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Application of computed tomography and magnetic resonance imaging fusion images for delineating gross tumor volume in three-dimensional conformal radiotherapy of nasopharyngeal carcinoma

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► ***Original article***

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ABSTRACT

Background: To evaluate computed tomography (CT) and magnetic resonance imaging (MRI) fusion images for delineating gross tumor volume (GTV) in three-dimensional conformal radiotherapy (3D-CRT) of nasophanrygeal carcinoma (NPC), and compare treatment outcomes between CT- and CT+MRI-based targets. ***Materials and Methods***: A total of 120 NPC patients treated with 3D-CRT were included, in which, 60 each were treated with CT-based and 60 with CT+MRI fusion targets. We explored the clinical application of CT+MRI fusion targets and compared the 1-, 3-, and 5-year survival and relapse rates between both targets. ***Results:*** The clinical characteristics and treatment factors were well balanced. The differences in public volume using CT alone in the CT+MRI (Group A) and the CT arm (Group B) were not significant (33.6±2.18 vs. 34.3±2.98, $P > 0.05$). The public volumes of GTV in the two arms were 49.48±2.46 cm^3 and 33.6±2.18 cm^3 respectively ($P < 0.05$). CT+MR fusion images did not influence the one-, three-, and 5-year survival rates (100% vs. 98.3%, 85.0% vs. 81.2%, and 73.3% vs. 68.3%, respectively). The three- and 5-year out-of-field progression was reduced in the CT+MRI arm. However, only the difference in 3-year out-of-field relapse rate was significant (3.3% vs. 13.3%; $P < 0.05$). The incidence of acute toxicities was similar between groups. ***Conclusion:*** The variability in GTV delineation in NPC was ascribed to intermodality and not interobserver variability. CT+MR fusion images likely reduced the 3-year out-of-field relapse rate.

Keywords: *Nasophanrygeal carcinoma, image fusion, three-dimensional conformal radiation therapy.*

INTRODUCTION

Because radiotherapy for head and neck cancer, especially nasopharyngeal carcinoma (NPC), can lead to development of severe acute and late side effects [1, 2], damage to adjacent unaffected tissues should be minimized. Uncertainty in target delineation may affect the dose administered to the target and to other organs; thus, the target should be determined as accurately as possible, especially with the growing use of three-dimensional conformal radiation therapy (3D-CRT). Gross tumor volume (GTV) has been most commonly defined by computed tomography (CT)-based imaging, but several studies have shown that CT imaging alone to be inadequate to outline targets. Magnetic resonance imaging (MRI) is preferred over CT to detect the extent of disease and more accurately determine the pathological specimen measurements [3-7]. However, MRI alone cannot be used for radiation treatment planning

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because of image artifacts and the lack of electron density information necessary for RT dose calculations [8]. While the addition of MRI to CT-based delineation has proven useful for delineation in the head and neck region [9], the effect of CT+MRI targets on survival rates and tumor recurrence rates remains to be determined, especially for developing radiotherapy treatment schedules and planning tumor treatment.

This study evaluated the accuracy and consistency of CT and CT+MRI fusion images to determine GTV during 3D-CRT treatment planning for NPC, and compared the one-, three-, and 5-year survival and recurrence rates between CT- and CT+MRI-based treatment planning.

MATERIALS AND METHODS

Clinical features

From August 2005 to September 2006, a randomized controlled trial was undertaken at the fourth affiliated hospital of Guangxi Medical University. A total of 120 eligible patients with stage I-IV (Chinese, 92 staging systems) NPC with evaluable tumor lesions were included in the study. This study was approved by the ethical review board of Guangxi Medical University and in compliance with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent regarding the treatment course was obtained from all participants.

The inclusion criteria included those patients fit enough to receive radical RT, with biopsy-proven squamous cell carcinoma (SCC), between 19 and 75 years of age, and willing to provide informed consent for study randomization and registration. The Karnofsky performance status scores were greater than 90 in all patients. Patients in both groups completed the planned dose of RT, and concurrent chemoradiotherapy (CCRT) was administered for locally advanced disease (stages III and IV) according to the American Joint Committee on Cancer (AJCC) 2009 staging system. The con current chemotherapy protocol was two to three cycles of cisplatin 75 mg/m^2 dL administered every three weeks. Patient and tumor characteristics were equally balanced across both arms of the trial (table 1). There were no statistically significant differences between the two groups.

Table 1. Patient and tumor characteristics of eligible patients entered on study.

