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ORIGINAL ARTICLE

Clinical role of ^{18}F-FDG PET/CT-based simultaneous modulated accelerated radiotherapy treatment planning for locally advanced nasopharyngeal carcinoma*

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Abstract

Objective The aim of this study was to compare the long-term local control, overall survival, and late toxicities of positron emission tomography/computed tomography (PET/CT)-guided dose escalation radiotherapy versus conventional radiotherapy in the concurrent chemoradiotherapy treatment of locally advanced nasopharyngeal carcinoma (NPC).

Methods A total of 48 patients with stage III–IVa NPC were recruited and randomly administered PET/CT-guided dose escalation chemoradiotherapy (group A) or conventional chemoradiotherapy (group B). The dose-escalation radiotherapy was performed using the simultaneous modulated accelerated radiotherapy technique at prescribed doses of 77 gray (Gy) in 32 fractions (f) to the gross target volume (GTV): planning target volume (PTV) 1 received 64 Gy/32 f, while PTV2 received 54.4 Gy/32 f. Patients in group B received uniform-dose intensity-modulated radiotherapy, PTV1 received 70 Gy/35 f and PTV2 received 58 Gy/29 f. Concurrent chemotherapy consisted of cisplatin [20 mg/m^2 intravenous (IV) on days 1–4] and docetaxel (75 mg/m^2 IV on days 1 and 8) administered during treatment weeks 1 and 4. All patients received 2–4 cycles of adjuvant chemotherapy of the same dose and drug regimen.

Results The use of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT significantly reduced the treatment volume delineation of the GTV in 83.3% (20/24) of patients. The 5-year local recurrence-free survival rates of the two groups were 100% and 79.2%, respectively (P = 0.019). The 5-year disease free survival (DFS) rates were 95.8% and 75.0%, respectively (P = 0.018). The 5-year local progression-free survival and DFS rates were significantly different. The 5-year overall survival (OS) rates were 95.8% and 79.2%, respectively. Differences in OS improvement were insignificant (P = 0.079). Late toxicities were similar in the two groups. The most common late toxicities of the two arms were grade 1–2 skin dystrophy, xerostomia, subcutaneous fibrosis, and hearing loss. There were no cases of grade 4 late toxicity.

Conclusion The use of ^{18}F-FDG PET/CT-guided dose escalation radiotherapy is well tolerated and can reduce local recurrence rates for patients with locally advanced NPC compared to conventional chemoradiotherapy.

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Nasopharyngeal carcinoma (NPC) is a common head and neck cancer in Southeast Asia; more than 70% of pa-

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tients with NPC present with locally advanced stage cancer [1–2]. The traditional treatment for NPC, a radiosensitive tumor, has primarily consisted of radiotherapy (RT) due to an inaccessible anatomic site and the high likelihood of early-stage lymph node metastasis [3–4]. However, conventional RT is associated with high rates of local recurrence, especially in patients with locally advanced NPC [5–6].

The local control rate of NPC is highly correlated with the total dose of radiation delivered to the tumor [7]. Intensity-modulated RT (IMRT) facilitates the delivery of high radiation doses to the target volume [8]. However, due to the large number of critical anatomical structures near the nasopharynx, dose escalation in NPC can also lead to increased toxicity. A variation of IMRT, simultaneous modulated accelerated RT (SMART), is used to treat primary tumors and regional nodes with daily fractionation using differing fraction sizes for gross tumor versus at-risk areas [9]. This approach reportedly increases the biologically effective dose delivered to the tumor target by elevating the total and fractionated doses and shortening the treatment course [7]. In recent years, the radiation oncology community has been widely adopting fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in the planning of RT [3]. The major motivation for using this method is that it enables better staging and target volume delineation [10].

We hypothesized that the use of PET/CT in treatment planning can improve dose escalation RT for NPC, which, in turn, can improve therapeutic efficacy while reducing toxicity. Given the clinical trials that directly compared conventional chemoradiotherapy to ^{18}F-FDG PET/CT–guided dose escalation chemoradiotherapy in locally advanced NPC, our study aimed to compare the response rate, local control, overall survival (OS), and toxicities of the two regimens.

