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Original Article

Dose Escalation of Three-dimensional Conformal Radiotherapy for Locally Recurrent Nasopharyngeal Carcinoma: A Prospective Randomised Study

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ABSTRACT:
Aims: **To investigate prospectively the feasibility and efficacy of dose escalation using three-dimensional conformal radiotherapy (3D-CRT) boost technique for locally recurrent nasopharyngeal carcinoma (NPC) in a randomised study.**
Materials and methods: **Thirty-six patients with locally recurrent NPC (>6 months interval from previous radical radiotherapy, no cervical lymph-node involvement and no distant metastasis) were enrolled. Treatment included conventional external-beam radiotherapy to 54 Gy, followed by a 3D-CRT boost to the gross tumour region. Patients were randomised to three boost dose levels: 16 Gy, 20 Gy and 24 Gy for groups I, II and III, respectively, with 12 patients in each group. All boost doses were delivered in 4-Gy fractions and 3 fractions per week. Median follow-up was 27 months (range 14–44 months).**
Results: **Three-year, local-recurrence-free survival rate was significantly higher (72%) for the high-dose group III than for groups I and II (37% and 28%, respectively, $P = 0.047$). No significant difference was found in the 3-year overall survival rate among the three groups (72%, 59% and 82% for groups I, II and III, respectively). Three-year distant metastases rates were 17%, 0% and 18%, respectively. Skull-base invasion ($P = 0.017$) and pathology ($P = 0.0006$) correlated with overall survival. Treatment was well tolerated and no significant difference was observed among the three groups in acute and late toxicities (grade III toxicity is minimal: 17%, 17%, 0% of oral mucositis and 25%, 17%, 17% of nasopharyngeal mucositis in groups I, II, III, respectively, and 8% leukocytopenia only in group II; no grade IV toxicity occurred in any of the groups except for a fatal bleeding in group III).**
Conclusions: **Re-irradiation with high-dose 3D-CRT boost technique results in high local control rate and acceptable toxicity in patients with recurrent NPC. Dose escalation to the boost volume to 78 Gy (54 Gy + 24 Gy boost) results in improved recurrence-free survival compared with lower doses. Li, J.-C. *et al*. (2006). *Clinical Oncology* 18, 293–299**

Key words: 3D-CRT, dose escalation, nasopharyngeal carcinoma, recurrence, re-irradiation

Introduction

Radiotherapy is the primary treatment option for patients with non-metastasic nasopharyngeal carcinoma (NPC). Despite recent advances in outcome, local recurrence represents a critical component of treatment failure after initial external-beam radiotherapy (EBRT) [1–5]. Locally recurrent NPC is often treated again with radiotherapy [6,7].

To control the disease while maintaining quality of life is a challenge in managing patients with recurrent NPC. Local control for NPC overall highly correlates with the dose delivered to the tumour [8]. However, because the nasopharynx is surrounded by several critical normal structures, which had already received a high radiation dose from the first treatment course, re-irradiation carries a substantial risk of serious complications [2,9]. Attempts to achieve higher doses to the target volume while sparing critical normal structures have included intracavitary [10,11] or radioactive gold grain implantation brachytherapy [12,13], nasopharyngectomy [14–16] and stereotactic radiosurgery [17,18]. However, these are reserved for tumours with limited extent. Larger tumours that are close to critical normal structures remain a challenge. Two techniques, three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), have recently been used to treat NPC, and have shown incremental improvements in dose distribution and therapeutic outcome [18–21]. IMRT is a further advancement on 3D-CRT; however, it is a complex and expensive technique requiring extensive resources and quality assurance [20]. On the other hand, 3D-CRT is relatively simpler and is available in most centres worldwide, including those in developing countries.

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Earlier studies of dose intensification in NPC have been promising. Jen *et al*. [22] showed that 80 Gy, given in a twice-daily fractionation schedule, could be delivered safely, and improved tumour control of T_4 NPC patients. Lu *et al*. [23] applied high-dose-rate intracavitary brachytherapy as a 10 Gy boost to conventional EBRT of NPC, and showed that this technique was safe and feasible. Gwi *et al*. [24] showed that the dose escalation in 9 Gy increments using a 3D-CRT boost technique was relatively safe and effective enough to be used routinely for locally advanced NPC.

However, the maximum dose that can be safely delivered to generate a better therapeutic result in treating locally recurrent NPC has not been determined. Therefore, we conducted a prospective randomised dose-escalation trial in patients with locally recurrent NPC to test the hypothesis whether increasing the dose with 3D-CRT boost technique improves tumour control and survival in patients with recurrent NPC. The objective of the study was to determine the optimal dose that achieves best optimal tumour control and acceptable toxicity. For the three dose levels of the 3D-CRT boost, we aimed to assess local tumour control, local-recurrence-free survival and overall survival.

