

# Three-Phase Adaptive Radiation Therapy for Patients With Nasopharyngeal Carcinoma Undergoing Intensity-Modulated Radiation Therapy: Dosimetric Analysis

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## Abstract

Patients with nasopharyngeal carcinoma undergoing intensity-modulated radiation therapy may experience significant anatomic changes throughout the entire treatment course, and adaptive radiation therapy may be necessary to maintain optimal dose delivered both to the targets and to the critical structures. The timing of adaptive radiation therapy, however, is largely unknown. This study was to evaluate the dosimetric benefits of a 3-phase adaptive radiation therapy technique for nasopharyngeal carcinoma. Twenty patients with nasopharyngeal carcinoma treated with intensity-modulated radiation therapy were recruited prospectively. After fractions 5 and 15, each patient had repeat computed tomography scans, and adaptive replans with recontouring the targets and organs at risk on the new computed tomography images were generated and used for subsequent treatment (replan 1 and replan 2). Two hybrid intensity-modulated radiation therapy plans (plan 1 and plan 2) were generated by superimposing the initial plan (plan 0) to each repeated new computed tomography image, reflecting the actual dose delivered to the targets and organs at risk if no changes were made to the original plan. Dosimetric comparisons were made between the adaptive replans (adaptive radiation therapy plans: plan 0 + replan 1 + replan 2) and their corresponding nonadaptive radiation therapy plans (plan 0 + plan 1 + plan 2). Comparing with the nonadaptive radiation therapy plans, the adaptive radiation therapy plans resulted in a significant improvement in conformity index for planning target volumes for primary disease, involved lymph node, high-risk clinical target volume, and low-risk clinical target volume (PTVnx, PTVnd, PTV1, and PTV2, respectively). Median V95 for PTVnx; D95, D99, V100, V95, and V93 for PTVnd; D99 and V100 for PTV1; and D95, D99, V100, V95, and V93 for PTV2 were increased significantly. There were significant dose–volume reductions, including maximum doses to the brainstem and temporal lobes, mean doses to the glottis, V50 for the supraglottis,  $D_{\text{mean}}$  and V30 for the left parotid, median dose to the right optic nerve, and V55 for the skin. The 3-phase adaptive intensity-modulated radiation therapy for patients with nasopharyngeal carcinoma results in improvements in target coverage and conformity index and decreased doses to some organs at risk.

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## Keywords

nasopharyngeal carcinoma, head and neck cancer, adaptive radiation therapy, intensity-modulated radiation therapy, dosimetric analysis

## Abbreviations

ART, adaptive radiation therapy; CI, conformity index; CT, computed tomography; IMRT, intensity-modulated radiation therapy; NPC, nasopharyngeal carcinoma; OARs, organs at risk; PET-CT, positron emission tomography computed tomography; RT, radiation therapy.

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## Introduction

Intensity-modulated radiation therapy (IMRT), as one of the milestone innovations in the history of radiation oncology, has now been widely used to treat patients with nasopharyngeal carcinoma (NPC) since early 1990s. This technique provides adequate target coverage while maintaining steep dose gradients at the border between the targets and adjacent normal tissues, through which dose escalation for the targets may be achieved without delivering excessive dose to the organs at risk (OARs).<sup>1</sup>

However, small changes in patients or tumor position may produce large dosimetric consequences due to the sharp dose gradients at the border. There are, indeed, large anatomic changes both in the targets and in OARs, which subsequently result in underdose to the targets and/or overdose to the surrounding critical structures according to studies from other investigators and ours.<sup>2-5</sup> Thus, the initial planning based on pretreatment condition may not truly reflect the dosimetric variations during the course of IMRT, and an intervention with adaptive radiation therapy (ART) is indicated.

In our previous study, patients with NPC receiving IMRT had repeat computed tomography (CT) scans after each 5 fractions and at treatment completion. Automatic recontouring the targets and OARs using deformable registration algorithm was conducted through CT-CT fusion. Anatomic changes were assessed by comparing the initial CT and repeated CT. Hybrid plans with recontouring were generated, and the dose-volume histograms of the hybrid plan and the original plan were compared. We found that the target dose coverage in the hybrid plans did not get worse, but overdose occurred in some critical structures. Significant dosimetric changes were observed, and 2 trigger points (at fractions 5 and 15 during the treatment course) at which adaptive replanning should be initiated were identified and recommended. The current study aimed to prospectively evaluate the dosimetric benefits of this ART technique for patients with NPC undergoing IMRT.

