates of the group with five treatments per week were 3.3% and 9.2% and there was one case with reaction of grade IV. There was no evidence of aggravated late stage reactions (Table 2).

Recurrence, metastasis, mortality and survival rate without cancer. In the group with six treatments per week, 15 patients died from recurrent tumor in the laryngeal region, and eight of these cases had remote metastasis. Three patients, who died from recurrent tumor at lymph nodes of neck, also had remote metastasis. Forty patients died from remote metastatic sites (bones, liver, lungs, brain, etc.). In the group with five treatments per week, 23 patients died from recurrent tumor at laryngeal region, where 15 were complicated with remote metastatic sites. Five patients, who died from recurrent tumors in the lymph nodes of neck, also had remote metastasis. Fifty-four patients died from remote metastatic sites. Of the group with six treatments per week (68.0%) survived...
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They divided the 580 patients into two groups, where they received a total dosage of 66 Gy, which was fractioned for 33–37 times, yielding 1.8–2.0 Gy per administration. One hundred and fifty-eight cases were in the group with six treatments per week and 167 cases were in the group with five treatments per week. The local control rates for patients in stage T3 and T4 were 87% and 62%, respectively, and the difference was significant without cancer which was a significantly improvement over the group with five treatments per week (48.1%). This difference had statistical significance (p < 0.05).

Discussion

In many clinical researches, the increased proliferation of tumor stem cells is considered as an independent factor for affecting prognostic outcome of radiotherapy, while the time factor is also getting more attention in radiotherapy. The re-proliferation of survived tumor cells after fractional radiotherapy is one of the important factors in the relationship between the course of treatment and the therapeutic effect.1,2 By continuing the conventional fractionated radiotherapy (CF) for more than half a century, with a dosage of external exposure at 60-70Gy/30-35fx/6-7w, a more ideal balance can still be reached between the control rate, the acute reaction, and the complication rate in late stage, as most malignant tumors are usually located locally in a region exposed to radiation. Thus, radiotherapy continues to be accepted for clinical treatment of tumors. As the professional concept of radiology for tumor updates and the theories advance, it is now proven that elongation of radiotherapy can cause a decrease in local control rate and an increase in the recurrence rate.3 For the question on the beginning and duration of increased re-proliferation, it still remains controversial. There are reports that tumors of the neck may increase proliferation three to four weeks after the start of treatment.4,5 Therefore, clinically, there are different proposals for increased fractionated radiotherapy. Further research suggests that the increased re-proliferation of a tumor is related to the duration of radiotherapy. As the course elongates, the number of increased re-proliferated cells increases. For tumor of \( T_{pot} = 3 \) d and for each delayed day in the course of treatment, an additional dosage of 0.66 Gy will be required to compensate the proliferation of tumor in the day.6 Therefore, the author employed the increased fractioned radiotherapy with six treatments per week to shorten the total course and to reduce the increased re-proliferation of tumor cells. In the equation of linear quadratic model (LQ):7

\[
BED = D[1 + d(\alpha/\beta)] - K(T - Tk)
\]

where the variables are the followings: BED is the biological effective dose; D is the total dosage (Gy); d is the dosage per trial (Gy); K is 1.98/\( T_{pot} \) (Fowler); T is the total course of treatment (days); and Tk is the delayed time from the first treatment to the beginning of proliferation (days).

In this study, the calculation was based on the start of increased re-proliferation four weeks after treatment and the radiation dosage for nasopharyngeal region would be 64–72 Gy. The BED for the group with six treatments per week was around 72.86 to 77.16 Gy, while the BED for the group with five treatments per week was 68.24 to 71.88 Gy. This was relatively increased by 4.62–5.28 Gy. Therefore, it could be assumed that to increase the local control rate, the total course of treatment under the same dosage must be shortened, in order to reduce re-proliferation of tumors and to decrease the number of tumor cells. Lee et al.8 conducted a research on 325 patients with nasopharyngeal carcinoma and divided them into two groups, where they received a total dosage of 66 Gy, which was fractioned for 33–37 times, yielding 1.8–2.0 Gy per administration. One hundred and fifty-eight cases were in the group with six treatments per week and 167 cases were in the group with five treatments per week. The local control rates for patients in stage T3 and T4 were 87% and 62%, respectively, and the difference was significant.