Characteristic	CT arm	CT+MRI arm	P value
Gender			0.451
Male	47	45	
Female	13	15	
Age mean±SE (range)	5.7±47.3	5.4±48.2	0.423
Stage groups			0.645
I+II	19	22	
III+IV	41	38	
Pathologic types (WHO)	41/60	38/60	0.238
II	55	57	
III	5	3	

Imaging technique and data acquisition

Treatment-planning CT scans were obtained prior to radiotherapy treatment for all 120 patients, of whom 60 in the experimental arm underwent additional MRI scans. Complete blood count, renal and liver function, and dental status were also assessed. Additional investigations were performed as indicated clinically. Before CT scans, patients were immobilized in a customized thermoplastic head -and-shoulder mask system extending from the vertex of the scalp to the shoulders. CT scans were performed using a 16-slice spiral CT (GE Medical Systems, Waukesha, USA) with

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intravenous contrast from about the mid-brain to below the clavicular junction. CT images with 2.5-mm slice thickness were acquired for treatment planning. MRI scans with intravenous contrast were also performed at 3-mm slice thickness from about the mid-brain to below the clavicular junction with patients in the supine position with the same positioning and immobilization conditions using a Siemens 1.5-T superconducting magnetic resonance instrument (Siemens Medical Systems, Munich, Germany). For every patient, transverse, sagittal, and coronal T1-weighted images were obtained, in addition to transverse T2-weighted and T1-weighted images after injection of gadolinium.

Image data were transferred and registered in the PLATO RT treatment planning system (Nucletron Company, Veenendaal, Holland) used to delineate the targets and organs at risk (OARs) and for 3D-CRT treatment planning. In addition, sagittal MRI scans were taken for localization purposes. MRI distortion was measured by scanning a head phantom consisting of various geometric shapes with precisely known locations in space. A comparison of these points with the corresponding points on the image set showed that the image distortion was <1 mm and thus could be ignored in target volume delineation. Fusion of CT and MRI images was performed for the 60 patients in the CT+MRI arm using an automatic multimodality image registration algorithm, which used the brain as an internal reference for registration.

Target delineation

GTV was defined as the macroscopic extent of the primary tumor that was demonstrable on CT (CT arm) or CT+MRI fusion (CT+MRI arm) images. During a consensus meeting, the four senior oncologists agreed upon the guidelines for delineation of the GTV, which included the primary disease and nodes greater than 1 cm in diameter or nodes with necrotic centers. The GTV as well as the high-risk subclinical disease sites were then delineated slice by slice on the axial contrast-enhanced CT images in the treatment planning system. Clinical target volume 1 (CTV1) was individually delineated for each patient to cover high-risk regions based on tumor invasion patterns. CTV2s were delineated to cover low-risk and neck nodal regions. The target volumes were defined in accordance with the International Commission on Radiation Units and Measurements Reports 50 and 62 by four senior head and neck radiation oncologists. Planning target volumes (PGTV) for all GTVs were generated automatically with 3-mm margins after delineation of tumor targets in order to include biological and technical uncertainties. Each oncologist used the same personal computer installed with delineation software together with patient data. Front three oncologists contoured CT-based target (GTV-ct1, GTV-ct2, and GTV-ct3) and fusion target (GTV-f) on the CT and CT+MRI fusion images, respectively. The volume of the GTV was calculated by the radiation treatment planning system. The public target volume (GTV-com) between CT- and CT+MRI-based targets was outlined by the last one. The public index (PI) was then calculated using the formula: PI = public volume^3/(GTV-ct1 × GTV-ct2 × GTV-ct3)×100%.

Treatment

Senior physicists used the PLATO RT system (Nucletron company, Veenendaal, Holland) for treatment planning for all 120 patients. Patients were treated using 6-MV photon linear accelerator beams using 3D-CRT. Electron beams were used to augment doses in the posterior neck after introducing spinal cord shielding. Conventional once-daily RT treatment with 95% isodose line encompassing the targets were prepared for each patient. The prescription dose for the planning target volume of GTV (PGTV) was 76-80 Gy per 38-40 fractions at 2 Gy per fraction. The involved nodes received 64-66 Gy over 32-33 fractions, while the low neck and supraclavicular fields were treated with conventional anterior-posterior (AP) or anterior -posterior/posterior-anterior (AP/PA) fields for a total of 50 Gy at 2 Gy per fraction. Some patients were treated with concurrent chemoradiotherapy (CCRT), which was initiated on the first day of RT. The chemotherapy

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protocol included 80 mg/m^2 cisplatin administered by iv infusion every three weeks.

Follow-up

The duration of follow-up was calculated from the first day of treatment to either the day of death or day of the last follow-up. Response to therapy was evaluated by clinical examination, endoscopy, and MRI or PET-CT imaging of the neck and nasopharynx 2 months after treatment, according to guidelines from the Response Evaluation Criteria in Solid Tumors (RECIST) [10]. Repeat imaging was generally done at 3-month intervals during the first 2 years, followed by 6-month intervals thereafter. Acute toxicities were scored according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0).