## Methods and Materials

### Eligibility Criteria

Patients with histologically proven NPC and treated with curative IMRT were enrolled into this prospective study. Inclusion criteria were as follows: aged 18 to 70 years, Karnofsky

Performance Score  $\geq 70$ , and stages I to IVb according to the 2010 American Joint Committee on Cancer (AJCC) staging system. Patients diagnosed with, or treated for other malignancies, or treated with non-IMRT techniques were excluded in the study. Written informed consent was obtained for all patients. The study was approved by the institutional review board of the People's Hospital of Guangxi Zhuang Autonomous Region.

### Immobilization and Simulation

All patients were required to lie down on a wide-bore CT simulator couch (Somatom Sensation Open; Siemens Medical Solutions, Erlangen, Germany) in a supine position with the head in a neutral position. Individualized thermoplastic masks were designed to cover the head, neck, and shoulders. Intravenous contrast-enhanced CT using 2-mm slice from the vertex to the manubriosternal joint was performed for planning. The CT data were imported to a treatment planning system (Pinnacle<sup>3</sup>, version 9.2).

### Delineation of the Targets and OARs

The target delineation for patients with NPC at our institution has been described previously.<sup>2</sup> Briefly, GTVnx and GTVnd included the primary gross volume and the involved cervical lymphadenopathy, respectively, determined by the imaging, clinical, and endoscopic findings. The high-risk clinical target volume (CTV1) was defined as GTVnx plus 5-mm margin and entire nasopharyngeal mucosa plus 5-mm submucosal volume. The low-risk CTV2 covered CTV1, entire nasopharynx, parapharyngeal space, pterygopalatine fossa, posterior third of the nasal cavity and maxillary sinuses, inferior sphenoid sinus, posterior ethmoid sinus, skull base, and anterior half of the clivus. CTV2 also covered the entire neck nodal regions for node-positive patients. However, for node-negative patients, only the upper neck was included in CTV2. Level 1b was not routinely irradiated unless there was confirmed lymphadenopathy in level 1b, or large metastatic node size ( $\geq 3$  cm)/extracapsular spread was present in level 2a. PTVnx, PTVnd, PTV1, and PTV2 were generated by adding 5-mm margin to GTVnx, GTVnd, CTV1, and CTV2, respectively. The contoured critical structures included the brain stem, chiasm, optic nerves, spinal

cord, eyes, lens, parotid glands, oral cavity, larynx, mandible, skin, and temporomandibular joints.

### Intensity-Modulated Radiation Therapy Design and Delivery

The plans were designed and optimized using the Pinnacle inverse planning system. The prescribed radiation dose was 66 to 71.6 Gy at 2.17 to 2.20 Gy per fraction delivered to the PTVnx and PTVnd and 60 to 66 Gy at 2.0 Gy per fraction delivered to the PTV1. The PTV2 was treated to 54 to 56 Gy at 1.64 to 1.70 Gy per fractions. All patients were treated once daily, 5 fractions weekly. Dose constraints to the critical structures were within the tolerance according to the Radiation Therapy Oncology Group (RTOG) 0225 protocol, and efforts were made to meet the criteria as closely as possible. Intensity-modulated radiation therapy was delivered via 7 fixed gantry angles with an Elekta Synergy Linear Accelerator (Elekta Ltd, Stockholm, Sweden) with step-and-shoot treatment techniques.

### Designing and Implementing ART

Repeat CT scans were acquired for each patient with the same mask and isocenter as the initial simulation CT scan after fractions 5 and 15 using the same CT simulator. Each new CT data set was registered with the initial planning CT data set through VoxAlign Deformation Engine provided by the MiM Maestro software (Ver. 5.2; MIM Software Inc., Cleveland, US). Auto-propagating the planning contours on the new CT was conducted, and the manual modification was performed if needed. Changes in the volume of GTVnx and GTVnd were calculated by comparing the new CT and the planning CT. PTVnx and PTVnd on the new CT data sets remained, in general, the same as on the original ones. However, modifications were allowed for CTV1 and CTV2, and thus for PTV1 and PTV2, if necessary. In addition, to minimize interpersonal variation during contouring process, 1 junior physician was designated to delineate the targets and OARs on the 3 CT data sets (ie, data sets obtained during simulation and after fractions 5 and 15) for each patient, and the final results were reviewed and approved by an assigned senior physician before they were ready for treatment planning.

