·Intensity-Modulated Radiotherapy Column·

Impact of changing gross tumor volume delineation of intensity-modulated radiotherapy on the dose distribution and clinical treatment outcome after induction chemotherapy for the primary locoregionally advanced nasopharyngeal carcinoma

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[Abstract] Background and Objective: The gross tumor volume (GTV) obviously reduces after induction chemotherapy (IC) for primary locoregionally advanced nasopharyngeal carcinoma (NPC). This study was to investigate the impact of changing gross tumor volume delineation on the dose distribution and clinical treatment outcome after IC. **Methods:** From January 2008 to April 2009, 24 patients with Stage Ⅲ–Ⅳb primary locoregionally advanced NPC were treated with TPF regimen IC followed by intensity-modulated radiotherapy (IMRT) with concurrent chemotherapy . The primary GTVs were delineated into two parts: the post-IC primary GTV (GTVpost-IC-NP), and the region of pre-IC primary GTV minus GTVpost-IC-NP (GTVpre-post-IC-NP). The dose distributions of two plans with GTVpost-IC-NP or pre-IC primary GTV were assessed by analyzing ten cases. The clinical treatment outcome and toxicity of all patients were observed. **Results:** The post-IC GTV was significantly smaller than the pre-IC GTV (primary GTV 25.5 cm^3 vs. 51.1 cm^3, P=0.001; lymph nodes GTV 9.1 cm^3 vs. 31.4 cm^3, P=0.035; primary + lymph nodes GTV 33.2 cm^3 vs. 82.6 cm^3, P=0.004), the overall GTV with an average shrinkage of 61%. The high dose region was also smaller after IC (volumes covered by 64.4 Gy were 422.9 cm^3 vs. 457.9 cm^3, P=0.003; 274.2 cm^3 vs.334.5 cm^3 by 68 Gy, P=0.041). The complete response rate was 38% after IC, and 100% three month after radiotherapy. The toxicity of following IMRT with concurrent chemotherapy was similar to that of IMRT with concurrent chemotherapy alone. With median follow-up of 9 months, the locoregionally control rate was 100% and only one patient presented metastasis 15 months after treatment. **Conclusions:** TPF regimen IC could significantly reduce tumor volume. The following IMRT with GTVpost-IC-NP plan reduced the high dose region, which didn't add toxicity while had excellent short-term treatment outcome.

Key words: nasopharyngeal neoplasm, induction chemotherapy, intensity-modulated radiotherapy, radiotherapy, target volume delineation, dose distribution, clinical therapeutic effect, toxicity

Treatment failure in patients with locally advanced nasopharyngeal carcinoma (NPC) is mainly the result of local recurrence and distant metastasis, so a comprehensive program of chemotherapy and radiotherapy is the main treatment. Intensity-modulated radiotherapy (IMRT) has substantially improved the rate of locoregional control for advanced NPC patients, but the distant metastasis rate is still as high as 25%.[1] Distant metastasis has become an important factor in prognosis, suggesting that modern advanced radiotherapy techniques need to be combined with intensive chemotherapy.

Currently, induction chemotherapy, especially with a Taxotere-Platinol-Fluorouracil (TPF) regimen plus IMRT, has become a focus of NPC research. Induction chemotherapy significantly reduces gross tumor volume (GTV).[2] This reduction raises a question of whether GTV should be determined from imaging acquired before or after chemotherapy in the IMRT treatment plan. The general consensus is that GTV should be based on pre-chemotherapy imaging without dose reduction,[3] but

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this consensus is not yet supported by evidence. On the basis of imaging and the relationship between tumor density and radical dose, we propose to determine GTV after induction chemotherapy, allowing us to give a slightly lower dose to those regions in which the tumor has regressed after chemotherapy. In so doing, we expect to reduce the dose to the previous high-dose region, which should reduce radiation side effects without compromising locoregional control.

