Clin Transl Oncol (2017) 19:470–476
DOI 10.1007/s12094-016-1551-8

RESEARCH ARTICLE

Effect of adaptive replanning in patients with locally advanced nasopharyngeal carcinoma treated by intensity-modulated radiotherapy: a propensity score matched analysis

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Received: 18 May 2016 / Accepted: 19 September 2016 / Published online: 7 October 2016

Abstract
Purpose Limited data have been published regarding the effect of adaptive radiotherapy (ART) on clinical outcome in patients with nasopharyngeal carcinoma (NPC). We compared the long-term outcomes in patients with locally advanced NPC treated by adaptive intensity-modulated radiotherapy (IMRT) replanning versus IMRT.
Methods 200 NPC patients with stage T3/T4 were included between October 2004 and November 2010. Patients in both treatment groups were matched using propensity score matching method at the ratio of 1:1. Clinical outcomes were analyzed with Kaplan–Meier method, log-rank test and Cox regression.
Results After matching, 132 patients (66 patients in each group) were included for analysis. The median follow-up for the IMRT replanning group was 70 months, while the IMRT group was 69 months. The 5-year local–regional recurrence-free survival (LRFS) rate was higher in IMRT replanning group (96.7 vs. 88.1 %, $P = 0.022$). No significant differences in distant metastasis-free survival (DMFS), progression-free survival (PFS) and overall survival (OS) were observed between the two groups. 21.2 % patients in IMRT replanning group and 28.8 % patients in IMRT group had distant metastasis. In multivariable analysis, IMRT replanning was identified as an independent prognostic factor for LRFS (hazard ratio 0.229; 95 % CI 0.062–0.854; $P = 0.028$), but not for DMFS, PFS and OS.
Conclusions IMRT replanning provides an improved LRFS for stage T3/T4 NPC patients compared with IMRT. Distant metastasis remains the main pattern of treatment failure. No significant advantage was observed in DMFS, PFS and OS when adaptive replanning was used.

Keywords Nasopharyngeal carcinoma · Intensity-modulated radiotherapy · Adaptive · Replanning

Introduction

Intensity-modulated radiotherapy (IMRT) has gradually replaced two-dimensional radiotherapy due to its dosimetric advantages including highly conformal dose distributions and steep dose gradients [1, 2]. Previous studies about the treatment of nasopharyngeal carcinoma(NPC) have reported that IMRT improved locoregional control, reduced the treatment-related toxicity [3–5], and improved overall survival in specific NPC patients, such as stage N2, III or IV patients [6, 7]. As a local treatment method, the survival benefits of IMRT may derive from the improved local control [4]. Therefore, it is expected to further improve survival rate by higher local control with the advanced radiotherapy technology, especially for locally advanced disease.

NPC is sensitive to radiotherapy. During the course of radiotherapy, most patients experience anatomic structure changes due to tumor shrinkage, weight loss and parotid shrinkage [8], which leads to underdosage to target volumes and/or overdosage to organs at risk. Recently, adaptive radiotherapy (ART) has been studied in the setting of IMRT. The impact of ART on dose distributions and the advantages were evaluated by dosimetric analysis [9–11]. In clinical practice, there was no standard for determining

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whether the ART and the intervention time were successful. In addition, ART process requires both additional use of planning equipment and staff time. So limited data has been published regarding the effect of ART on clinical outcome. Two studies reported that ART can improve local–regional control and the study from Yang et al. indicates that ART improves quality of life (QOL) after treatment [12–14].

As the excellent treatment outcome in early stage NPC patients, the increased local control may lead to a more pronounced survival benefit in patients with late stage tumor. Thus, in this study, treatment results from cases of late T stage NPC were retrospectively analyzed, the potential clinical benefit of adaptive replanning is discussed. To minimize the bias, a propensity-matched analysis was performed.

Materials and methods

Patients

A total of 200 newly-diagnosed, histologically confirmed, non-metastatic and stage T3/T4 NPC patients that treated at our hospital were included between October 2004 and November 2010. All patients underwent a pretreatment workup that included complete medical history evaluation and physical examination; hematological and biochemistry profile analysis; endoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) of the nasopharynx and neck, chest CT or radiography, abdominal ultrasound, and emission computed tomography. Patients without the full course of radiotherapy were excluded. Medical records were analyzed retrospectively. This study was approved by the Ethics Committee. All patients were restaged according to the American Joint Committee on Cancer (AJCC) 2010 staging system [15].