Off-line adaptive replans after fractions 5 and 15 were generated and used for subsequent treatment (replan 1 and replan 2). Two hybrid IMRT plans (plan 1 and plan 2) were generated by superimposing the initial plan (plan 0) to each repeated new CT image, reflecting the actual dose delivered to the targets and OARs if the original plan was used to treat the new deformed anatomy. Dosimetric comparisons were made between the adaptive replans (ART plans: plan 0 + replan 1 + replan 2) and their corresponding non-ART plans (non-ART plans: plan 0 + plan 1 + plan 2).

### Statistical Analysis

The Kolmogorov-Smirnov test was used to test the data for normality. Mean (standard deviation) was used for data with

**Table 1.** Patient Characteristics.

Characteristics	Patients, n (%)
Sex	
Male	14 (70)
Female	6 (30)
Age, years	
Range	14-62
Median	43
KPS score	
90	20 (100)
T stage	
T2	10 (20)
T3	4 (20)
T4	6 (30)
N stage	
N0	1 (5)
N1	4 (20)
N2	15 (75)
AJCC stage grouping	
II	6 (30)
III	11 (55)
IVA	3 (15)
Treatment scheme	
Concurrent chemo	17 (85)
Concurrent chemo plus nimotuzumab	1 (5)
Concurrent nimotuzumab	2 (10)

Abbreviation: KPS, Karnofsky Performance Score.

normal distribution, whereas median (interquartile range) was used for data with skewed distribution. A paired sample *t* test or Wilcoxon rank sum test was chosen based on the data types. A probability value less than .05 was considered significant. Analyses were performed using SPSS 16.0 software (SPSS, Inc, Chicago, Illinois).

## Results

### Patient Characteristics

Between April 2014 and August 2016, a total of 20 patients diagnosed with undifferentiated nonkeratinizing NPC were enrolled into this study. There were 14 men and 6 women with median age of 43 years. Stage distributions according to the 2010 AJCC staging system were as follows: stage II, 6 patients; stage III, 11 patients; and stage IV, 3 patients. Concurrent platinum-based chemotherapy was given to 17 patients, concurrent nimotuzumab, a humanized antibody that targets epidermal growth factor receptor, to 1 patient, and concurrent platinum-based chemotherapy plus nimotuzumab to 2 patient. The characteristics of the patient cohort are listed in Table 1.

### Changes in Conformity Index and Homogeneity Index

The ART plans had significantly increased conformity indices (CIs) for PTVnx, PTVnd, PTV1, and PTV2, compared with the non-ART plans, whereas no significant differences were found in homogeneity index for all targets between ART and non-ART plans (Table 2).

