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Original article

Treatment outcomes after reduction of the target volume of intensity-modulated radiotherapy following induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: A prospective, multi-center, randomized clinical trial

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ABSTRACT

Purpose: To investigate whether reducing the target volume of intensity-modulated radiotherapy (IMRT) after induction chemotherapy (IC) improves the quality of life (QOL) in locoregionally advanced nasopharyngeal carcinoma (NPC) without decreasing the local control and survival rate.

Patients and methods: A total number of 212 NPC patients staged as III–IVb were randomly assigned to group A ($n = 97$) or group B ($n = 115$) in this prospective clinical trial. All patients received IC followed by cisplatin concurrent with IMRT. IMRT was planned using the images of pre-IC in group A and post-IC in group B.

Results: The dose received by normal tissues in group B was lower than that of group A ($P < 0.05$). The recovery of the dry mouth symptoms in group B was significantly improved than group B. The quality of life (QOL) scores in group B were higher than group A. With a median follow-up of 35 months, the 1-year estimated overall survival (OS), progression-free survival (PFS), locoregional failure-free survival (LRFFS), distant metastasis-free survival (DMFS) in group A versus group B were 97.9% vs 97.3%, 90.7% vs 92,2%, 99.0% vs 98.2%, 91.8% vs 94.8%. The 2-year OS, PFS, LRFFS, DMFS in group A versus group B were 93.7% vs 92.9%, 83.4% vs 84.3%, 96.8% vs 95.5%, 86.5% vs 89.5%. The 3-year OS, PFS, LRFFS, DMFS in group A versus group B were 82.3% vs 87%, 74.7% vs 83.4%, 91.8 vs 93.9%, 81.3% vs 88.6%, respectively.

Conclusion: Reducing the IMRT target volume after IC did not reduce the local control and survival rate in locoregionally advanced NPC but the doses received by normal tissues were decreased, and the QOL scores were improved.

The current standard treatment for locoregionally advanced nasopharyngeal carcinoma (NPC) is concurrent chemoradiotherapy (CRT) with or without induction chemotherapy (IC) [1,2]. Although the 3–5 year overall survival rate can be as high as 80% or more after CRT in patients with locoregionally advanced NPC [3], radiotherapy late complications seriously affect patients' quality of life (QOL) and functional status.

IC has potential advantages of shrinking the tumor volume before radiotherapy. Several studies showed [4,5] response rates from 76.5% to 82.0% after IC with various regimens in locoregionally advanced NPC. In addition, Lee [6] reported a primary tumor volume decrease from 55.6 cc to 22.9 cc after IC. However, under the current consensus [7], planning intensity-modulated radiation therapy (IMRT) with pre-IC gross tumor volume of nasopharynx (GTVnx) is not corresponding to a tumor volume reduction by IC, and in addition evidence-based reports are lacking. On the other hand, several studies [8,9] indicated that planning IMRT with post-IC GTVnx could not only ensure a safe radiotherapy dose to normal tissues, but could also guarantee a satisfactory treatment

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result. Nevertheless, information is missing regarding the use of pre- or post-IC GTVnx to plan IMRT.

Therefore, the aim of this study was to investigate whether planning IMRT with post-IC GTVnx can reduce the radiation dose to normal tissues without reducing the clinical efficacy in locoregionally advanced NPC.

Patients and methods

Patient eligibility and random assignment

Patients were considered eligible under the following circumstances: (1) biopsy-proven NPC; (2) no previous treatment; (3) locoregionally advanced NPC according to the American Joint Committee on Cancer (AJCC) 2010, stages III to IVb. Other eligibility criteria included Karnofsky score >70, age 18–70 years, normal electrocardiography (ECG), adequate bone marrow reserve, liver function, and renal function. Baseline imaging consisted of bone scan, thorax and abdomen computed tomography (CT), nasopharynx and neck magnetic resonance imaging (MRI).

The study protocol was approved by the Hospital Ethics Committee and was performed in accordance with the principles of the Declaration of Helsinki.

The non-inferiority test was used to calculate the sample size. Considering the factors such as falling off, we expanded the sample by 20%. The registration and randomization procedure were carried out using Excel rand function to generate a random number. Patients were randomized to one of the treatment groups: group A (IMRT with pre-IC GTVnx) or group B (IMRT with post-IC GTVnx).

Preparation before treatment

Before treatment, patients were immobilized with a thermoplastic head and shoulder mask, and CT simulation according to standard procedures. MRI fusion with simulation CT images were performed to assist the targets delineation. These first CT simulation and MRI scans performed before IC were named CT1 and MRI1.