IMRT

All patients underwent IMRT with 6-megavoltage (MV) photons. The gross tumor target of the nasopharynx (GTVnx) and involved lymph nodes (GTVln) were outlined based on CT and MRI scans. Clinical target volume 1 (CTV1) included the GTVnx with a 5–10 mm margin and high risk structures. Clinical target volume 2 (CTV2) included regions of the nasopharyngeal cavity, maxillary sinus, pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of clivus, inferior sphenoid sinus, and cavernous sinus. CTVln included the upper neck lymphatic drainage regions. Organs at risk were also outlined. The lower neck fields were matched to the IMRT field using a split-beam technique.

IMRT plan was generated using the CORVUS 3.4–4.2 system (Peacock, Nomos, Deer Park, IL, USA) and implemented with a MIMI multi-leaf collimator (NOMOS Corporation, Sewickley, PA, USA). The prescribed doses were defined as follows: 66–76 Gy for GTVnx; 60–70 Gy for GTVln; 60–66 Gy for CTV1; 54–60 Gy for CTV2 and 50–54 Gy for CTVln using the simultaneous integrated boost technique, each was divided into 30–33 fractions. The dose limits for normal organs were set according to the RTOG protocol 0225 [5]. The prophylactic radiation dose to neck field was 45–50 Gy by using ^{60}Co or 6 MV X-ray, given in 25 fractions at 1.8–2.0 Gy/fraction. Positive cervical lymph nodes in the lower neck were boosted to a total dose of 60–70 Gy by electron beam irradiation. All patients were treated with one fraction daily for 5 days per week, for a total of 6–7 weeks.

IMRT replanning

The decision to replanning was made at the physician's discretion and multiple factors were considered: weight loss, nutritional status, changes in palpable or visible tumor size, an ill-fitting mask, and the extent of acute radiation reactions. When a tumor was close to the spinal cord or brainstem and other important organs, replanning was typically needed early in the intervention process, and additional replans could be made if needed. The first replan was implemented at a median dose of 44 Gy (range 8.8–60.0). Patients received 1–3 replans (median 2). During each repeat CT scan, the patient maintained the same position and the new CT scan was used to generate a new IMRT plan for the corresponding fractions of treatment. To ensure relative consistency of target delineation, a CT–CT fusion was used by rigid registration and was adjusted manually according to the region of interest. Then the original contours were copied into the new CT scans. GTVnx, GTVln and the organs at risk were contoured on the new CT scans. The CTV was maintained and modified according to the changes in anatomic structure that occurred. The time from re-simulation to implementation of the new plan was generally 1–3 days.

Chemotherapy and targeted therapy

Chemotherapy was administrated for all patients. Chemotherapy strategies included induction chemotherapy (NACT) and concurrent chemotherapy (CCT). NACT regimens were either TP (docetaxel 75 mg/m^2, Day 1 + cisplatin 80 mg/m^2, Day 1) or PF (cisplatin 80 mg/m^2, Day 1 + 5-FU 1000 mg/m^2/day, Days 1–5) every 3 weeks for 1–2 cycles. CCT included cisplatin 80 mg/m^2 every 3 weeks for 2–3 cycles, TP or PF regimen (the same as NACT). 43 patients received cetuximab targeted therapy. Cetuximab was administered at an initial dose of 400 mg/m^2, followed by weekly doses of 250 mg/m^2 concurrent with radiotherapy or NACT.

Follow-up

All patients were evaluated weekly during receiving radiotherapy, examined in follow-up appointments that were scheduled up to 1 month after the completion of radiotherapy, and then every 3 months in years 1–2, every 6 months in years 3–5, and annually thereafter. Each follow-up included a flexible fiberoptic endoscopy, abdominal ultrasound, chest X-ray and basic serum chemistry. Either CT or MRI of the head-and-neck was performed after completion of IMRT and thereafter every 6 months.

Statistical analysis

To reduce bias associated with retrospective data, propensity score matching was used. Propensity scores were estimated using a logistic regression model based on all the included variables. A one-to-one matching without replacement was performed using a 0.2 caliper width. The χ^2 tests and two sample t tests were used to test the baseline balance over two groups. The actuarial rates of local–regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan–Meier method and compared with log-rank test. All the endpoints were defined as the interval from the date of initiation of treatment to the date of the failure or death, or last follow-up date. Multivariate analyses were performed using Cox proportional hazards model. Associations were quantified using hazard ratios and the 95 % confidence intervals. All data were analyzed by using the SPSS 22.0 software package (IBM Corporation, Armonk, NY, USA). Propensity score matching was performed using the MatchIt package of the R program, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two sided, $P < 0.05$ was considered to be statistically significant.