Materials and methods

Study objectives and eligibility criteria

This study was approved by the Institutional Review Board of Xuzhou Medical School. Between February 2009 and March 2011, patients who fulfilled all of the following criteria were eligible for participation in this study: (1) biopsy-proven primary NPC, (2) stage III–IVa NPC according to the staging system of the Sixth American Joint Committee on Cancer (AJCC) and Chinese 2008 staging system for NPC, (3) no evidence of distant metastasis, (4) no previous treatment for NPC; (5) Karnofsky performance status ≥ 70; (6) adequate liver and renal function (albumin ≥ 30 g/L, creatinine ≤ 100 μmol/L); (7) adequate bone marrow function (white blood cell count ≥4.0 × 10^9/L, platelets ≥100 × 10^9/L); and (8) age 18–70 years. The exclusion criteria were as follows: (1) presence of distant metastases, (2) previous malignancy or other concomitant malignant disease, and (3) currently pregnant or lactating. Clinical stage was determined based on all information provided by examinations including contrast-enhanced CT and magnetic resonance imaging (MRI) of the head and neck, chest radiography, liver sonography, bone scanning, and ^{18}F-FDG-PET.

The primary objective of our study was to compare the local progression-free survival (LPFS) rates of the two treatment regimens. The secondary objective was to compare their associated disease-free survival (DFS), OS, and late toxicities.

Study design

Patients who met the eligibility criteria were randomized 1:1 into the two treatment arms: PET/CT-guided dose escalation chemoradiotherapy (group A) and conventional chemoradiotherapy (group B). Randomization was stratified for gender, age, tumor (T) stage, lymph node (N) stage, and tumor histology. All patients were given concurrent chemoradiotherapy (CCRT) within 2 weeks of diagnosis. Concurrent chemotherapy consisted of cisplatin [20 mg/m^2 intravenously (IV) days 1–4] and docetaxel (75 mg/m^2 IV days 1 and 8) administered during treatment weeks 1 and 4. All patients received 2–4 cycles of adjuvant chemotherapy of the same dose and drug regimen.

^{18}F-FDG PET/CT and CT simulation

Patients were immobilized in the supine position with a thermoplastic mask extending to the shoulders. All patients initially underwent contrast-enhanced CT scanning (light speed; GE Medical System, USA) from the parietal bone to the tracheal bifurcation with the following parameters: 200 mAs, 140 kV, 3.75-mm slice thickness, 0.938 pitch, and 16 × 0.625 collimation. A total of 100 mL of contrast media was administered at an injection rate of 1–2.5 mL/s after an initial 5 mL test dose.

The whole-body ^{18}F-FDG PET/CT scanning was performed using an integrated PET/CT scanner (Gemini GXL 16; Philips Medical Systems, USA), which integrates a PET scanner with gadolinium oxyorthosilicate crystals and a 16-slice multidetector CT scanner. Patients were asked to fast for at least 6 hours before the IV injection of 4.44 MBq/kg of FDG with a radiochemical purity > 95%, while the imaging was started 60 min after the injection. Contrast-enhanced CT scanning was performed before the PET/CT scanning, typically from the parietal bone to the mid-thigh, to correct attenuation and anatomic reference points with the following parameters: 200 mAs, 140 kV, 4-mm slice thickness, 0.938 pitch, and 16 × 1.5 collimation. Emission data were then acquired for 8–10 beds with an acquisition time of 1.5 min/bed and the same CT

scanning range. The iterative reconstruction 3D-row-action maximum-likelihood algorithm was used to reconstruct the PET/CT images.

Radiotherapy

The target volumes were defined in accordance with the International Commission on Radiation Units and Measurements Reports 50 and 62. All target volumes were outlined slice by slice on the axial contrast-enhanced CT images in the treatment planning system. For group A, images from a diagnostic PET/CT were fused to the treatment CT. Areas with a standardized uptake value ≥ 2.5 were used as the gross target volume (GTV). In group B, each GTV was delineated based on the fusion of diagnostic CT images with the simulation CT images and defined as GTV_{CT}. Clinical target volumes (CTVs) CTV1 and CTV2 were delineated: CTV1 was defined as GTV plus a 5–10-mm margin (2–3 mm margin posteriorly) to encompass the high-risk sites of microscopic extension (including the parapharyngeal spaces, posterior third of the nasal cavities and maxillary sinuses, pterygoid processes, base of the skull, lower half of the sphenoid sinus, anterior half of the clivus, and petrous tips), and the level of the involved lymph node (bilateral levels IIa, IIb, III, and Va were routinely covered for all N0 patients, whereas ipsilateral level IV or Vb or the supraclavicular fossae were also included for N1 patients). CTV2 was defined as the CTV1 plus a 5–10 mm-margin (2–3 mm margin posteriorly) to encompass the low-risk sites of microscopic extension. The planning target volume (PTV) was defined as the CTV plus a 3-mm margin. In group A, the GTV received 77 Gy in 2.4 Gy per fraction (f), PTV1 received 64 Gy/32 f, and PTV2 received 54.4 Gy/32 f. Group B received uniform-dose IMRT, PTV1 received 70 Gy in 2 Gy per fraction and PTV2 received 58 Gy in 2 Gy per fraction. The dose received by each organ at risk was limited to tolerance according to the Radiation Therapy Oncology Group (RTOG) 0225 protocol. The maximum doses to these structures were as follows: 54 Gy for the brainstem; 45 Gy for the spinal cord; 55 Gy for the temporal lobes; 5 Gy for the lens; and 50 Gy for the optic nerves, chiasm, temporomandibular joints, and mandible. The parotid gland dose was limited to a mean < 30 Gy.

