

Treatment of Locally Advanced Nasopharyngeal Carcinoma by Helical Tomotherapy: An Observational, Prospective Analysis



Zhigang Liu^{*,1}, Chenyang Xu^{†,‡,1}, Rong Jiang^{†,‡,1}, Guiyun Liu^{†,‡}, Qiaodan Liu^{*}, Jiao Zhou^{†,‡}, Fengxin Liu^{†,‡}, Jijin Yao^{*}, Siyang Wang^{*} and Wen Jiang[§]

^{*}Department of head and neck oncology, Phase 1 clinical trial ward, The cancer center of the fifth affiliated hospital of Sun Yat-sen University, Zhuhai, 519001, China; [†]Department of Radiation Oncology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, 410000, China; [‡]Department of Clinical Medicine, University of South China, Hengyang, 421000, China; [§]Department of Radiation Oncology, The University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Nasopharyngeal carcinoma (NPC) is endemic in southern China. Due to the unique anatomical and biological properties of NPCs, radiotherapy or combined modality based on radiotherapy is an effective treatment option. Helical tomotherapy (HT) is an emerging intensity modulated radiotherapy technology. The advantages of dose homogeneity, steepness of dose gradient, and protection of normal organs are reflected in the treatment of head and neck cancers. We present the preliminary (2-year) clinical outcomes of HT in 85 patients with locally advanced NPC (LA-NPC). Of these patients, 3 patients (3.5%) experienced treatment interruption due to severe pulmonary infection, and 82 (96.5%) completed radiation treatments. The 2-year estimate of progression-free survival, local relapse-free survival, nodal relapse-free survival, distant metastases-free survival, and overall survival rate were 90%, 96.3%, 98.8%, 96.3%, and 96.3%, respectively. Among the three patients that died, one had stage III disease and died from fatal nasopharyngeal bleeding after radiotherapy, while the other two patients succumbed to local recurrence. Our experience suggests that HT can achieve promising disease control and survival in the treatment of LA-NPC patients with mild acute and late toxicity profiles.

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Introduction

Nasopharyngeal carcinoma (NPC) is highly prevalent in Southern China, with an annual incidence rate of about 20–50 per 100,000 people [1]. Due to anatomic locations of the nasopharynx and atypical early symptoms of NPC, majority (~70%) of patients are diagnosed with stage III or IV disease. Pathologically, a large portion of NPCs is composed of poorly differentiated and undifferentiated squamous cells, which are more aggressive and prone to distant spread. As radical resection of NPCs results in severe morbidity, radiotherapy (RT) or combined treatment based on RT is recognized as an effective radical therapy [2].

Multiple dosimetry studies have demonstrated that intensity-modulated RT (IMRT) has better dosimetric advantages over two-dimensional RT (2-DRT) and three-dimensional conformal RT

Address all correspondence to: Zhigang Liu, Department of head and neck oncology, Phase 1 clinical trial ward, The cancer center of the fifth affiliated hospital of Sun Yat-sen University, Zhuhai, 519001, China.

E-mail: zhigangliu1983@hotmail.com

¹These authors contributed equally to this work.

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(3D-CRT) [3,4]. The conformal IMRT dose distribution thus allows higher and more homogeneous doses to be delivered to the tumor, thus improving local disease control and reducing acute or chronic toxicities [5–7]. Although IMRT can achieve excellent 5-year local control rates $\geq 95\%$ for T1-2 disease, the corresponding rates are poor for T3-4 disease, ranging from 83% to 87.5% [8,9]. Experts have tried to improve local control by increasing chemotherapy and dose escalation [2,10]. The researchers found that increased doses may lead to better local control but also increased late toxicity [11]. Some patients may even have serious, potentially life-threatening complications. Hence, in order to protect normal tissues, the target dose is often compromised, and it is necessary to find a more compliant treatment.

Helical tomotherapy (HT) was an emerging IMRT technology that mounts a 6-MV linear accelerator on a ring frame around the accelerator couch 360. While rotating the irradiation target area, the treatment couch advances axially through the center of the stand. The advantages of dose homogeneity, steepness of dose gradient, and protection of normal organs are reflected in the treatment of head and neck cancers. This system has many dosimetric advantages, but only a few clinical observations of the toxic side effects and dosimetric advantages of NPC patients treated with HT-based IMRT have been reported [12,13]. Here, we present the preliminary (2-year) clinical outcomes of HT in 85 patients with locally advanced nasopharyngeal carcinoma.