Table 1 Patients characteristics and treatment details before and after propensity score matching

Characteristics	Before matching				After matching			
	IMRT replanning ($n = 93$)	IMRT ($n = 107$)	*P*	S.D.	IMRT replanning ($n = 66$)	IMRT ($n = 66$)	*P*	S.D.
Age (years)			0.809	0.033			0.879	0.028
Mean	46.3	46.8			46.2	46.6		
SD	12.4	11.7			12.2	11.5		
Gender			0.289	0.100			0.840	0.068
Male	67 (72.0)	84 (78.5)			50 (75.8)	52 (78.8)		
Female	26 (28.0)	23 (21.5)			16 (24.2)	14 (21.2)		
T stage			0.294	0.147			1.000	0.000
T3	46 (49.5)	45 (42.1)			32 (48.5)	32 (48.5)		
T4	47 (50.5)	62 (57.9)			34 (51.5)	34 (51.5)		
N stage			0.791	0.081			0.696	0.067
N0-1	25 (26.9)	27 (25.2)			19 (28.8)	17 (25.8)		
N2-3	68 (73.1)	80 (74.8)			47 (71.2)	49 (74.2)		
Clinical stage			0.590	0.076			0.861	0.030
III	40 (43.0)	42 (39.3)			30 (45.5)	29 (43.9)		
IV	53 (57.0)	65 (60.7)			36 (54.5)	37 (56.1)		
GTVnx (cc)			0.004	0.412			1.000	0.000
≤61.4	57 (61.3)	44 (41.1)			37 (56.1)	37 (56.1)		
>61.4	36 (38.7)	63 (58.9)			29 (43.9)	29 (43.9)		
Chemotherapy			0.523	0.090			0.727	0.061
CCT	52 (55.9)	55 (51.4)			34 (51.5)	36 (54.5)		
NACT	41 (44.1)	52 (48.6)			32 (48.5)	30 (45.5)		
Targeted therapy			0.000	0.581			0.627	0.063
No	59 (63.4)	98 (91.6)			55 (83.3)	57 (86.4)		
Yes	34 (36.6)	9 (8.4)			11 (16.7)	9 (13.6)		

Numbers in parentheses indicate percentages

S.D. standardized difference, *SD* standard deviation

Results

Patients and characteristics

Before matching, 93 and 107 patients were treated with IMRT replanning and IMRT, respectively. Significant differences were observed with respect to volume of GTVnx ($P = 0.004$) and targeted therapy ($P = 0.000$). After matching, 66 patients treated with IMRT replanning and 66 patients treated with IMRT remained in the analysis. The matched patients in both groups had balanced characteristics (standardized difference ≤ 0.068). All subsequent analysis was based on the propensity-matched cohort. The characteristics of patients before and after propensity score matching were shown in Table 1.

Survival and patterns of failure

After a median follow-up of 70 months (12–107 months) in the IMRT replanning group, and 69 months (17–107 months) in the IMRT group, the 5-year LRFS rate was significantly higher in patients treated with IMRT replanning than those treated with IMRT (96.8 vs. 88.1 %, $P = 0.022$, HR: 0.244, 95 % CI: 0.066–0.895, Fig. 1). No significant difference were observed in DMFS, PFS, and OS rates between the two groups (Figs. 2, 3, 4). The 5-year DMFS, PFS and OS were 78.8, 77.5 and 72.6 % in the IMRT replanning group, and 69.4, 65.4 and 69.0 % in the IMRT group, respectively ($P = 0.277$, HR: 0.684, 95 % CI: 0.343–1.365; $P = 0.073$, HR: 0.568, 95 % CI: 0.303–1.066; $P = 0.636$, HR: 0.866, 95 % CI: 0.475–1.578; respectively). Additionally, we performed subgroup analysis according to the TNM classification (Table 2). In the stage T3N2-3 group, the 5-year LRFS rate was higher in patients treated with IMRT replanning than those treated with IMRT with a marginal significance (100 vs. 87.3 %, $P = 0.073$). The IMRT replanning group showed a trend towards better 5-year DMFS, PFS and OS rates in patients with stage T3N2-3, T4N0-1 and T4N2-3. But these differences were not significant. Patterns of treatment failure are summarized in Table 3. Distant metastasis was the main pattern