Methods and Materials

Study Design

The study population included patients with recurrent NPC after radical radiotherapy. The diagnosis of locally recurrent NPC was based on (1) clinical evidence of recurrence and reappearance of the nasopharyngeal tumour on imaging studies (computed tomography [CT], magnetic resonance imaging [MRI], or both) after complete response to the initial course of radiation therapy for more than 6 months; (2) persistence of the nasopharyngeal tumour at the end of radiotherapy, progression in more than 6 months after the initial treatment, or both; and (3) histological tissue diagnosis of the recurrent tumours if accessible for biopsy in the nasopharyngeal cavity, or imaging finding without histology if inaccessible (skull base or the parapharyngeal space).

Patient eligibility criteria included (1) recurrent tumour confined to the nasopharynx and local extension without lymph-node involvement after primary radiotherapy of NPC; (2) interval between the end of primary radiotherapy and recurrence 6 or more months later; (3) no cervical lymph node or distant metastases. Exclusion criteria were lymph-node involvement at the time of recurrence, distant metastasis, inability to tolerate radiotherapy, or a life expectancy of less than 6 months. Informed consent was obtained according to institutional protocol.

Pre-treatment evaluations included complete history, physical examination, diagnostic imaging, complete blood count, blood chemistries, including liver and kidney function tests, and electrocardiogram. Routine imaging studies included CT, MRI, or both, of the head and neck and chest X-ray. CT or MRI of the chest, abdominal ultrasound and bone scans were carried out when clinically indicated by symptoms or findings suggestive of metastasis disease.

Patients were randomly assigned to three study arms to test the dose level of the 3D-CRT boost to the recurrent tumour: arm I: 16 Gy in 4 fractions; arm II: 20 Gy in 5 fractions, and arm III: 24 Gy in 6 fractions. Twelve patients were included in each arm.

Radiotherapy

Radiotherapy was divided into two stages. Before 3D-CRT, all patients initially received EBRT consisting of two lateral-opposed conformal fields to maximally exclude spinal cord and brainstem, an anterior field, or both. The dose reference point was the centre of target. The prescription dose was 54 Gy delivered in daily fractions of 2 Gy. After EBRT, a 3D-CRT boost was used for dose escalation. The gross tumour volume (GTV) and clinical target volume (CTV) were contoured. The CTV was derived by expanding the GTV by a 5-mm margin. Five to seven coplanar or non-coplanar beams were used for the 3D-CRT boost. Prescription dose was delivered to the isodose line (typically 90% isodose) that covered the CTV. The boost dose was delivered in 4 Gy per fraction, three times per week, and the total boost dose was escalated from 16 Gy to 24 Gy (4 fractions to 6 fractions). The dose constraints were 40% of prescription dose to spinal cord, 45% to brainstem, and 45% to temporal lobes.

For radiation therapy, each patient with recurrent NPC was immobilised in the supine position with an aquaplast mask during the simulation, planning CT and treatment. CT images for conformal therapy planning were obtained at 5-mm intervals from the top of the vertex to the level of the hyoid bone, and the CT data were transferred to the planning system. Conformal treatment plans were computed (START 2000, Da-Hen Corporation, Chinese Academy of Science, Beijing).

If the recurrent tumour extent corresponded to a stage as T_3 or higher, patients received two to four cycles of chemotherapy before radiotherapy. The regimen of chemotherapy was cisplatin 25—30 mg/m^2 on days 1—3, and 5-fluorouracil 0.4—0.5 mg/m^2 on days 1—3, every 3 weeks. Three patients in group I, three patients in group II, and two patients in group III received chemotherapy.

End Points and Analysis

Tumour control, overall survival, local-recurrence-free survival and distant metastasis were the primary end points of the study. Acute and late toxicities were the secondary study end points. Patients were followed after treatment in 2- or 3-monthly intervals for at least 2 years. The survival time was scored from the date of diagnosis of the local recurrence of NPC. End points were analysed in September 2003. All end points were analysed by the intention-to-treat principle. Freedom of recurrence to compute local-recurrence-free survival was defined as no recurrent or residual enlargement of the nasopharynx or nasopharyngeal mass on CT or MRI, and no clinical findings for more than 6 months after completing re-irradiation.

The sample size of the study was based on the relative rarity of the tumour, taking into consideration that