Follow-up

The follow-up period was from the first day of treatment initiation until death or the last visit. Patients were followed every 3 months in the first 2 years, every 6 months in the following 3 years, and then once a year thereafter. In each visit, the patient's medical history was collected and physical examinations including fiber optic nasopharyngoscopy were performed. Nasopharyngeal MRI was performed 3 months and 1 year after the completion of RT, every 6 months in the second to fifth years, and then yearly thereafter. Chest CT or radiography, abdominal sonography, and a bone scan were performed at least once a year when clinically indicated. Acute radiation-related toxicities were classified according to the US Common Toxicity Criteria system version 3.0. Late radiation-related toxicities were classified according to RTOG criteria.

Statistical analysis

All analyses were performed using SPSS version 17.0 software (SPSS Inc., USA). The actuarial rates were estimated using the Kaplan–Meier method. The primary endpoint was LPFS, while the secondary endpoints were DFS and OS. All of the endpoints were defined as the interval from the date of initiation of treatment to the date of the failure, death, or last follow-up. Disease progression was defined as the development of local or regional recurrence or distant metastasis. The survival curves were compared with the log-rank test results. All statistical analyses were two-sided and P values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 48 eligible patients (32 men, 16 women) with a mean age of 48.4 years (range, 19–68 years) were enrolled in the study. As this trial was initiated in February 2009, the patients were initially staged according to the Sixth AJCC/Union for International Cancer Control (UICC) system in our protocol. All of the enrolled patients were restaged according to the criteria of the Seventh AJCC/UICC system upon its publication. The treatment groups were balanced in terms of patient and tumor characteristics (Table 1). All patients successfully completed treatment within 7 weeks. The mean treatment time was 46 days (range, 44–49 days) and all patients received 32–35 fractions. All patients received the prescription dose of RT and concurrent chemotherapy.

Impact of ^{18}F-FDG PET/CT on NPC and GTV staging

In group A, the staging of 4 patients (16.7%) was changed on the basis of PET/CT scan findings. In one patient, PET/CT imaging revealed a tumor invading the orbit and base of skull as well as bilateral level II lymph node metastases, requiring a change in stage from T3N0M0 to T4N2M0. Another patient was also upstaged from T3N2M0 to T3N3M0 due to the identification of subclavicular lymph node metastases. In the third patient, clinical stage was upstaged from T3N2M0 to T4N2M0 due to masticator space involvement. In the fourth patient, PET/CT identified a second primary tumor, a papillary thyroid carcinoma, confirmed by biopsy, for which thy-

Table 1 Patient Characteristics

Characteristics	Group A (n = 24)	Group B (n = 24)	P value
Gender			
Male	17	15	0.540
Female	7	9	
Age (years)			
Range	19–64	25–67	0.085
Mean	46	50	
Clinical stages			
III stage	15	14	0.768
IV a stage	9	10	
T stage			
T1–2	10	11	0.771
T3–4	14	13	
N stage			
N0–1	3	4	0.683
N2–3	21	20	
Pathologic types			
WHO II	3	5	0.439
WHO III	21	19	

WHO, World Health Organization

Table 2 Patterns of Failure (n)

Failure	Group A	Group B
Local recurrence	0	1
Nodal recurrence	0	1
Distant metastasis	1	1
Local recurrence & distant metastasis	0	4
Death	1	5

roidectomy was performed after chemoradiotherapy for NPC.

In group A, the GTV was drawn using both PET/CT and planning CT (contrast-enhanced), defined as $GTV_{PET/CT}$ and GTV_{CT}, respectively. The median $GTV_{PET/CT}$ and GTV_{CT} volumes were 19.51 ± 14.86 cm^3 and 39.52 ± 26.03 cm^3, respectively ($P < 0.05$). The change of GTV volume was calculated as. $(GTV_{PET-CT} - GTV_{CT})/GTV_{CT}$. An absolute volume change > 25% was considered a significant change. The GTV volume changed significantly in 13 patients (54.2%); 83.3% (20/24) of the patients' GTV were smaller based on PET/CT; and 16.7% (4/24) of the patients' GTV were larger due to tumor stage changes.