Statistical analyses

Statistical analysis was performed using SPSS® for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Data are presented as means ± standard deviation (SD). X^2-tests were used for group comparisons. Survival analyses were performed using log-rank tests. $P < 0.05$ were considered statistically significant.

RESULTS

Comparison of GTV public volumes

CT+MRI fusion images were obtained for patients in Group A (CT+MRI arm), but only CT images were obtained for the patients in Group B (CT arm). As shown in table 2, the differences in public volume based on CT alone in the CT+MRI (Group A) and CT (Group B) arms were not statistically significant (P >0.05). However, there were significant differences in public volumes between CT+MRI and CT-based targets in Group A (t = 37.42, $P < 0.05$).

Comparison of public indexes

The public index was significantly superior in the experimental arm different stages of NPC ($P < 0.05$) (table 3).

Table 2. Comparison of public volume of GTV between CT- and CT+MRI-based targets (cm^3).

Modality	Group A (n=60)	Group B (n=60)	t	*P*
CT	2.18±33.6	2.98±34.3	1.650	*0.05<
CT+MRI fusion	2.46±49.48	-	37.422	**0.05>

*Comparison of the public volume by using CT image alone between CT+MRI arm and CT arm.
**Comparison of the public volume of GTV between CT- and CT+MRI-based targets in the experimental.
There are CT+MRI fusion image in Group A (CT+MRI arm), but only CT image in Group B (CT arm).

Table 3. Comparison of the public index on CT+MRI image and CT image alone.

Stage	Experimental arm				Control arm	t*	*P**
	CT arm	CT+MRI arm	t	*P*			
I	2.34±92.1	2.98±95.86	7.687	0.05>	2.16±89.56	6.178	0.05>
II	2.26±88.5	2.28±93.83	12.788	0.05>	2.38±86.32	5.216	0.05>
III	3.53±82.4	3.57±91.34	13.793	0.05>	3.59±84.15	2.692	0.05>
IVa	2.45±74.1	2.20±90.73	39.073	0.05>	2.12±77.42	7.899	0.05>

*Comparison of the public index on CT+MRI image in the CT+MRI arm and CT image alone in the CT arm.
There are CT+MRI fusion image in Group A (CT+MRI arm), but only CT image in Group B (CT arm)

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Compatibility conditions for patients with different stages of NPC

The results showed that for T1 and T2 lesions, GTV-ct was usually larger than GTV-f; however, for T3 and T4 lesions, GTV-f was usually larger than GTV-ct. GTV-ct is a complementation with GTV-f in different patients, as shown in table 4.

Treatment outcomes

All patients tolerated treatment well and completed their prescribed doses of RT. Clinical follow-up was available for all patients, with a median follow-up of 52.0 months. This report provides 5-year results. The complete response (CR) rate for primary tumors at 3 months 96.7% (58/60) in the CT+MRI arm and 93.3% (56/60) in the CT arm. This difference was marginally not significant (P = 0.675). The one-, three-, and 5-year overall survival (OS) rates for the CT+MRI arm were 100% (60/60), 85.0% (51/60), and 73.3% (44/60), respectively. In comparison, the rates were 98.3% (59/60), 81.2% (49/60), and 68.3% (41/60), respectively, in the CT arm. These differences were not statistically significant (P > 0.05). The relapse rates at one-, three-, and 5 years were 3.3% (2/60), 8.3% (5/60), and 13.3% (8/60) in the for CT+MRI arm. The rates were 5.0% (3/60), 16.67% (10/60), and 18.3% (11/60) in the CT arm. Further analysis revealed that the three- and 5-year out-of-field relapse rates were lower in the CT+MRI arm compared to those of the CT arm (3.3 vs. 13.3% and 6.7 vs. 16.6%). However, only the difference in 3-year out-of-field relapse rates was statistically significant (P < 0.05).

Acute toxicities

Acute toxicities were similar in both groups (table 5). No treatment-related deaths and grade 4 toxicity were observed in either arm. The most common hematological adverse events (leucopenia, anemia, and throm bocytopenia) occurred in 10% of patients in the CT and CT+MRI arms. The most common non-hematological adverse event was grade 3–4 mucositis, which occurred in 17 patients (28.3%) in the CT arm and 18 patients (30.0%) in the CT+MRI arm (P > 0.05).

Table 4. The Compatibility condition of CT- and CT+MRI-based targets for different stage patients.

