

Treatment of nasopharyngeal carcinoma using simultaneous modulated accelerated radiation therapy via helical tomotherapy: a phase II study

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Background. The aim of the study was to evaluate short-term safety and efficacy of simultaneous modulated accelerated radiation therapy (SMART) delivered via helical tomotherapy in patients with nasopharyngeal carcinoma (NPC).

Methods. Between August 2011 and September 2013, 132 newly diagnosed NPC patients were enrolled for a prospective phase II study. The prescription doses delivered to the gross tumor volume (pGTV_{nx}) and positive lymph nodes (pGTV_{nd}), the high risk planning target volume (PTV1), and the low risk planning target volume (PTV2), were 67.5 Gy (2.25 Gy/F), 60 Gy (2.0 Gy/F), and 54 Gy (1.8 Gy/F), in 30 fractions, respectively. Acute toxicities were evaluated according to the established RTOG/EORTC criteria. This group of patients was compared with the 190 patients in the retrospective P70 study, who were treated between September 2004 and August 2009 with helical tomotherapy, with a dose of 70-74 Gy/33F/6.5W delivered to pGTV_{nx} and pGTV_{nd}.

Results. The median follow-up was 23.7 (12-38) months. Acute radiation related side-effects were mainly problems graded as 1 or 2. Only a small number of patients suffered from grade 4 leucopenia (4.5%) or thrombocytopenia (2.3%). The local relapse-free survival (LRFS), nodal relapse-free survival (NRFS), local-nodal relapse-free survival (LNRFS), distant metastasis-free survival (DMFS) and overall survival (OS) were 96.7%, 95.5%, 92.2%, 92.7% and 93.2%, at 2 years, respectively, with no significant difference compared with the P70 study.

Conclusions. SMART delivered via the helical tomotherapy technique appears to be associated with an acceptable acute toxicity profile and favorable short-term outcomes for patients with NPC. Long-term toxicities and patient outcomes are under investigation.

Key words: nasopharyngeal carcinoma; simultaneous modulated accelerated radiation therapy; helical tomotherapy; acute toxicities, clinical outcome

Introduction

Nasopharyngeal carcinoma (NPC) is a kind of head and neck cancer with a good prognosis, and can be cured by radiation therapy especially inten-

sity-modulated radiation therapy (IMRT) alone or in combination with chemotherapy and/or anti-epithelial growth factor receptor (anti-EGFR) monoclonal antibody (Mab) treatment.¹ The curative effect and radiation injury are closely related to radi-

ation techniques. Simultaneous modulated accelerated radiation therapy (SMART) has been clinically confirmed as safe and effective, and widely used in the treatment of NPC.² This technique can simultaneously deliver different doses to different targets, and improve local control through increasing the fraction dose and shortening the overall treatment time (OTT), so as to reduce post-procedure accelerated repopulation of tumor cells.

Helical tomotherapy (HT) is believed to excel in realizing the function of SMART. Providing better dose conformity and uniformity, HT could improve local control with less radiation damage. The first HT unit in China was installed in September 2007 at our center; and by December 2014, nearly 500 NPC patients had received treatment. The prescription dose of 70 Gy was given to the target volume in 33 fractions (2.12 Gy per fraction) in a previous study (P70 study) conducted by our team, and the clinical efficacy was satisfactory with an acceptable safety profile. The local relapse-free survival (LRFS), nodal relapse-free survival (NRFS), local-nodal relapse-free survival (LNRFS), distant metastasis-free survival (DMFS) and overall survival (OS) were 96.1%, 98.2%, 94.2%, 95.5% and 91.4%, at 2 years, respectively.³ The present phase II study (P67.5) was based on P70, starting from September 2011. In P67.5 we shortened the treatment time to 6 weeks by designing a hypofractionated regimen with a total dose of 67.5 Gy (2.25 Gy/F). By comparison with the P70 study, we evaluated the feasibility and short-term outcomes of this new hypofractionated regimen.