Local control and survival

All patients were regularly followed up until death or December 31, 2014. The median follow-up was 53 months (range, 10–71 months). In group A, one patient (4.2%) died of a distant metastasis (lung and bone metastasis; survival time, 35 months), while the other patients were free of local and regional recurrence. In group B, 5 patients (20.8%) died of NPC (two of local recurrence and three of metastatic disease with survival times of 10, 15, 18, 22, and 37 months, respectively), while 5 patients (20.8%) developed local recurrence (all with T4 disease and in-field failures in the GTV). One patient (4.2%) had regional nodal recurrence and 5 (20.8%) developed distant metastases (lung metastasis in 2, bone metastases in 2, bone and liver metastases in 1; Table 2). The 5-year LPFS rates of the two groups were 100% and 79.2%, respectively (P = 0.019). The 5-year DFS rates were 95.8% and 75.0%, respectively (P = 0.018). The 5-year LPFS and DFS rates were statistically significant (Fig. 1). The 5-year OS rates were 95.8% and 79.2%, respectively. The improvement in OS was insignificant (P = 0.079, Fig. 2).

Late toxicities

Late toxicities were assessed for close to 5 years of follow-up (Table 3). Late toxicities were similar in the two groups. The most common late toxicities of the two arms were grade 1–2 skin dystrophy, xerostomia, subcutaneous fibrosis, and hearing loss. There were no cases of grade 4 late toxicities. We did not observe any cases of radiation brain necrosis in the PET/CT-guided treatment arms. However, 2 patients (for a total of three temporal lobes) suffered temporal lobar injuries in conventional chemoradiotherapy, while two patients had primary bulky tumors with extensive skull base and intracranial tissue invasion.

Discussion

CCRT has been shown to improve tumor control and survival in patients with locally advanced NPC [11]. However, some disease recurrence has been known to occur after treatment [5, 12]. Newer drugs such as docetaxel and gemcitabine have exhibited promising results in NPC despite no improvement in OS [13–14]. One strategy for improving NPC is adding inductive and/or adjuvant chemotherapy before and/or after CCRT. In this study, all patients were assigned to receive 2 cycles of concurrent chemotherapy (docetaxel plus cisplatin) and 2–4 cycles of adjuvant chemotherapy (docetaxel plus cisplatin). All patients recruited into this study completed the treatment as planned, and no delays or dose reductions occurred. This finding indicates that this treatment strategy had acceptable compliance, so further improvements in tumor control were considered.

The local control rate of NPC is highly correlated with the total radiation dose delivered to the GTV. The SMART-IMRT technique is a more effective technique for escalating the dose to the GTV. A recent study showed that SMART-IMRT plus cisplatin and 5-FU chemotherapy showed promising activity with manageable toxicity and improved locoregional disease control [15]. In that trial, the full-course SMART-IMRT technique was utilized in group A consisting of 32 fractions of RT with doses of 77 Gy and 2.4 Gy, respectively, which enabled escala-

Table 3 Frequency of Late Toxicities

Type	Grade 0		Grade 1		Grade 2		Grade 3	Grade 4
	n	%	*n*	%	*n*	%		
Skin dystrophy								
Group A	15	62.5	7	29.2	2	8.3	0	0
Group B	14	58.3	8	33.3	3	12.5	0	0
Xerostomia								
Group A	5	20.8	11	45.8	8	33.3		0
Group B	4	16.7	13	54.1	7	29.2	0	0
Subcutaneous fibrosis								
Group A	4	16.7	14	58.3	6	25.0	0	0
Group B	3	12.5	13	54.2	8	33.3	1(4.2)	0
Hearing loss								
Group A	7	29.2	12	50.0	5	20.8	0	0
Group B	3	12.5	14	58.3	7	29.2	0	0
Trismus								
Group A	22	91.7	2	8.3	0			0
Group B	21	87.5	3	12.5	0		0	0
Temporal lobe necrosis								
Group A	24	100	0		0		0	0
Group B	22	91.7	2	8.3	0		0	0