Patients and Methods

Enrollment and exclusion criteria

Patients were eligible for the study if they were 18 to 65 years old and had: 1) a pathologic diagnosis of NPC of WHO type 2 or 3 and 2002 UICC stage III-IVa; 2) a Karnofsky performance score of 80 or higher; 3) a white blood cell count equal to or greater than 4.0×10^9/L, a neutrophil count equal to or greater than 2.0×10^9/L, and a platelet count equal to or greater than100×10^9/L; 4) indicators of liver function within 2 times the upper limit of the normal range and a renal creatinine clearance equal to or greater than 60 mL/min; 5) and no imaging evidence of distant metastasis.

The exclusion criteria were: 1) pregnant or breast-feeding; 2) contraindications to radiotherapy and chemotherapy; 3) no clear treatment response; 4) a history of radiotherapy or chemotherapy; 5) the presence of grade II or higher (Common Terminology Criteria for Adverse Events v3.0) peripheral nerve toxicity, mental disease, congestive heart failure, angina, uncontrolled hypertension, myocardial infarction within 6 months, active infectious disease, active peptic ulcer, uncontrolled diabetes, large doses of steroids taken within 6 months (20 mg of prednisone or the equivalent amount of other steroids), and 6) other medical complications.

Between January 2008 April 2009, 24 patients (19 men) were enrolled. Median age was 45 years (range, 25–61 years). Of the 24 patients, 23 had undifferentiated non-keratinizing carcinoma, and 1 had differentiated non-keratinizing carcinoma. According to whether the base of the skull, oropharynx, choana, retropharyngeal lymph nodes, and paranasal sinuses were invaded, 10 patients were selected for dosimetric analysis.

Treatment

Induction and concurrent chemotherapy

Each patient received induction chemotherapy with TPF: docetaxel and cisplatinum (DDP) with doses of 60 mg/m^2 given intravenously on day 1; 5-FU with a dose of 450 to 550 mg$\cdot$m$^{-2}\cdot$d^{-1} was continuously infused for 120 h from day 1 to day 5; and a cycle was given every 3 weeks for 3 cycles. During radiotherapy, single-agent chemotherapy, DDP 80 mg/m^2, was given every 3 weeks on days 1 and 22. If the patient could not complete radiotherapy by day 42 because of objective reasons such as mechanical failure, a third cycle of concurrent chemotherapy was given on day 43.

Intensity-modulated radiation therapy

IMRT was administered 3 weeks after the third induction chemotherapy. Before induction chemotherapy, patients were fitted with a head-neck-shoulder thermoplastic mask and scanned with a CT simulator before and after chemotherapy to obtain two sets of plain and enhanced images. Target volume was determined from a composite of enhanced images before induction chemotherapy and on plain images after induction chemotherapy. The Corvus planning system in the Peacock IMRT system and a MiMi multi-diaphragm collimator were used for planning and treatment. All patients were treated with radical irradiation. The target volume of the nasopharynx and upper neck received a full course of IMRT, and the lower neck and supraclavicular area received conventional anterior tangential irradiation.

Target volume determination and dose

Gross tumor volume after induction chemotherapy to the nasopharynx was based on nasopharynx lesions (which included retropharyngeal lymph nodes) observed clinically and radiologically after induction chemotherapy; GTV before and after induction chemotherapy was based on areas of nasopharynx in which the tumor had regressed and without enhancement after induction chemotherapy. After induction chemotherapy to the lymph nodes, GTV was based on visible metastatic lymph nodes of neck. High-risk areas (clinical target volume 60 Gy) included an 8-to-10-mm margin around the primary gross tumor before induction chemotherapy and on a 5-mm margin around the involved lymph nodes of the neck after induction chemotherapy, which could be adjusted according to some characteristics of adjacent tissues Low-risk areas (clinical target volume 54 Gy) included possible areas invaded by NPC, such as the base of the skull, the posterior third of the nasal cavity, the posterior ethmoid sinus, the lower part of the sphenoid sinus, the retropharyngeal space, the parapharyngeal space, the pterygoid process, the pterygopalatine fossa, the foramen ovale, the carotid artery tube and lymph node drainage area with 1–2 cervical lymph node areas beyond the metastatic lymph node sites (Fig. 1). Planning treatment volume (PTV) was automatically generated by the system on the basis of uncertain factors.