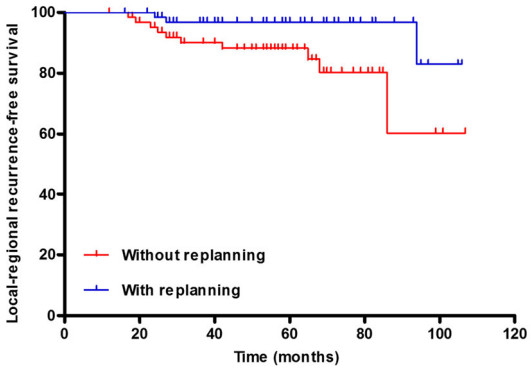

Fig. 1 LRFS of the two groups. The LRFS of IMRT with replanning and without replanning groups was 96.8 and 88.1 %, respectively; the difference was significant ($P = 0.022$)

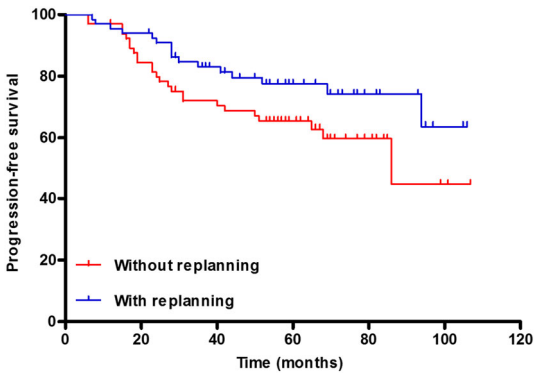

Fig. 3 PFS of the two groups. The PFS of IMRT with replanning and without replanning groups was 77.5 and 65.4 %, respectively; no difference was observed ($P = 0.073$)

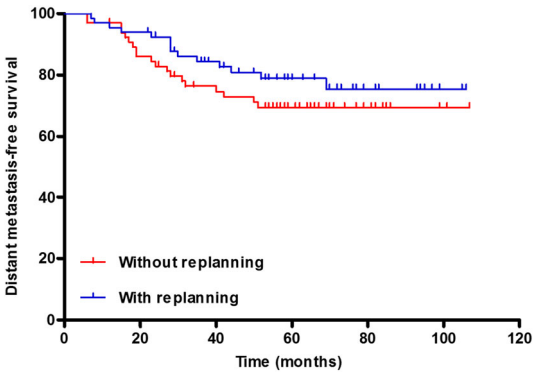

Fig. 2 DMFS of the two groups. The DMFS of IMRT with replanning and without replanning groups was 78.8 and 69.4 %, respectively; no difference was observed ($P = 0.277$)

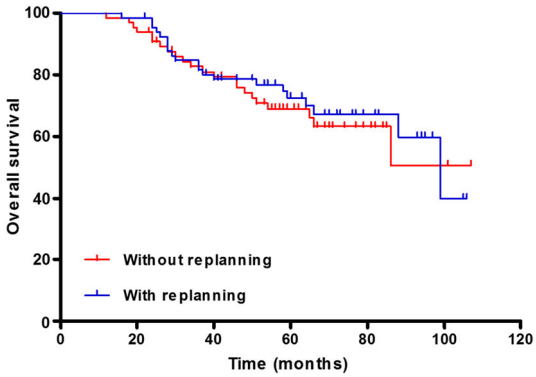

Fig. 4 OS of the two groups. The OS of IMRT with replanning and without replanning groups was 72.6 and 69.0 %, respectively; no difference was observed ($P = 0.636$)

Table 2 Comparison of survival in different subgroups according to T/N/M stage

Group	LRFS (%)[a]	P**	DMFS (%)[a]	P**	PFS (%)[a]	P**	OS (%)[a]	P**
T3N0-1		0.116		0.221		0.769		0.305
No	83.3		100.0		83.3		75.0	
Yes	100.0		74.1		74.1		64.8	
T3N2-3		0.073		0.898		0.503		0.713
No	87.3		79.5		76.0		83.7	
Yes	100.0		80.9		80.9		85.4	
T4N0-1		0.157		0.330		0.200		0.112
No	80.0		56.3		56.3		55.6	
Yes	100.0		90.0		90.0		90.0	
T4N2-3		0.770		0.207		0.262		0.415
No	86.2		57.0		53.0		51.3	
Yes	91.5		73.7		70.3		66.4	