**Table 2.** Dosimetric Comparison of the Targets Between the ART and Non-ART Plans.<sup>a</sup>

Parameters	Non-ART	ART	P Value
<b>PTVnx</b>			
HI	1.12 (0.03)	1.11 (0.04)	.076
CI	0.94 (0.01)	0.97 (0.02)	.045 <sup>b</sup>
D <sub>max</sub> (Gy)	78.12 (2.55)	77.15 (1.25)	.034 <sup>b</sup>
D <sub>min</sub> (Gy)	63.42 (1.74)	64.30 (2.17)	.219
D <sub>mean</sub> (Gy)	72.66 (72.38-73.55)	73.29 (72.31-73.74)	.335
D95 (Gy)	70.26 (1.07)	70.61 (1.17)	.067
D99 (Gy)	68.24 (1.05)	68.91 (1.57)	.096
V110 (%)	0.40 (0.00-1.99)	0.05 (0.00-0.23)	.033 <sup>b</sup>
V100 (%)	94.77 (2.20)	96.01 (2.50)	.104
V95 (%)	99.81 (99.56-100.00)	99.94 (99.66-100.00)	.011 <sup>b</sup>
V93 (%)	99.99 (99.89-100.00)	100.00 (99.94-100.00)	.068
<b>PTVnd</b>			
HI	1.11 (0.01)	1.09 (0.03)	.796
CI	0.85 (0.05)	0.90 (0.01)	.028 <sup>b</sup>
D <sub>max</sub> (Gy)	76.77 (2.29)	76.71 (1.37)	.877
D <sub>min</sub> (Gy)	44.31 (8.69)	47.38 (9.99)	.191
D <sub>mean</sub> (Gy)	71.52 (1.61)	72.42 (1.57)	.057
D95 (Gy)	66.33 (2.85)	68.55 (1.91)	.021 <sup>b</sup>
D99 (Gy)	58.90 (5.74)	63.43 (2.85)	.031 <sup>b</sup>
V110(%)	0.00 (0.00-0.07)	0.07 (0.00-0.74)	.807
V100 (%)	86.25 (5.17)	91.78 (3.99)	.038 <sup>b</sup>
V95 (%)	95.17 (2.08)	98.01 (1.78)	.041 <sup>b</sup>
V93 (%)	96.11 (2.32)	98.48 (1.17)	.038 <sup>b</sup>
<b>PTV1</b>			
HI	1.28 (0.03)	1.27 (0.03)	.178
CI	0.98 (0.05)	0.99 (0.07)	.019 <sup>b</sup>
D <sub>max</sub> (Gy)	77.50 (1.37)	77.12 (1.85)	.208
D <sub>min</sub> (Gy)	51.89 (6.95)	52.87 (6.15)	.407
D <sub>mean</sub> (Gy)	70.36 (0.71)	70.66 (1.09)	.285
D95 (Gy)	63.71 (1.06)	64.21 (1.10)	.219
D99 (Gy)	60.16 (2.58)	61.09 (1.55)	.037 <sup>b</sup>
V100 (%)	98.01 (1.14)	98.71 (0.97)	.028 <sup>b</sup>
V95 (%)	99.51 (99.07-100.00)	99.78 (0.59)	.291
V93 (%)	99.23 (99.51-100.00)	99.74 (0.24)	.185
<b>PTV2</b>			
HI	1.45 (0.07)	1.44 (0.09)	.418
CI	0.93 (0.07)	0.98 (0.01)	.009 <sup>b</sup>
D <sub>max</sub> (Gy)	78.55 (1.84)	77.90 (1.47)	.531
D <sub>min</sub> (Gy)	28.17 (25.06-34.17)	28.44 (26.09-35.91)	.882
D <sub>mean</sub> (Gy)	63.03 (2.55)	63.10 (1.98)	.207
D95 (Gy)	53.10 (1.13)	55.02 (1.07)	.018 <sup>b</sup>
D99 (Gy)	49.11 (1.78)	50.58 (1.57)	.029 <sup>b</sup>
V100 (%)	95.14 (1.55)	96.01 (1.17)	.023 <sup>b</sup>
V95 (%)	97.62 (1.29)	98.07 (1.01)	.030 <sup>b</sup>
V93 (%)	98.01 (0.24)	99.00 (0.18)	.041 <sup>b</sup>

Abbreviations: ART, adaptive radiation therapy; CI, conformity index; D<sub>max</sub>, maximum dose; D<sub>min</sub>, minimum dose; D<sub>mean</sub>, mean dose; D95, dose to 95% of the volume; D99, dose to 99% of the volume; HI, homogeneity index; V93, percentage of the volume receiving more than 93% of the prescription dose; V95, percentage of the volume receiving more than 95% of the prescription dose; V100, percentage of the volume receiving more than 100% of the prescription dose; V110, percentage of the volume receiving more than 110% of the prescription dose.

<sup>a</sup>Difference was calculated by paired sample *t* test or Wilcoxon rank sum test according to data types. Mean (standard deviation) was used for data with normal distribution, whereas median (interquartile range) was used for data with skewed distribution.

<sup>b</sup>Statistical significance.