In 10 patients, GTV before IC-NP and GTV before IC-LN were determined on the basis of the primary gross tumor and metastatic lymph nodes before induction chemotherapy, and the corresponding treatment plans were compared with the above for dosimetry, whereas CTV60 and CTV54 were consistent with the above mentioned target volumes (Fig. 2).

The prescribed target volume was given by simultaneous integrated boost. Specifically, the prescription doses to the GTV before IC-NP and to the GTV after IC-NP were both 68 Gy; to the GTV before and after IC-NP, 63 Gy; to the GTV after IC-LN, 64 Gy; to CTV60, 60 Gy; and to CTV54, 54 Gy, all in 30 fractions over 42 days. Doses to organs at-risk were restricted to the TD5/5 dose criteria and adjusted according to the location of the primary tumor. Limited doses to organs at risk were the same in both plans so that dosimetry could be compared.

Dosimetric evaluation

Tumor volume was evaluated mainly by GTV size. In this study, evaluation indicators of the high-dose region included the volume in the 64.6 Gy isodose line ($V_{64.6Gy}$) and the volume in the 68 Gy isodose line (V_{68Gy}). Common clinical indicators were

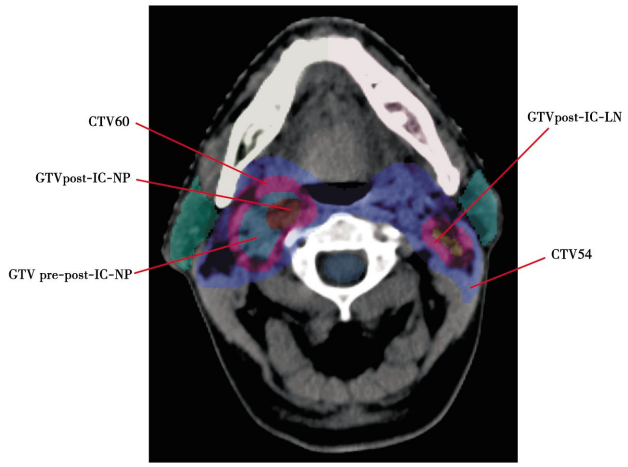

Figure 1 Target volumes in plan of post-induced chemotherapy gross tumor volume

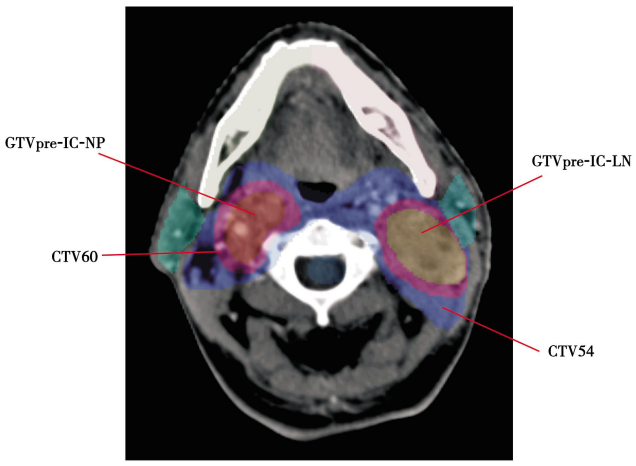

Figure 2 Target volumes in plan of pre-induced chemotherapy gross tumor volume

selected as evaluation indicators for organs at risk, including the volume dose of 1 cm^3 and 3 cm^3 to the spinal cord (D_{1cc}, D_{3cc}), the volume dose of 1% to the brain stem (D_1), the volume dose of 1% to the temporal lobe (D_1), the mean dose to the parotid gland (D_{mean}), and the volume in the 26 Gy isodose line (V_{26Gy}).

Clinical efficacy and toxicity evaluation

Locoregional control, distant metastasis, and normal tissue toxicity were the main clinical indicators of treatment. Clinical efficacy was evaluated with the Response Evaluation Criteria in Solid Tumors (RECIST)[4] 3 weeks after the third induction chemotherapy with MRI of the nasopharynx and neck. The nasopharynx and neck were evaluated clinically and with MRI at the end of treatment, every 3 months in the first year, every 3 to 6 months in the second year, and every 6 months in the third year and thereafter. Toxicity was evaluated with the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0)[5] during the concurrent chemoradiotherapy and every 3 months after treatment in the first year, every 3 to 6 months in the second year, and every 6 months in the third year and thereafter.