** *P* values were calculated with the Log-rank test

[a] The estimated survival rates were calculated by using the Kaplan–Meier method

Table 3 Patterns of failure in propensity score-matched cohort after treatment

Patterns of failure	IMRT replanning ($n = 66$) No. %	IMRT ($n = 66$) No. %
Recurrence	2 (3.0)	6 (9.1)
Primary	0 (0.0)	4 (6.1)
Nodal	2 (3.0)	1 (1.5)
Primary and nodal	0 (0.0)	1 (1.5)
Distant metastasis	13 (19.7)	15 (22.7)
Distant metastasis, primary and/or nodal recurrence	1 (1.5)	4 (6.1)

of failure. 21.2 % patients in IMRT replanning group and 28.8 % patients in IMRT group had distant metastasis. Notably, compared with the IMRT group, the locoregional control appeared better for the IMRT replanning group (3.0 vs. 9.1 %).

Prognostic factors

We performed multivariate analyses to evaluate the prognostic value of age, gender, T stage, N stage, chemotherapy strategy, volume of GTVnx, targeted therapy and IMRT replanning (Table 4). IMRT replanning was identified as an significant prognostic factors for a better local control (HR = 0.229; 95 % CI, 0.062–0.854; $P = 0.028$), but not for DMFS, PFS and OS. Gender was identified as an independent factor for LRFS (HR = 3.257; 95 % CI, 1.084–9.784; $P = 0.035$). T stage was identified as an independent factor for OS (HR = 2.005; 95 % CI, 1.065–3.776; $P = 0.031$). There was no significant association between the remaining predictors and the survival, recurrence or metastasis rates.

Discussion

In this study, we compared the long-term outcomes in patients with T3/T4 NPC treated with IMRT replanning versus IMRT. While these data are retrospective, our results are strengthened by a propensity score analysis that addresses the potential bias of comparing two groups. Our results showed that IMRT replanning provides a significant improved 5 year LRFS compared with IMRT. But no significant advantage was observed in DMFS, PFS and OS. Taking into account the possible benefits of quality of life (QOL), we suggest that adaptive replanning should be considered for patients with late-stage disease treated with IMRT.

Previous studies have reported favorable clinical outcome of ART in patients with NPC and head and neck cancer, including an improved local control and easing late effects [12, 13]. Both above two studies concluded that ART should be recommended for late stage patients. Because the overall survival in early staged NPC patients is good, the effect of ART on local control may be concealed. Based on this hypothesis and the previous studies, we are focus on the effect of ART in patients with late-stage tumor. In this study, the 5-year LRFS rate was significantly higher in patients treated with IMRT replanning than those treated with IMRT (96.7 vs. 88.1 %, $P = 0.022$). Furthermore, replanning was identified as an independent protective prognostic factor for LRFS by multivariable analysis. Unfortunately, the improved local control did not convert to the benefits of distant metastasis and overall

Table 4 Multivariate analyses of prognostic factors in propensity score-matched cohort

	HR (95 % CI)	*P**
LRFS		
IMRT replanning	0.229 (0.062–0.854)	0.028
Age	1.039 (0.975–1.108)	0.241
Gender	3.257 (1.084–9.784)	0.035
T stage	1.434 (0.430–4.786)	0.558
N stage	1.501 (0.362–6.227)	0.575
GTVnx(cc)	1.988 (0.590–6.700)	0.268
Chemotherapy	2.022 (0.658–6.218)	0.219
Targeted therapy	0.461 (0.057–3.699)	0.473
DMFS		
IMRT replanning	0.660 (0.331–1.317)	0.239
Age	1.006 (0.975–1.039)	0.697
Gender	1.185 (0.524–2.681)	0.683
T stage	2.125 (1.030–4.384)	0.041
N stage	1.423 (0.630–3.215)	0.396
GTVnx(cc)	1.146 (0.524–2.507)	0.732
Chemotherapy	1.147 (0.564–2.333)	0.706
Targeted therapy	0.630 (0.220–1.808)	0.391
PFS		
IMRT replanning	0.547 (0.291–1.029)	0.061
Age	1.009 (0.979–1.039)	0.568
Gender	1.496 (0.761–2.934)	0.243
T stage	1.844 (0.975–3.489)	0.060
N stage	1.209 (0.582–2.510)	0.611
GTVnx(cc)	1.110 (0.547–2.249)	0.773
Chemotherapy	1.385 (0.737–2.605)	0.312
Targeted therapy	0.525 (0.186–1.485)	0.225
OS		
IMRT replanning	0.814 (0.443–1.496)	0.508
Age	1.021 (0.992–1.051)	0.164
Gender	1.356 (0.612–3.003)	0.453
T stage	2.005 (1.065–3.776)	0.031
N stage	1.427 (0.683–2.98)	0.344
GTVnx(cc)	1.289 (0.662–2.508)	0.455
Chemotherapy	1.557 (0.850–2.851)	0.152
Targeted therapy	0.320 (0.098–1.043)	0.059