### Dosimetric Differences in Targets Between ART and Non-ART Plans

The ART plans had significant improvements in more than half of the dosimetric parameters for the targets, comparing with the

non-ART plans. The 2-phase adaptive replans created an increased V95 and decreased D<sub>max</sub> and V110 for PTVnx. D95, D99, V100, V95, and V93 for PTVnd in the ART plans were increased by 2.22 (1.76) Gy, 4.53 (2.63) Gy, 5.53 (4.02%), 2.84 (2.71%), and 2.37 (2.91%), respectively; D99

**Table 3.** Dosimetric Comparison of OARs Between the ART and Non-ART Plans.

Parameters	Non-ART	ART	P Value
Skin			
V55 (%)	9.98 (1.51)	9.07 (1.27)	.036
Left parotid			
D <sub>mean</sub> (Gy)	37.07 (3.42)	35.79 (3.03)	.031
V30 (%)	52.75 (7.28)	48.64 (7.24)	.038
Right parotid			
D <sub>mean</sub> (Gy)	37.73 (7.19)	37.13 (5.45)	.450
V30 (%)	53.70 (16.21)	50.47 (10.44)	.155
Brain stem			
D <sub>max</sub> (Gy)	54.47 (3.62)	52.05 (3.29)	.012
Glottis			
D <sub>mean</sub> (Gy)	41.55 (4.83)	37.89 (4.27)	.015
Supraglottis			
V50 (%)	45.21 (6.17)	41.54 (6.07)	.027
Right optic nerve			
D <sub>max</sub> (Gy)	50.15 (42.63-52.49)	47.98 (38.12-51.09)	.024
Left optic nerve			
D <sub>max</sub> (Gy)	47.01 (10.96)	43.05 (12.14)	.182

Abbreviations: ART, adaptive radiation therapy; OARs, organs at risk.

and V100 for PTV1 were increased by 0.93 (0.78) Gy and 0.70 (0.64%), respectively; and D95, D99, V100, V95, and V93 for PTV2 were increased by 1.92 (1.01) Gy, 1.47 (1.23) Gy, 0.87 (1.37%), 0.45 (0.41%), and 0.99 (0.46%), respectively. No significant differences were found in other dosimetric parameters between the 2 plans, as shown in Table 2.

### Dosimetric Changes in OARs

As for OARs, significant differences were found in some dosimetric parameters between the ART and non-ART plans. In the ART plans, D<sub>max</sub> for the brain stem was decreased by 2.42 (1.67) Gy, comparing with the non-ART plans. A similar trend of dosimetric changes could also be found in other structures. Median D<sub>max</sub> for the right optic nerves was decreased by 2.21 Gy; V50 for the supraglottis, D<sub>mean</sub> for the glottis, D<sub>mean</sub> and V30 for the left parotids, and V55 for the skin were decreased by 3.67 (3.78) Gy, 3.66 (3.14) Gy, 1.27 (1.05) Gy, 4.12 (3.58%), and 0.91 (1.83%), respectively (Table 3). No significant differences were found in dosimetric parameters between the 2 plans in other OARs including the eye balls, lens, optic chiasm, optic nerves, mandible, temporomandibular joints, esophagus, oral cavity, and cochleae (not shown in Table 3).

### Discussion

One of the main objectives of radiation therapy (RT) is to deliver radiation dose to the targets precisely. In patients with head and neck cancer including patient having NPC who undergo IMRT, however, the actual delivered doses may deviate from the anticipated ones, resulting from the shrinkage of tumor volume and weight loss. Castadot et al<sup>6</sup> evaluated 13

patients with head and neck cancer using weekly CT and positron emission tomography computed tomography (PET-CT) scans and found that there was an increase between the planned and the delivered high-dose volumes, which correlated with the slope of the GTV shrinkage. Another study in which 13 patients with head and neck cancer undergoing IMRT were enrolled found that 92% of patients had decreased D95 for PGTV and PCTV, ranging from 0.8 to 6.3 Gy and from 0.2 to 7.4 Gy, respectively.<sup>7</sup> In a study by Lu et al,<sup>8</sup> repeated CT images were obtained after fraction 25 of IMRT for patients with NPC. Both sets of original and new CT images, RT structures, and doses were transferred to a workstation, and then a hybrid IMRT plan was generated by deforming doses of original plan to the new CT data set. Subsequently, an accumulated plan was generated to quantify the actual dosimetric effects during the course. The investigators found significant reductions in D95 and D<sub>mean</sub> for PGTV and PTV2, and D95 for PTV1 if no treatment replanning was initiated. Therefore, to offset the variation of dose distribution during the entire course of RT, it is necessary to identify the anatomic and physical changes through image-guided approaches like CT or electronic portal imaging device or to find out the differences between actual delivered dose and prescribed dose through feedback information about changes of tumor size and position. Replanning may be needed for subsequent treatment based on the findings during RT.