Statistical software and methods

Indicators between the two groups were compared with paired *t* tests. Alpha was set at 0.05, and the SPSS16.0 statistical software was used in the analyses.

Results

Tumor volume

The GTV was (25.5± 26.1) cm^3 after IC-NP and (51.1± 22.0) cm^3 before IC-NP (P=0.001), (9.1± 9.2) cm^3 after IC-LN and (31.4 ± 36.5) cm^3 before IC-LN (P=0.035), and (33.2± 26.8) cm^3 after IC-NP+LN and (82.6± 48.9) cm^3 before IC-NP+LN (P=0.004). After induction chemotherapy, tumor volume was reduced by 61%.

Volume of high-dose region

After induction chemotherapy, the volume of the high-dose region was significantly reduced, including the PTV of the target volume and the PRV of the organ at risk. Before and after induction chemotherapy, the $V_{64.6Gy}$ was (439.7±122.6) cm^3 and (406.6 ±111.8) cm^3, respectively (P=0.001), and V_{68Gy} was (310.3±133.7) cm^3 and (259.3±88.0) cm^3, respectively (P = 0.02).

Dose of normal tissues surrounding target volume

The dose to normal tissues surrounding the target volume did not differ significantly between the two plans in which the target volume was determined before or after induction chemotherapy, except for the brainstem (all P values were greater than 0.05) (Table 1).

Table 1 The dose of normal tissues in two treatment plans derived from pre- or post-IC-GTV

Normal tissues	Pre-IC GTV plan	Post-IC GTV plan	*P*
Spinal cord			
D_{1cc} (Gy)	28.2±1.2	28.0±1.1	0.227
D_{3cc} (Gy)	26.1±0.8	25.8±0.9	0.114
Brain stem			
D_1 (Gy)	53.5±8.1	54.5±8.2	0.003
Left temporal lobe			
D_1 (Gy)	57.9±4.0	57.9±3.7	0.952
Right temporal lobe			
D_1 (Gy)	61.6±4.7	62.3±5.0	0.096
Left parotid			
D_{mean} (Gy)	31.6±2.0	31.6±1.4	0.945
V_{26Gy} (Gy)	17.0±4.7	17.5±4.9	0.192
Right parotid			
D_{mean} (Gy)	33.0±3.2	33.2±3.0	0.065
V_{26Gy} (Gy)	19.2±5.2	20.0±5.3	0.059

IC, induction chemotherapy; GTV, gross tumor volame.

Clinical efficacy

All patients completed 3 cycles of induction chemotherapy and 2 cycles of concurrent chemotherapy. Clinical examination and MRI scans of the nasopharynx and neck revealed an overall response rate of 100% after 3 cycles. The complete remission rate was 42% (10/24) for the nasopharynx, 71% (17/24) for lymph nodes, and 38% (9/24) for both the nasopharynx and lymph nodes.

At the end of treatment, the complete remission rate was 79% (19/24) for the nasopharynx, 92% (22/24) for the lymph nodes, and 79% (19/24) for both the nasopharynx and lymph node. Two patients had residual metastatic lymph nodes: one had tumor regression after boost radiotherapy and the other was lost to follow-up within 3 months. Of the 5 patients with nasopharyngeal residues, 3 had evidence of regression 3 months after radiotherapy, and 2 were lost to follow-up within 3 months. The complete remission rate for the nasopharynx and lymph nodes was 100% in patients with at least 3 months of follow-up. After a median follow-up of 9 months, the locoregional control rate was 100% in all patients, although 1 patient had multiple lung and bone metastasis.

Table 2 The toxicity grading of concurrent chemoradiotherapy in 24 patients (CTCAE v3.0)

Toxicity	Grade 1 or 2 (number)	Grade 3 or 4 (number)
Anemia	8	2
Neutropenia	14	3
Thrombopenia	4	2
Radiation-related dermatitis	23	1
Xerostomia	23	1
Oral cavity mucositis	18	6
Vomit	18	3
Kidney injury	5	0
Liver injury	4	0

The treatment toxicity of concurrent chemotherapy

The treatment toxicity after IMRT with concurrent chemotherapy was similar to that of IMRT with concurrent chemotherapy alone (Table 2).