Chemotherapy

All patients received IC and concurrent chemotherapy. IC consisted of TP or PF. TP: paclitaxel 175 mg/m^2 through intravenous (IV) infusion over 1 h on day 1 and cisplatin 75 mg/m^2 IV over 1 h with hydration on day 1. PF: 5-Fluorouracil 1000 mg/m^2/day on day 1 to day 4 through continuous IV infusion for 96 h and cisplatin 75 mg/m^2 IV over 1 h with hydration on day 1. Cycles were repeated every 3 weeks for a total of two cycles, followed by radiotherapy (RT) performed concurrently with cisplatin 40 mg/m^2 IV over 2 h on weeks 7 through 14 [5].

Radiotherapy

On the 14th day after the second IC cycle, the second CT simulation (CT2) was performed using the same mask for each patient. If the patient's weight changed significantly resulting in mask loose, the mask was remade. The second MRI scans (MRI2) were also performed.

Image Fusion modality: in the center of the nasopharynx, CT1 fusion with CT2, MRI1 fusion with MRI2, MRI1 fusion with CT1, MRI2 fusion with CT2, and MRI1 fusion with CT2 were performed to assist the targets delineation.

All patients were treated with IMRT definitively. Separate target volumes in the nasopharynx and nodal regions were defined according to the ICRU 50 [10], 62 [11], 71 [12] and 83 [13] recommendations.

In group A, GTVnx (metastatic retropharyngeal nodes were also delineated in GTVnx) was defined as all known gross disease determined from clinical and imaging CT1/MRI1 examinations before IC (named pre-IC GTVnx). The clinical target high-risk volume (CTV1) was defined as a subclinical disease consisting of a 0.5–1 cm margin surrounding the pre-IC GTVnx, and it must include the whole nasopharynx wall, as well as 0.5 cm margin under normal nasopharyngeal mucosa (named pre-IC CTV1). The clinical target low-risk volume (CTV2) consisted of pre-IC CTV1, the posterior part of the nasal cavity, the posterior part of the maxillary sinus, the pterygopalatine fossa, part of the posterior ethmoid sinus, the parapharyngeal space, the skull base, part of the clivus (when invaded, the whole clivus was covered), GTVnd (gross tumor volume of neck metastasis lymph node), and lymph node drainage area needed to be prophylactically irradiated (named pre-IC CTV2).

In group B, the GTVnx was defined as all the known gross disease determined from clinical and imaging CT2/MRI2 examinations after IC (named post-IC GTVnx). CTV1 was defined as a subclinical disease consisting of a 0.5–1 cm margin surrounding the post-IC GTVnx. Other areas included the whole nasopharynx wall, as well as 0.5 cm margin of the normal nasopharyngeal mucosa. Post-IC CTV1 included the disappeared GTVnx, which is the nasopharyngeal area in which the tumor disappeared after IC. CTV2 consisted of post-IC CTV1 and other areas were defined the same as those of group A (named post-IC CTV2).

For all patients, GTVnd was determined by the second CT/MRI (CT2/MRI2), except for the lymph node capsule invasion that was determined by CT1/MRI1. A range of 3–5 mm around the above targets were required in all directions to define each respective planning (P-) target volume (P-GTVnx, P-GTVnd, P-CTV1, and P-CTV2).

In group A and group B, the doses prescribed on P-GTVnx, P-GTV-nd, P-CTV1 and P-CTV2 were 70 Gy, 70 Gy, 64 Gy, and 54 Gy (in 33 fractions), respectively. Radiotherapy was delivered once daily, 5 fractions per week, for approximately 7 weeks. Details of the planning system are shown in Appendix. For all plans, 7–9 coplanar 6-MV photon beams were evenly distributed around the patient's head and neck.

Volume and dosimetric comparisons

Target volumes (pre-IC GTVnx in group A vs post-IC GTVnx in group B, pre-IC CTV1 in group A vs post-IC CTV1 in group B) were compared.

For each IMRT plan, dose–volume histograms (DVHs) were calculated for target volumes and normal tissues. The evaluation P-GTVnx, P-GTVnd, P-CTV1 and P-CTV2 indexes was respectively the mean dose (Dmean), D2%, D98%, D95% and D50% of the volumes.

For vital structures including the brainstem, spinal cord, optic chiasm, optic nerves, temporal lobe, inner and middle ear, we chose D2% as endpoint. For bilateral parotids, the mean dose and the doses encompassing 50% and 33% of the volumes were chosen as endpoints. DVHs of IMRT plans were compared between groups A and B.

Assessment and follow-up

Tumor response was evaluated by physical examination, nasopharyngoscopy, head and neck MRI/CT, and abdomen ultrasound scan 1 month after CRT. Tumor response was classified according to RECIST1.1 Criteria [14].

Adverse events were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTC 3.0) by medical doctors. Acute toxicities were evaluated during IC and CRT, and 3 months after radiotherapy.

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