Methods

Eligibility criteria

P67.5 is a single-center, prospective, phase II clinical study, with a registration code of ChiCTR-ONC-14004895. The research ethics board of the Chinese PLA General Hospital approved the study with an official number of S2014-048-01, and all eligible patients provided informed consent in written form.

Inclusion criteria were as follows: histologically proven type I and II NPC according to World Health Organization (WHO) criteria; stage I–IVa according to the Union for International Cancer Control (UICC) 2002 Staging System; aged between 15 and 75 years; Karnofsky performance status score ≥ 70 ; white blood cell count $\geq 3,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, serum creatinine concentration $< 133 \mu\text{mol/L}$, and liver transaminase level < 2.0 times of

the upper normal value. Exclusion criteria were as follows: distant metastasis; concomitant diseases (heart disease, tuberculosis, *etc.*) that interfere with the completion of treatment, increase incidence of adverse reactions or influence the prognosis; withdrawal during the treatment or violation of the protocol due to any factors; diagnosed with or treated for other malignances.

Patient characteristics

Between August 2011 and September 2013, 132 newly diagnosed non-metastatic NPC patients were included in the study. There were 95 males and 37 females. The median age was 47 years old. All patients underwent nasopharyngeal and skull base magnetic resonance imaging (MRI), chest computed tomography (CT), endoscopic evaluation, complete blood counts, hepatic and renal function tests, neck and abdomen ultrasound, and bone scans. Positron emission tomography (PET) was optional. Clinical stage was practiced according to the UICC 2002 staging system (Table 1).

We compared the preliminary results of the P67.5 study with the retrospective P70 study, in which a dose of 70–74 Gy (2.12–2.24 Gy per fraction) was delivered to the primary tumor (pGT-Vnx) and metastatic nodes (pGTVnd), 60–62.7 Gy (1.82–1.89 Gy per fraction) to the high risk planning target volume (PTV1) and 52–56 Gy (1.63–1.70 Gy per fraction) to the low risk planning target volume (PTV2), in 33 fractions.³ Table 2 summarizes patients' characteristics in the two studies.

Radiation therapy

Patients were placed in the supine position and the head and neck immobilized with a thermoplastic mask. Plain and enhanced CT images with 3-mm slice thickness were taken for treatment planning then transmitted to the Pinnacle³ 8.0 workstation and fused. Enhanced CT, MRI or PET images were

TABLE 1. Distributions of patients in P67.5/P70 study according to the Union for International Cancer Control (UICC) 2002 staging system

Stage	N0	N1	N2	N3	Total
T1	6/16	13/27	11/15	3/3	33/61
T2	3/13	15/24	23/22	3/2	44/61
T3	2/8	15/11	18/18	3/3	38/40
T4	2/3	3/10	11/11	1/4	17/28
Total	13/40	46/72	63/66	10/12	132/190

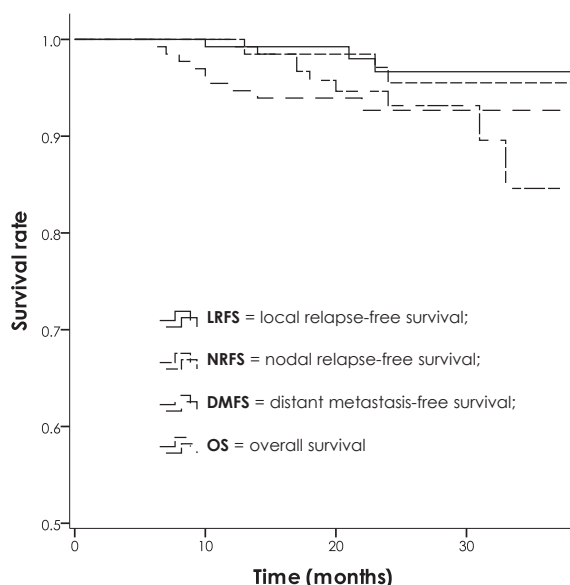


FIGURE 1. Different survival rates for patients in the P67.5 study.