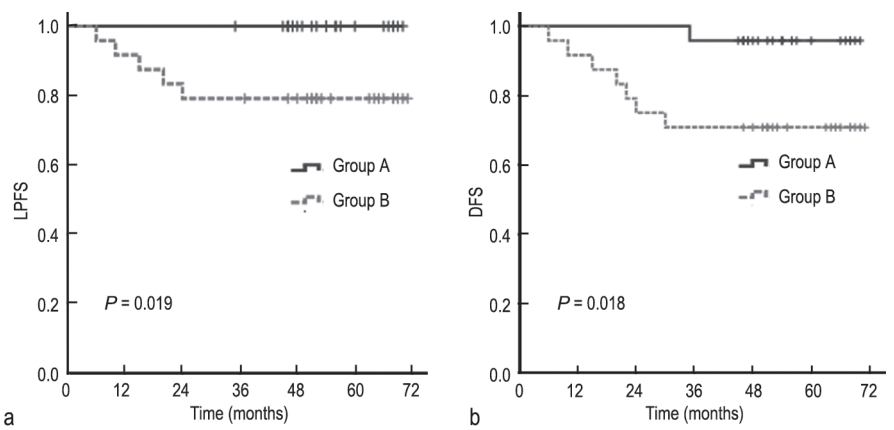

Fig. 1 Kaplan–Meier survival curves analysis of the two treatment groups. (a) The 5-year local progression-free survival rates, (b) disease-free survival rates.

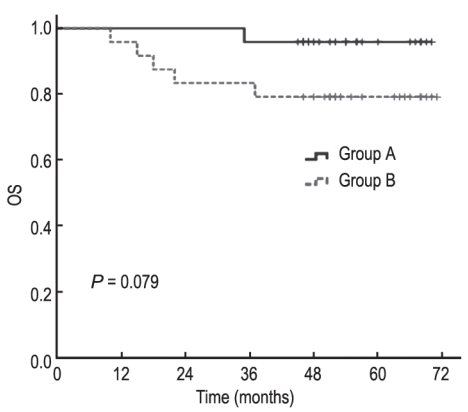

Fig. 2 Kaplan–Meier survival curves of overall survival of the two treatment groups, the difference of which was insignificant ($P = 0.079$)

tion of the mean BED for GTV to 95 Gy. Compared with conventional RT (65–70 Gy), a 13% increase in tumor dose was administered. Our study showed that the 5-year LPFS rates of the two groups were 100% and 79.2%, respectively ($P = 0.019$). The 5-year DFS rates were 95.8% and 75.0%, respectively ($P = 0.018$). The 5-year OS rates were 95.8% and 79.2%, respectively ($P = 0.079$). Although distant metastasis was the major cause of death in patients after treatment, our results confirmed that the risk of distant metastasis was decreased as local control rates increased. However, it is important to note the limitation of our study that our data were generated from a single institution pilot trial, meaning that the study may be underpowered. Our data generate a hypothesis that should be further validated in a large multi-center randomized trial.

A critical factor in treatment planning is accurately delineating the GTV that requires irradiation [16]. The use

of ^{18}F-FDG PET/CT reportedly has a positive impact on RT planning and patient management [17–18]. The use of PET/CT enables better staging and target volume delineation and then improves and optimizes treatment planning and implementation [19]. Our study aimed to be the first to directly compare the CT- and FDG PET/CT-defined GTV. The GTV volume changed significantly in 13 patients (54.2%); 83.3% (20/24) of the patients' GTV were smaller based on PET/CT findings; and 16.7% (4/24) of the patients' GTV were larger due to tumor stage changes. The median $GTV_{PET/CT}$ and GTV_{CT} volumes were 19.51 ± 14.86 cm^3 and 39.52 ± 26.03 cm3, respectively ($P < 0.05$). Our result is not surprising, as Guido *et al* [20] evaluated the effect of ^{18}F-FDG PET/CT compared with CT alone in RT target delineation for head and neck cancer. In 35 (92%) of 38 cases, the CT-based GTV were larger than the PET/CT-based GTV. The average total GTV from the CT and PET/CT scans were 34.54 cm^3 and 29.38 cm^3, respectively ($P < 0.05$).

Late toxicities were similar in the two groups. The most common late toxicities of the two arms were grade 1–2 skin dystrophy, xerostomia, subcutaneous fibrosis, and hearing loss. Bakst RL *et al* [21] reported the incidence of in-field brain radiation necrosis at 2.34 Gy per fraction. In our trial, no patients in the dose-escalation treatment arm had temporal lobe damage in the follow-up period.

Conclusions

The use of ^{18}F-FDG PET/CT has a growing role in the diagnosis and management of NPC. In fact, the fusion of PET and CT may have a significant impact on staging and RT treatment delineation in NPC. PET/CT-guided dose escalation RT appears to be well tolerated, while the SMART-IMRT technique combined with concurrent chemotherapy is completely feasible for local advanced NPC. New strategies combining different treatment modalities that can effectively reduce the rate of distant metastases require future development.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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