HR hazard ratio, *95 % CI* 95 % confidence interval

* *P* values were calculated with an adjusted Cox proportional-hazards model

survival. These results were consistent with the previous studies [12–14]. The possible reason is, for locally advanced NPC with a large tumor volume, the possibility of tumor residues after radiotherapy is high due to the adverse radiobiological parameters, including an increased clonogen number and hypoxia [16, 17]. These residues tumor cell can not be eliminated by physical dose alone, thus resulting in recurrence or distant metastasis and a poor overall survival. Therefore, the increasing radiation dose or the alternating dose fractionation that combining with the effective multimodality therapy is the direction of further improving the OS for locally advanced NPC.

In this study, distant metastasis was the main pattern of failure. A total of 13 patients experienced locoregional failure and total distant metastasis occurred in 33 patients. In addition, 21.2 % patients in IMRT replanning group and 28.8 % patients in IMRT group had distant metastasis. Based on these results, we may conclude that replanning did not alter the failure pattern in the IMRT setting, which is similar to the findings of study in head and neck cancer [13]. These results are consistent with the conclusions proposed by Leibel et al. They stated that tumors of the hypopharynx and nasopharynx have a higher probability of micrometastatic dissemination at the time of initial diagnosis, and until effective methods to treat disseminated disease are developed. The effect of local control on survival would not be readily discerned [18]. Therefore, treatment modalities that effectively reduce the rate of metastasis need to be explored. In subgroup analysis, a higher LRFS rate was observed in patients with stage T3N2-3 (100 vs. 87.3 %, $P = 0.073$). In addition, the IMRT replanning group showed a trend towards better 5-year DMFS, PFS and OS rates in patients with stage T3N2-3, T4N0-1 and T4N2-3. The survival advantage may be attributed to a better control of local and metastasis, thus, a better OS was archived. Although these differences were not statistically significant, the results could give some hints for future research of expanding sample size.

Radiation-induced complications have a significant adverse impact on QOL [19]. QOL has been used in clinical oncology trials to compare different treatment strategies. Locoregional relapses in NPC are generally difficult to treat and has severe symptoms. The mental stress from the fear of relapse and the felling of symptoms can be of some extent seriously affecting the QOL more than some radiation-induced complications (e.g., xerostomia). There are increasing evidences indicating that QOL may have prognostic significance for the survival of patients with cancer [20, 21]. We believe that the significant reduction in the rate of locoregional failure by adaptive replanning in NPC patients should be considered clinically significant.

There were several limitations in this study. One of the limitations is the lack of toxicity data, because of the retrospective nature and a long time span between the first and the last included cases. A relatively small sample size is another limitation. Although this study used the propensity score method to reduce the biases, differences remain between the two groups due to the retrospective design. For instance, heterogeneity of chemotherapy regimens was observed. Furthermore, propensity score matching controls only for the differences in the included variables. Since this

study is an early exploration, off-line images and rigid registration were used and no standard criteria was applied in the selection or intervening time and the frequency of ART. These limitations may potentially affect the clinical outcomes observed. As a result, the current findings could only be taken as preliminary and need to be confirmed by future research.

In conclusion, based on a propensity score matched analysis, our results demonstrated that, for patients with locally advanced(T3/T4)NPC treated with IMRT, adaptive replanning can provide an improved locoregional control, but without significant advantages in metastasis rate and overall survival. Distant failure remains a challenge in the treatment of locally advanced NPC. Prospective randomized trials are needed for the ultimate confirmation of our findings.

Compliance with ethical standards

Funding None.

Conflict of interest The authors declare that they have no competing interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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