TABLE 2. Patients' characteristics

Characteristics	P67.5 study		P70 study		p
	n.	%.	n.	%	
Age (median)	15–75	(47)	10–81	(44)	0.527
Gender					
Male	95	72.0	144	75.8	0.441
Female	37	28.0	46	24.2	
Region					
Northern China	110	83.3	159	83.7	0.933
Southern China	22	16.7	31	16.3	
KPS					
90–100	105	79.5	133	70.0	0.055
70–80	27	20.5	57	30.0	
Pathology					
WHO type I	2	1.5	3	1.6	0.964
WHO type II	130	98.5	187	98.4	
UICC 2002 Stage					
I	6	4.5	16	8.4	0.045
II	31	23.5	64	33.7	
III	68	51.5	71	37.4	
IVa-b	27	20.5	39	20.5	

KPS = Karnofsky performance status; UICC = Union for International Cancer Control; WHO = World Health Organization

used as a guide for target contours. Target naming and delineation were consistent with the P70 study³, and CT images together with the contour objects created by the physicians were transferred to Hi Art TomoTherapy 2.2.4.1 workstation. Physicists in the same group designed and verified the treatment plans. The three main parameters of field width, pitch, and modulation factor were set to the same values as in the P70 study.

During HT treatment, all patients underwent megavoltage computed tomography (MVCT) imaging everyday to rectify setup errors. The range of the CT scans typically included the central area of the whole target volume, ensuring that crystals were avoided. Automated and manual registration of the MVCT images with the planning CT images was based on bone and tissue anatomy.

The planned D95 was 67.5 Gy for pGTVnx and pGTVnd, 60 Gy for PTV1 and 54 Gy for PTV2, in 30 fractions. No more than 5% of the PTV received more than 110% of the prescribed dose. The dose-volume constraints for OARs (organs at risk) were the same as the P70 study.³

Biological effective dose (BED) is calculated with linear quadratic (LQ) radiobiological model: $BED = nd \times [1 + d/(\alpha/\beta)]$.⁴ In the formula, “n” represents the number of fractions and “d” fraction dose. The α/β value of tumor tissue or early response normal tissues is 10 Gy and that of late response normal tissues is 3 Gy or 5 Gy. If the impact of overall treatment time (OTT) and tumor proliferation is considered, the adjusted formula is $BED = nd \times [1 + d/(\alpha/\beta)] - \gamma/\alpha \times (T - Tk)$.⁵ The “ γ/α ” equals 0.6. “T” and “Tk” represent OTT (including weekends) and 7 days, respectively.

Chemotherapy and anti-EGFR monoclonal antibody (Mab) treatment

In this study, patients at stage III or IV (including stage II with lymph node metastasis) generally underwent neoadjuvant chemotherapy plus concurrent chemotherapy. Two cycles of neoadjuvant chemotherapy were routinely used, some patients with stage III and IV or whose tumor volume reduced less than 30% had additional 1–2 cycles. One hundred and one patients underwent 1–4 cycles of neoadjuvant chemotherapy with DP (docetaxel 75 mg/m², d1, and cisplatin 75 mg/m², d1, every 3 weeks) according to the primary tumor size or chemotherapy response. In accordance with the physical condition, clinical staging, treatment tolerance, 115 cases underwent two patterns of concurrent chemotherapy: 1) cisplatin 80 mg/m², d1,

every 3 weeks; 2) cisplatin 60 mg/m² and docetaxel 60 mg/m², d1, every 3 weeks. Concurrent anti-EGFR Mab treatment (cetuximab with a loading dose of 400 mg/m² and then 250 mg/m² or nimotuzumab 200 mg every week) was used in 45 patients. Adjuvant DP chemotherapy as used in the neo-adjuvant setting was administered in 68 patients (range 1–4 cycles, median 1.93 cycles).