Compatibility condition	T1	T2	T3	T4	Total
GTV-ct = GTV-f	2	3	3	0	8
GTV-f contain GTV-ct	2	3	11	9	25
GTV-ct contain GTV-f	3	6	1	1	11
Complementarity	2	3	6	5	16

Table 5. Acute toxicity according to CTCAE v3.0.

Toxicity	CT arm (n=60)					CT+MRI arm (n=60)					*P* value
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
Hematological											
Leucopenia	17	20	19	4	0	19	21	17	3	0	0.05<
Anemia	39	15	6	0	0	41	13	5	1	0	0.05<
Thrombocytopenia	51	5	2	2	0	50	7	2	1	0	0.05<
Non-hematological											
Dermatitis	0	47	10	3	0	0	45	12	3	0	0.05<
Mucositis	0	18	25	17	0	0	20	22	18	0	0.05<
Dysphagia	23	26	8	3	0	20	29	7	4	0	0.05<
Xerostomia	15	21	23	1	0	13	25	22	0	0	0.05<
Neurotoxicity	53	6	1	0	0	56	4	0	0	0	0.05<

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DISCUSSION

The results of the present study demonstrated that CT+MR fusion images (CT+MRI arm) better delineated GTV compared to CT alone (CT arm). A previous study by Rasch *et al.* reported that combined MRI and CT images decreases observer variation and plays an important role in determining target volume coverage and sparing of critical structures [11, 12]. The same combination was studied by other authors with similar results [13-16]. Emami's study reported that MRI-based targets were 74% larger, more irregularly shaped, and did not always include the CT targets, compared with CT [17]. Our study used a dedicated MRI protocol and co-registered MRI for radiotherapy GTV delineation and showed there was significant discordance between the CT- and MRI-based targets, a finding in accordance with the results of other studies [18, 19]. Thus, it appears that there are differences between CT- and MRI-based targets. CT+MRI target volumes were smaller than those of CT-based targets in early-stage NPC. However, for locally advanced disease, CT+MRI target volumes were considerably larger than CT-only volumes (GTV-ct contain GTV-f). For different stages of NPC, CT and MRI images can be complementary to each other, similar to the results of previously published reports by Jager *et al.* [9]. Additionally, the results showed that there were no significant differences in public volumes based only on CT images between the CT+MRI and CT arms ($t = 1.65$, $P > 0.05$), which indicates that there was no interobserver variability in GTV delineation in simulation CT images of NPC. However, the public GTV volumes in the CT+MRI and CT arms were 49.48±2.46 cm^3 and 33.6±2.18 cm^3 respectively, a significant difference ($P < 0.05$), as shown in tables 1 and 2. This finding is attributed to the CT/MRI fusion technique because it can provide more image information and improve the accuracy and consistency of GTV delineation. Unlike findings from most published articles stressing the importance of interobserver variability in GTV delineation, we found that variability in GTV delineation was due to intermodality rather than interobserver variability.

Moreover, the fusion of CT and MRI images can reduce the 3-year out-of-field recurrence rates, however, the addition of MRI to CT-based delineation did not influence the one-, three-, and 5-year survival rates for 3D-CRT in NPC (100% vs. 98.3%, 85.0% vs. 81.2%, and 73.3% vs. 68.3%, respectively). To our knowledge, this is the first single-institution study to evaluate treatment outcomes in CT- and CT+MRI-based targets.

The acute toxicity profiles of both arms were similar. No instances of grade 4 toxicity were observed in either arm. Most of the patients developed grades 1–2 acute hematological toxicities (leucopenia, anemia, or thrombocytopenia). The most common grade 3 hematological adverse event was limited to 10% in CT arm and CT+MRI arm. The major acute non-hematological adverse effects of grade 3 events was mucositis, which occurred in 17 (28.3%) and 18 (30.0%) patients in the CT and CT+MRI arms, respectively ($P > 0.05$). A likely reason for the similar acute toxicities demonstrated in this trial is that CT+MRI image fusion method mainly affects the GTV, and not the CTV. However, CTV may mainly influence the rate of acute toxicities.

CONCLUSION

The present study revealed the potential utility of CT-MRI image fusion in GTV determination for 3D-CRT for NPC and reducing 3-year out-of-field relapse rates. However, the limitations of this analysis should also be noted. First, there were functional imaging techniques, such as ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) [20]. Second, there are currently no consensus guidelines for delineation of GTV from MRI images. Further studies are necessary to define a multi-modality image fusion method for improved target delineation in patients with NPC.

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Disclosure statement

No competing financial interests exist.

These authors contributed equally to this work and should be considered co-first authors.

Conflict of interest**:** *Declared none.*

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