Discussion

The principle of radiation therapy is to kill the maximum number of tumor cells while protecting as much normal tissue as possible. Identifying the target volume is the basis for implementing this principle, so target determination is very important, especially for the inverse planning. Gross tumor volume refers to lesions of the nasopharynx and lymph nodes, identified by clinical and radiographic examination, whose identification criteria are basically the same in all tumor centers.[6-11]

We determined that the GTV of nasopharyngeal carcinoma can be significantly reduced after induction chemotherapy with a TPF regimen. Therefore, we wanted to learn how to best determine the GTV for radiotherapy delivered after induction chemotherapy. Current consensus is that GTV should be delineated on the basis of pre-chemotherapy imaging and the dose should not be reduced, but this consensus is based mainly on speculation.[3] On the basis of the International Commission on Radiation Units and Measurements 62 report and the relationships among imaging, tumor density, and radical dose, we proposed determining the GTV after induction chemotherapy and to administer a lower dose of 63 Gy to the regions where the tumor had regressed. The rationale is that the density of a tumor visible on imaging is generally greater than $1\times10^9/cm^3$, whereas that of a tumor that cannot be visualized is generally less than $1\times10^9/cm^3$.[12] For head-and-neck squamous cell carcinoma, 6.5 to 7.0 Gy can reduce tumor density by one order of magnitude,[12] so 63 Gy can be a radical dose for tumors with densities less than $1\times10^9/cm^3$.

The proposed method of determining GTV could reduce the volume of the high-dose region in IMRT and the amount of normal tissue irradiated with high doses, thereby reducing radiotherapy toxicity, especially to the normal tissues in the target volume, such as the sheath of blood vessels surrounded by the tumor. The dose to normal tissues outside the high-dose region, such as the spinal cord, temporal lobe, and parotid gland, did not differ significantly between the two treatment plans. The mean dose to 1% volume (D_1) of the brainstem increased slightly after chemotherapy, probably because patients' mouths were kept opened with a stent and because the tumor regressed after chemotherapy, factors that led to radiation being attenuated less through a reduced tumor and thus more radiation reached the brainstem.

Accurately determining GTV from CT images and giving different doses in a radiotherapy plan before and after chemotherapy is also a challenge in treatment planning after induction chemotherapy. In this study, patients were fitted with the same mask and scanned with the same location markers before and after chemotherapy, and composite images were used for target delineation, which made measurements more accurate. Patients tolerated the TPF regimen well and had adequate nutritional support, with weight gain of 0 to 5 kg at the second scan, therefore, the fixation was not affected.

This study had an overall response rate of 100% after 3 cycles of induction chemotherapy, and the complete remission rate was 38% for lesions in the nasopharynx and lymph nodes, a result consistent with the results for head-and-neck cancer obtained by the Dana-Farber Cancer Institute in United States, which has reported total response rates of between 90% and 100% and complete remission rates of between 40% and 60%.[13-15] Induction chemotherapy did not delay the duration of radiotherapy, and the toxicity of concurrent chemoradiotherapy was similar to that of concurrent chemoradiotherapy alone. The complete remission rate for lesions in the nasopharynx and lymph nodes was 79% at the end of treatment and 100% in patients with more than 3 months of follow-up after treatment. The locoregional control rate was 100% for all patients after a

median follow-up of 9 months, suggesting that it is feasible to determine GTV after induction chemotherapy and to give a lower dose of 63 Gy to regions where the tumor has regressed without decreasing the short-term locoregional control rate.

In conclusion, tumor size is substantially reduced after induction chemotherapy with TPF. Determini ng GTV after induction chemotherapy and giving a lower dose of 63 Gy to regions where the tumor has regressed can reduce exposure in the high-dose regions of IMRT and can maintain a high short-term locoregional control rate without increased toxicity of concurrent chemoradiotherapy.

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