Statistical analysis and follow-up

Acute side-effects were evaluated weekly and peak toxicities were recorded. Acute and late side-effects were identified according to the established RTOG/EORTC criteria.⁶ The preliminary response was evaluated 1–3 months after the end of radiation therapy based on the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.⁷ Patients received follow-up examinations including nasopharyngeal and skull base MRI, nasopharyngoscopy, neck ultrasound, *etc.*, to evaluate the therapeutic effects every 3 months during the first year, and then every 6 months afterwards. By the end of October 2014, the median follow-up period was 23.7 (12–38) months with a follow-up rate of 100%. Survival analysis was performed with Kaplan-Meier method and Log-rank test was used to evaluate the differences between the 2 studies. Comparison of rates and means between the two groups was performed by Pearson χ^2 test and t test, respectively. A two-sided value of $p < 0.05$ was considered significant. The analyses were executed with SPSS 19.0 (Statistical Product and Service Solutions Inc., Chicago, IL).

Results

BED and dosimetric analyses

The prescription dose in the study for tumor targets was 67.5 Gy (2.25 Gy \times 30F) with a BED of 82.7 Gy. If the impact of OTT was considered, the adjusted BED would be 62.9 Gy, 0.9 Gy higher than that of the P70 study, and would theoretically result in better tumor control. For normal tissues, radiation doses to both early and late response tissues were lower in this study than in the P70 study (Table 3).

The mean dose (Dmean) to pGTVnx, pGTVnd, PTV1 and PTV2 was 70.2 Gy, 70.1 Gy, 64.9 Gy and 56.7 Gy, respectively (Table 3). Except the Dmean of inner ears and Dmean of both parotid glands, the dose delivered to OARs which generally met the established constraints were significantly lower in the P67.5 study than in the P70 study (Table 4).

TABLE 3. BED of the two SMART regimens (Gy)

	BED (P67.5)	BED (P70)
Tumor OTT disregarded ($\alpha/\beta = 10$ Gy)	82.7	84.8
Tumor OTT taken into account ($\alpha/\beta = 10$ Gy)	62.9	62.0
Normal tissue ($\alpha/\beta = 5$ Gy)	97.9	99.7
Normal tissue ($\alpha/\beta = 3$ Gy)	118.1	119.5

BED = biological effective dose; OTT = overall treatment time; SMART = simultaneous modulated accelerated radiation therapy

TABLE 4. Dosimetric data of organs at risk

	Mean value (Range)		P
	P67.5 study	P70 study	
Beam-on time (s)	413.8 (336.0–521.7)	455.8 (358.0–696.0)	0.674
Couch travel (cm)	21.4 (18.0–27.0)	22.6 (17.0–28.7)	0.000
pGTVnx Dmean	70.2 (69.2–72.6)	72.3 (70.4–75.6)	0.000
pGTVnd Dmean	70.1 (69.2–72.7)	72.3 (70.1–75.6)	0.000
PTV1 Dmean	64.9 (63.1–67.3)	64.6 (62.1–70.5)	0.083
PTV2 Dmean	56.7 (55.7–59.8)	57.4 (54.7–61.7)	0.000
Brainstem Dmax	51.1 (35.9–69.1)	54.5 (41.6–71.9)	0.000
Spinal cord Dmax	40.6 (35.2–51.1)	41.5 (33.7–51.8)	0.003
Optic nerve Dmax			
Left	29.0 (3.9–70.5)	38.3 (9.7–72.2)	0.000
Right	28.3 (4.6–70.8)	39.3 (9.2–72.9)	0.000
Eyeball Dmax			
Left	19.4 (4.0–38.9)	29.6 (10.0–65.4)	0.000
Right	19.1 (5.3–38.8)	29.6 (11.2–57.7)	0.000
Lens Dmax			
Left	3.2 (2.0–5.3)	4.1 (2.2–8.1)	0.000
Right	3.2 (2.2–8.3)	4.1 (2.2–8.3)	0.000
TMJ Dmean			
Left	33.7 (22.6–60.4)	38.7 (22.9–58.5)	0.000
Right	33.1 (22.5–64.7)	38.2 (21.1–51.8)	0.000
Inner ear Dmean			
Left	45.4 (27.4–67.1)	43.1 (12.3–58.0)	0.055
Right	44.7 (26.3–61.7)	44.4 (11.6–65.2)	0.815
Parotid gland Dmean			
Left	30.8 (25.2–39.9)	31.2 (23.8–55.1)	0.334
Right	30.7 (22.9–65.2)	31.0 (22.0–47.9)	0.636
Oral cavity Dmean	34.2 (26.6–42.0)	38.8 (11.5–50.2)	0.000
L-E-T Dmean	32.7 (24.2–38.8)	38.7 (19.1–49.6)	0.000