Wang et al<sup>5</sup> found that adaptive replans before fractions 25 during IMRT for 28 patients with NPC resulted in significantly increased doses in GTVnx and CTV1, ranging from 0.48 to 15.98 Gy and 0.68 to 9.12 Gy, respectively, compared with phantom plans that were generated by applying the beam configurations of the initial plan to the anatomy of the new simulation CT. In addition, adaptive replans also contributed to significant reductions in the maximum dose to the spinal cord, mean dose to the left parotid, and V30 to the right parotid. In a study on 13 patients with head and neck cancer having locally advanced, nonmetastatic stage III or IV disease, repeat CT imaging and replanning determined by tumor shrinkage or weight loss during the course of IMRT significantly improved D95, and V93 for both PTV<sub>GTV</sub> and PTV<sub>CTV</sub>.<sup>7</sup> Unlike the aforementioned studies, Fung et al<sup>4</sup> redesigned treatment plans after fractions 25 and 35 and found that, when replanning versus not replanning was compared, adaptive IMRT plans increased D95 to the CTV for the primary disease, planning target volume for the primary disease, planning target volume for the left involved lymph nodes, and planning target volume for the right involved lymph nodes by 0.54 (1.86%), 2.02 (2.09%), 0.62 (1.03%), and 0.43 (1.01%), respectively, although only the dose change in NP-PTV demonstrated a significant difference.

In the present study, we found a significant improvement in CI for PTVnx, PTVnd, PTV1, and PTV2. Median V95 for PTVnx; D95, D99, V100, V95, and V93 for PTVnd; D99 and V100 for PTV1; and D95, D99, V100, V95, and V93 for PTV2 were increased significantly. Taken into account the results mentioned above and ours, it is suggested that adaptive

replanning during the course of IMRT improves target dose coverage or at least is not worse than the original plans.

Apart from the targets, parotid glands may also experience significant dosimetric changes during IMRT. Robar et al<sup>9</sup> found that the actual mean doses delivered to the left and right parotids were increased by 2.6 (4.3%) and 0.2 (4.0%), respectively, and V26 for the left and right parotids was increased by 3.5 (5.2%) and 0.3 (4.7%), respectively, compared with the original plan. A recent study has shown that the volume percentage of daily fractional dose over 0.75 Gy for the parotid gland increases by 23.6% at the end of tomotherapy if patients with head and neck cancer experience significant neck diameter decrease and/or weight loss.<sup>10</sup> Increased dose to the parotids due to changes both in the volume and in the displacement over the course of IMRT has been found by a number of studies, suggesting a modified treatment plan may be necessary.<sup>11-13</sup> Kuo et al<sup>14</sup> observed an outward movement of the parotid glands in the pretreatment CT images in 10 patients with head and neck cancer, pushed by enlarged neck lymph nodes. After 45 Gy of IMRT, nodal regression caused the parotid glands to shift inward into the high-dose area. When compared with those without replanning, the authors found the modification of IMRT plan after 45 Gy significantly reduced radiation dose to the left and right parotid glands by 2.95 (1.10) Gy and 3.23 (1.37) Gy, respectively. In a study by Wang et al,<sup>5</sup> replanning after fraction 25 reduced  $D_{\text{mean}}$  for the left parotid and V30 for the right parotid by 4.23 (10.03) Gy and 11.47 (18.89%), respectively. In the present study, we found  $D_{\text{mean}}$  and V30 for the left parotids were decreased by 1.28 (1.14) Gy and 4.11 (2.83%), respectively, when 2 modifications of treatment plan were carried out. The findings were consistent with those mentioned above.