### Table 2 Delayed radiation damage in patients of the accelerated and conventional fractionation groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Accelerated fractionation</th>
<th>Conventional fractionation</th>
<th>( \chi^2 )</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation brain damage</td>
<td>15 (8.3)</td>
<td>12 (7.6)</td>
<td>0.055</td>
<td>0.814</td>
</tr>
<tr>
<td>Radiation Myelopathy</td>
<td>11 (6.0)</td>
<td>8 (5.0)</td>
<td>0.164</td>
<td>0.686</td>
</tr>
<tr>
<td>Minor</td>
<td>9 (5.0)</td>
<td>6 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (1.0)</td>
<td>2 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trismus</td>
<td>48 (26.5)</td>
<td>40 (25.3)</td>
<td>0.064</td>
<td>0.801</td>
</tr>
<tr>
<td>Minor (1.5–3.0 cm)</td>
<td>32 (17.7)</td>
<td>28 (17.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (&lt;1.5 cm)</td>
<td>16 (8.8)</td>
<td>12 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral dryness</td>
<td>115 (63.5)</td>
<td>95 (60.1)</td>
<td>0.416</td>
<td>0.519</td>
</tr>
<tr>
<td>Minor</td>
<td>63 (34.8)</td>
<td>54 (34.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>52 (28.7)</td>
<td>41 (25.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>117 (64.6)</td>
<td>99 (62.7)</td>
<td>0.143</td>
<td>0.705</td>
</tr>
<tr>
<td>Minor</td>
<td>60 (33.1)</td>
<td>56 (35.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>36 (19.9)</td>
<td>27 (17.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaf/hearing aid</td>
<td>21 (11.6)</td>
<td>16 (10.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck skin fibrosis</td>
<td>93 (51.4)</td>
<td>78 (49.4)</td>
<td>0.137</td>
<td>0.711</td>
</tr>
<tr>
<td>Minor</td>
<td>62 (34.2)</td>
<td>53 (33.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>31 (17.2)</td>
<td>25 (15.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multi-factorial analysis revealed that the six treatments per week could significantly boost the local control rates in stage T2 and T3. Overgaard et al. reported on 1,476 cases of first-time squamous cancer of neck and head, which were randomly grouped into five or six fractions of weekly radiotherapy, from the multi-center research in Denmark. The results showed that the local control rate for the group with six treatments per week over five year period was significantly improved (p = 0.0005) and this improvement was much more prominent in patients with a primary tumor (p = 0.0001). The survival rate without cancer was also improved, but without statistical significance. The one year, three year and five year local control rates and survival rates in this study were much higher in the group with six treatments per week than in the group with five treatments per week. Also, the three year and five year local control rates and survival rates had statistical significances (both were p < 0.05). The survival rate without cancer also improved and had statistical significance (p < 0.05).

Although there are many factors that affect injury by radiation as the intensity, dosage, and time for radiotherapy increases, it will certainly aggravate the earlier reactions to radiation. Late reactions usually reflect whether normal tissues have none or some proliferation ability during radiotherapy. In terms of radiological injury, the primary task involves repair and such repair is usually complete when it only suffers a sub-lethal damage (SLD) by routine fractioned radiotherapy. According to the calculation using the clinical applicational equation:

$$BED = D[1 + d/(\alpha/\beta)]$$

of the LQ model, the group with six treatments per week was the same as the group with five treatments per week. Therefore, injury due to late stage complications were not aggravated. The report by Lee et al. indicated that in 325 patients with nasopharyngeal carcinoma, after respectively five and six treatments of weekly radiation, the number of patients suffering more than grade III of acute reactions to radiation were more often in the group with six treatments per week than in the group with five treatments per week (p < 0.01). However, patients were able to tolerate reactions and continued without further interruption to treatment. Nor did their injuries aggravate in late stage treatment. The report by Overgaard et al., which included 1,766 first-time cases of squamous cancers of the neck and head, receiving five or six treatments of weekly routine fractioned radiation, showed that patients from the group with six treatments per week suffered more aggravated acute reactions to radiation but those reactions were still in the tolerable range, while their injuries in late stage did not worsen. The research results of the early and late reactions by this study were also similar. No one chose termination to treat due to acute reactions to radiation.

This study’s results suggested that under the circumstances, with no aggravation in toxic adverse reactions to radiotherapy and no increased complications in late stage, patients of nasopharyngeal carcinoma could benefit more from six treatments per week than the routine fractioned radiotherapy. In addition, the treatment time could be shortened and the number of tumor cells could be reduced. These were all beneficial to the improvement of local control rate and survival rate. It suggested that this approach is plausible. The cancer-free survival rate improved and the rate of remote metastasis decreased. Whether these results are related to the shortening of the course of treatment requires a larger sample size to assess.

References