Dmean = mean dose (Gy); Dmax = maximum dose (Gy); L-E-T = Larynx-esophagus-trachea; pGTVnd = positive lymph nodes; pGTVnx = prescription doses delivered to the gross tumor volume; TMJ = Temporomandibular joint;

TABLE 5. Acute toxicities of normal organs [n (%)]

Toxicity	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		p
	P67.5	P70	P67.5	P70	P67.5	P70	P67.5	P70	P67.5	P70	
Skin reaction	6 (4.5)	7 (3.7)	92 (69.7)	137 (72.1)	27 (20.5)	37 (19.5)	7 (5.3)	9 (4.7)	0 (0.0)	0 (0.0)	0.961
Mucositis	2 (1.5)	4 (2.1)	54 (40.9)	72 (37.9)	64 (48.5)	108 (56.8)	12 (9.1)	6 (3.2)	0 (0.0)	0 (0.0)	0.100
Xerostomia	4 (3.0)	9 (4.7)	33 (25.0)	100 (52.6)	95 (72.0)	81 (42.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.000
Pharyngitis-esophagitis	0 (0.0)	7 (3.7)	51 (38.6)	83 (43.7)	79 (59.9)	99 (52.1)	2 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0.072
Leucopenia	29 (22.0)	86 (45.3)	32 (24.2)	42 (22.1)	39 (29.6)	50 (26.3)	26 (19.7)	10 (5.3)	6 (4.5)	2 (1.0)	0.000
Anemia	66 (55.0)	175 (92.1)	44 (33.4)	14 (7.4)	18 (13.6)	1 (0.5)	4 (3.0)	0 (0)	0 (0.0)	0 (0)	0.000
Thrombocytopenia	103 (78.0)	180 (94.7)	16 (12.1)	7 (3.7)	5 (3.8)	2 (1.1)	5 (3.8)	1 (0.5)	3 (2.3)	0 (0)	0.000

Acute and late side-effects

All patients completed radiation therapy but one who underwent 27 fractions because of severe gastrointestinal side-effects. One hundred and twenty-four cases finished their radiation therapy in 6 weeks, and radiation therapy was interrupted for 10.9 days on average in 7 patients because of grade 3 acute pharyngitis-esophagitis or hematologic toxicity. Acute radiation related side-effects were mainly problems graded as 1 or 2 with skin, oral mucosa, salivary glands, and pharynx-esophagus. Grade 3 skin toxicities were noted in 7 cases, mucositis in 12 and pharyngitis-esophagitis in 2. Some patients who received neoadjuvant and/or concurrent chemotherapy suffered from different degrees of hematologic toxicities. Distribution of acute side-effects is shown in Table 5. The differences were statistically significant between the incidences of xerostomia and hematologic toxicities of the two studies. At the end of radiation therapy, there was an average weight loss by 10.6%, ranging from 0% to 21.4%.

Late toxicities generally appeared 3 months after radiation therapy and the most common one was xerostomia. Although patients generally had less dry feeling as time passed by and 24 patients had no signs of late xerostomia at all, there were 102 and 6 cases suffering from grade 1 and 2 xerostomia during the follow-up, respectively. The sense of taste diminished in 6 patients and was lost completely in 1 patient. Forty-one patients had audition test abnormal on one side, 30 of whom had no obvious clinical symptoms; however, 12 and 5 cases appeared to have grade 1 and 2 hearing loss, respectively. Fifteen cases developed otitis media that needed surgical treatment. Seventeen patients

had a difficulty in opening mouth, and 3 of them had a mouth opening less than a one-finger width. Increased tooth sensitivity occurred in 30 patients; gingival recession in 16 patients; tooth fracture or loss in 10 patients. One 39-year-old female had a menstrual disorder and one female patient had hypothyroidism requiring medical treatment.