Although the parotids are the most frequently changed organs in patients with NPC throughout the treatment course, other critical structures such as brain stem, spinal cord, optic nerves, optic chiasm, eyes, oral cavity, and larynx are sometimes vulnerable to dosimetric changes.<sup>2</sup> Hansen et al<sup>7</sup> found increased maximum doses to the brain stem occurred in 85% of patients, and all patients had increased maximum doses to the spinal cord, if adaptive replanning was not considered. Another study by Fung et al showed that the actual delivered doses to all listed OARs were higher than expected. Without replanning, the total dose to 1% of brainstem and spinal cord significantly was increased by 7.87 (7.26%) and 10.69 (6.72%), respectively, in which 3 patients would have these structures overdosed when compared with those with 2 replannings. The total maximum doses to the optic chiasm and pituitary gland were increased by 10.50 (10.51%) and 8.59 (6.10%), respectively.<sup>4</sup> Cheng et al<sup>15</sup> performed CT and MRI scans at 30 and 50 Gy intervals for 19 patients with NPC treated with IMRT. When comparing the initial plan with the hybrid plans that were generated by superimposing the initial plan to the repeat CT images, they found that the hybrid plans demonstrated significantly higher maximum doses to the spinal cord and brainstem. In addition, the maximum doses to bilateral optic nerves and ipsilateral eye were markedly increased.

Adaptive replanning during IMRT is critical to keep radiation dose to some OARs within acceptable limits. In a study aiming to evaluate the benefits of routine midtreatment replanning to the targets or normal tissue dosimetry in patients with head and neck cancer, it was shown that patients with NPC received greatest benefits with treatment adaptation with reduction in spinal cord maximum 1.2 Gy, mean parotid dose 1.2 Gy, and parotid V26 6.3%.<sup>16</sup> Castadot et al<sup>6</sup> reimaged 10 patients during concomitant chemoradiotherapy using CT and [18F] fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) acquisition after a mean dose of 14.2, 24.5, 35.0, and 44.9 Gy. Adaptive replanning based on the updated images resulted in 10% smaller mean dose to oral cavity and 7.2% smaller dose to 2% of the spinal cord, as compared with the original plan. In our study, we found significant reductions in  $D_{\text{max}}$  to the brain stem, median  $D_{\text{max}}$  to the right optic nerve, mean dose to the glottis, V50 for the supraglottis, and V55 for the skin after 2 treatment modifications, indicating ART technique has a potential to better protect surrounding critical organs such as the brain stem and optic nerves. Dosimetric benefits derived from ART technique can also be found in other studies.<sup>4,7</sup>

Determining an appropriate time point at which ART is initiated in a timely manner is critical to ensure that the planned dose to the targets and OARs can be delivered faithfully throughout the entire IMRT course. Many reports in recent years suggested that mid-to-late phase of the treatment course was appropriate timing for ART.<sup>4,16</sup> Differing from those studies, our previous study selected parameters only related with dose distributions as the end point to determine whether a replan was needed. Since significant anatomic changes may not certainly result in remarkable changes in dosimetric effects, only significant dosimetric changes were chosen as determinant for ART replanning. By this means, we identified 2 trigger points and recommended 2 replans at fractions 5 and 15 should be initiated.<sup>2</sup> In the current study, the timing of replanning during IMRT was based on the previous findings; however, PTVnx and PTVnd on the new CT data sets remained, in general, the same as on the original ones to avoid possibly increased failure in the primary disease and involved lymph nodes because volume reductions in PTVnx and PTVnd based solely on shrinkage of the tumor over the entire treatment course may result in inadequate dose delivery to the areas in proximity to the shrunk lesions. By contrast, modifications were allowed for CTV1 and CTV2 and thus for PTV1 and PTV2, if necessary. Nevertheless, we found that the ART plans resulted in a significant improvement in CI for PTVnx, PTVnd, PTV1, and PTV2. Median V95 for PTVnx; D95, D99, V100, V95, and V93 for PTVnd; D99 and V100 for PTV1; and D95, D99, V100, V95, and V93 for PTV2 were increased significantly. There were significant dose-volume reductions, including maximum doses to the brainstem and temporal lobes, mean doses to the glottis, V50 for the supraglottis,  $D_{\text{mean}}$  and V30 for the left parotid, the median dose to the right optic nerve, and V55 for the skin. The findings suggest that patients with NPC did gain dosimetric benefits from this 3-phase ART approach.

The present study only enrolled a small number of patients, and thus further studies with larger patient population are needed to confirm the possibly different magnitudes of dosimetric benefits brought by this approach according to stratified factors like clinical stages. What's more, whether the dosimetric advantages can transfer into clinical benefits, remain largely unknown, and need to be clarified in the future.

In conclusion, the 3-phase adaptive IMRT for patients with NPC results in improvements in target coverage and CI and decreased doses to some OARs.

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