Short-term outcomes and patterns of failure

At a median time of 1.5 months (at least one month and no more than 3 months) after the end of radiation therapy, evaluation of primary tumors showed that 49 patients had complete responses (CR), 71 partial responses (PR), and 12 stable disease (SD); evaluation of involved nodes in 113 patients showed 42 CR, 62 PR, and 9 SD, with an effective rate of 100%.

Sixteen patients suffered from treatment failure during the follow-up, including 3 local recurrences (2 intra-target recurrences and 1 marginal recurrence), 4 regional recurrences and 9 distant metastases. In the patients with local recurrence, the T3N2M0 case received re-irradiation alone, the T3N0M0 case underwent re-irradiation with concurrent chemotherapy, and the T3N1M0 case refused salvage treatment. All these three patients died of bleeding with a mean survival time of 7.7 (3–10) months from recurrence to death. Among the regional recurrence patients, 3 had a neck node recurrence and 1 had an ipsilateral parotid metastasis; these patients underwent re-irradiation, chemotherapy, concurrent chemo-radiotherapy and brachytherapy respectively and were all alive throughout the follow-up. Distant metastasis was the most common failure pattern and the most

common distant organs involved were liver (4 cases), lung (2 cases), bone (2 cases), and liver-lung (1 case). Seven of the 9 cases received chemotherapy, of whom 2 had also concurrent Anti-EGFR Mab treatment (4 cases died, 3 cases alive); and the other 2 cases had no salvage treatment and died in 4 and 7 months, respectively (Table 6). The local relapse-free survival (LRFS), nodal relapse-free survival (NRFS), local-nodal relapse-free survival (LNRFS), distant metastasis-free survival (DMFS) and overall survival (OS) were 96.7%, 95.5%, 92.2%, 92.7% and 93.2%, at 2 years, respectively, with no significant difference compared with the P70 study.

Discussion

It is generally believed that, in order to obtain a satisfactory local control, the prescribed dose of radiation therapy (RT) in NPC should exceed 64 Gy⁸, but it does not mean higher doses lead to higher local control rate (LCR). In contrast, clinical and radiobiological evidence has proved OTT as an important factor impacting curative effect of RT. Some tumor cells exhibited accelerated repopulation during the late period of RT. As the treatment continued, the probability of proliferation of tumor stem cells increased and the total dose should compensate for the “wasted dose” in every extra day because of accelerated repopulation of stem cells (0.6 Gy/d, equal to γ/α value).^{5,9-11} At the same time, a higher prescribed dose would cause higher irradiation to OARs and increase the risk of radiation related injury.

When we prescribe the specific dose in radical RT for NPC with conventional fractionation, in addition to considering tumor extension or size, we must also pay attention to the impact of fraction size and OTT, so that the proper fraction dose can be chosen to avoid not only increased injury of late response normal tissues but also extended OTT. That was why a dose of more than 70 Gy was not recommended in conventionally fractionated RT for NPC. The limitation of conventionally fractionated RT in NPC seemed to have been solved by hyperfractionated radiation therapy which was however difficult to carry out in the past due to technical limitations of the two-dimensional conventional or three-dimensional conformal radiation therapy. After 20 years of continuous development and improvement, IMRT could solve the above problem through SMART which could deliver different doses to different targets according to the radiosensitivity (α/β value) of OARs and

TABLE 6. Patients with treatment failure

TNM stage	Failure time (month)	Failure site	Salvage treatment	Living status	Follow-up* (month)
1. T1N2M0	6	Bone	CT	Dead	17
2. T3N3bM0	7	Liver	CT	Dead	14
3. T2N2M0	8	Lung	CT+AT	Living	14
4. T1N2M0	9	Bone	CT+AT	Dead	12
5. T3N2M0	10	Lung	-	Dead	17
6. T1N2M0	10	Liver	CT	Living	16
7. T3N2M0	10	Local	RT	Dead	20
8. T3N1M0	12	Liver	CT	Dead	31
9. T3N2M0	13	Nodal	RT	Living	37
10. T1N3bM0	13	Nodal	BT	Living	26
11. T4N0M0	14	Liver	-	Dead	18
12. T3N1M0	21	Local	-	Dead	24
13. T3N1M0	22	Liver & Lung	CT	Living	33
14. T3N0M0	23	Local	CRT	Dead	33
15. T3N2M0	23	Nodal	CT	Living	27
16. T2N2M0	24	Nodal	CRT	Living	37

AT = anti-EGFR Mab therapy; BT = brachytherapy; CRT = concurrent chemoradiotherapy; CT = chemotherapy; RT = radiation therapy;

* The time from diagnosis.

boost doses to tumor targets within a limited time, so as to improve the efficacy with less normal tissue damage, and increase the gain ratio of RT.

A number of clinical studies of SMART in NPC have been reported, but prospective studies were lacking. Table 7 listed the results of some prospective studies with fractionation patterns, LCR, *etc.* It could be seen that fraction dose ranged from 2.12 to 2.4 Gy, and the total BED based on prescription doses all exceeded 80 Gy. An adjusted BED was obtained between 60 and 70 Gy. The 2–4 year LCR was beyond 90% except the 88% reported by Lee *et al.*, probably because of a small sample size and a high proportion (95% of patients) of advanced disease.¹² The RTOG 0225 study was a classic multi-center study which led the 70 Gy/33F SMART regimen to be used as the standard RT of NPC with a LCR of 92.6% at 2 years.¹⁴ Our center began to conduct P70 study with the same fractionated regimen in September 2007 when the HT system was first introduced into China; and achieved good outcomes with the 2-year LRFS of 96.1%.³ In the present study which was based on the P70 study, the fraction dose increased from 2.17 Gy to 2.25 Gy and the adjusted BED to tumor targets got higher, while BED to normal tissues was reduced. Xiao *et al.*¹⁵ conducted a

TABLE 7. Summary of reported prospective studies on simultaneous modulated accelerated radiation therapy (SMART) for nasopharyngeal carcinoma (NPC)

Author	N	T3-4 tumor n (%)	Positive node n (%)	Fractionation patterns for GTV					LCR (%)
				Fraction	Prescription dose (Gy)	Fraction dose (Gy)	BED* (Gy) OTT disregarded	BED* (Gy)	
Lee SW (2005) ¹²	20	8 (40)	18 (90)	30	72	2.4	89.3	69.5	88.0 (2-y)
Lin SJ (2009) ¹³	323	260 (80.5)	293 (90.7)	30 / 31	66 / 69.8	2.2 / 2.25	80.5 / 85.4	60.7 / 63.8	95.0 (3-y LRFS)
RTOG0225 (2009) ¹⁴	68	23 (33.8)	50 (73.5)	33	70	2.12	84.8	62.0	92.6 (2-y)
Xiao WW (2011) ¹⁵	81	81 (100)	56 (69.1)	30	68	2.27	83.4	63.6	94.9 (3-y)
Bakst RL (2011) ¹⁶	25	16 (64)	20 (80)	30	70.2	2.34	86.6	66.8	91.0 (3-y)
Wang RS (2013) ¹⁷	300	214 (71.3)	277 (92.3)	30-32	68-72	2.25-2.27	83.4-88.2	63.6-66.0	94.0 (4-y)
Author (2014) ³	190	68 (35.8)	150 (78.9)	33	70	2.12	84.8	62.0	96.1 (2-y LRFS)
Current study	132	55 (41.7)	119 (90.2)	30	67.5	2.25	82.7	62.9	96.7 (2-y LRFS)

*: $\alpha/\beta = 10\text{Gy}$; OTT = overall treatment time; LCR = local control rate; LRFS = local relapse-free survival; y = year

phase II study in T3-4 patients using a 68 Gy/33F regimen similar to ours and the 3-year LCR reached 94.9%. In the study of Wang *et al.*¹⁷, the 68 Gy/33F regimen was still applied although up to 83% of the patients had locally advanced disease; LCR remained to be 94%. In this study, the 2-year LRFS and NRFS achieved 96.7% and 95.5%, respectively, without difference compared with the P70 study, in which LRFS and NRFS being 96.1% and 98.2% ($\chi^2 = 0.469$, $p = 0.494$; $\chi^2 = 1.145$, $p = 0.285$).

As the prescription dose and fraction dose increase, the incidence of serious adverse reactions would become significantly higher. Kwong *et al.*¹⁸ set the prescribed dose as 76 Gy/35F with a BED of up to 92.5 Gy. Though higher prescription dose ensured the LCR (95.7% at 3 years), 78% and 46% of patients suffered from grade 3 mucositis and skin reactions, respectively. In the study of Bakst *et al.*¹⁶, the total dose was 70 Gy but the fraction dose increased up to 2.34 Gy, so about 12% of patients had temporal lobe necrosis of varying degrees, especially in patients with T4 whose pGTV included part of brain tissue. This situation did not appear in earlier study of the same authors in which 70 Gy/33F regimen was used.¹⁹ It could be seen that blind pursuit of high-dose or high fraction dose does not further improve LCR but might lead to more severe radiation related damage.

In recent years, the hot issues about IMRT for NPC have focused on how to minimize the dose

delivered to OARs and it might be realized in two main ways: 1) to improve the accuracy of radiation therapy; 2) to lower the total dose. Helical tomotherapy (HT) is a unique IMRT modality that combines elements of diagnostic radiology and radiation therapy in a single unit. In addition to the ability to deliver a highly conformal dose distribution, HT is equipped with xenon detectors designed to obtain MVCT images utilized for pre-treatment set-up verification, and some studies have confirmed the advantage of HT compared with step-and-shoot IMRT in dose distribution and OAR protection.²⁰⁻²²

In this study, the Dmean of pGTVnx and pGTVnd decreased by 2.1 Gy and 2.2 Gy, respectively, compared to the P70 study, which was equivalent to a 2.5 Gy reduction of prescription dose. The doses were statistically reduced almost in all OARs except in the inner ear of which the Dmean was a bit higher and in the parotid gland with a decline of the Dmean by only 0.3 Gy. The Dmax of both eyeballs and optic nerves decreased by about 34% and 25%, respectively; the Dmean of the temporomandibular joint fell by more than 5 Gy and the reduction in oral cavity was about 4.6 Gy. At the same time, the Dmean of the parotid gland remained at a high level and was far above the constraint of 28 Gy; and the incidence of grade 2 xerostomia was significantly higher than the P70 study ($\chi^2 = 27.225$, $p = 0.000$). After data analysis, we noticed that acute toxicity

ties were evaluated by different doctors in the two studies and acute xerostomia was underestimated in the P70 study. Leung *et al.*²³ summarized their 5-year experience in NPC treatment with HT and the Dmean of the ipsilateral and contralateral parotid gland was 22.1 Gy and 20.7 Gy, respectively, significantly lower than ours. The possible reason is delineation of the deep lobe of the parotid gland which was not spared from CTV1 in our studies. Because of the advantages of TH, the incidence of acute and late side-effects were low and acute toxicities in skin, oral mucosa, pharynx-esophagus and salivary glands were mainly graded as level 1-2 in this study. Moreover, as a proportion of locally advanced cases received neoadjuvant chemotherapy and/or concurrent chemo-radiotherapy, a higher incidence of grade 3-4 neutropenia can be accounted for.

In addition, the shortening of the treatment course from 33 fractions in 6.5 weeks to 30 fractions in 6 weeks reduced treatment costs for patients as well as improving equipment turnover.

Conclusions

A 67.5 Gy/30F SMART regimen delivered via the HT technique appears to be associated with acceptable toxicities and favorable short-term outcomes for patients with NPC. Long-term toxicities and outcomes are under investigation.

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