Methods and Materials

Patients

We retrospectively analyzed 85 primary NPC patients who were histologically confirmed, untreated, stage III-IVA (according to the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control staging system) [14] since December 2015 in Hunan Cancer Hospital, The affiliated Cancer Hospital of Xiangya School of Medicine (Central South University, Changsha, China). All patients had nasopharyngeal and skull base computed tomography (CT) or magnetic resonance imaging (MRI), nasopharyngoscope, complete blood tests, and bone scan. There were 59 males and 26 females, and the median age was 48.5 years (range 16 to 72 years). The distribution of clinical stages was established according to the American Joint of Cancer Committee (AJCC) staging system published in 2017; 35 patients were stage III, and 50 patients were stage IVA (Table 1). Informed consent was obtained from all patients before receiving treatment, and this study was approved by the ethics committee of the Hunan Cancer Hospital.

Treatment Planning

All patients were fixed in a specially made thermoplastic material from head to shoulder, and 3-mm-thickness enhanced CT, MRI, or PET images were used as a guide for target contours and organs at risk (OARs). The gross target volume of the primary tumor (GTVnx) and gross target volume of metastatic lymph nodes (GTVnd) were defined as the macroscopic primary cancer and nodes greater than 1 cm in diameter or nodes with necrotic centers on CT or MR images. The PGTVnx was obtained by expanding the corresponding GTVnx with a margin of 3-5 mm limited by the brainstem, spinal cord, optic chiasma, and optic nerve. The PGTVnd was the GTVnd with an expansion of 3-5 mm. The clinical target volume 1 (CTV1) was defined as a subclinical disease consisting of a 0.5- to 1-cm margin surrounding the GTVnx, and it must cover the whole nasopharynx wall, as well as 0.5-cm margin under normal

Table 1. Patient Characteristics ($N = 85$)

Variables	Number (%)
Age, median years (range)	48.5 (16-72)
Gender	
Male	59 (69.4%)
Female	26 (30.6%)
AJCC stage	
III	35 (41.2%)
IVA	50 (58.8%)
T stage	
T1	6 (7.1%)
T2	22 (25.9%)
T3	25 (29.4%)
T4	32 (37.6%)
N stage	
N0	3 (3.5%)
N1	6 (7.1%)
N2	56 (65.9%)
N3	20 (23.5%)
Chemotherapy	
Induction chemotherapy	83 (97.6%)
Concurrent chemotherapy	80 (94.1%)
Adjuvant chemotherapy	10 (11.8%)
None	2 (2.4%)

AJCC, American Joint of Cancer Committee in 2017.

nasopharyngeal mucosa. Clinical target volume 2 (CTV2) consisted of CTV1, at the same time, and some high-risk local structures (skull base, clivus, parapharyngeal space, retropharyngeal lymph nodes, sphenoid sinus, posterior part of the nasal cavity, maxillary sinus, and oropharynx). Each CTV was automatically expanded to generate the corresponding planned target volume (PTV) with an isotropic 5-mm margin while assuring the edge of the distribution was at least 2 mm from skin. The OARs, including pituitary gland, brainstem, eyeballs, lens, optic nerves, spinal cord, temporomandibular joints, inner ears, parotid glands, oral cavity, and larynx-esophagus-trachea, were also delineated. In areas where the target volume was adjacent to critical normal structures, the margin was accordingly reduced. The planning dose at D95 was prescribed to pGTVnx and pGTVnd at 70-74 Gy, PTV1 at 60-64 Gy, and PTV2 at 50-56 Gy in 33 fractions. No more than 5% of PTV volume received more than 110% of the prescribed dose. Based on RTOG H-0022 protocol and our own experiences, the following dose-volume constraints for OARs were utilized: brainstem $D_{max} < 54$ Gy, lens $D_{max} < 25$ Gy, optic nerve $D_{max} < 54$ Gy, spinal cord $D_{max} < 45$ Gy, temporomandibular joint $D_{max} < 60$ Gy, inner ear $D_{max} < 60$ Gy, parotid gland $V_{30} < 50\%$ or $D_{mean} < 28$ Gy; oral cavity $V_{40} < 30\%$; and larynx-esophagus-trachea $V_{40} < 30\%$.

Treatment was delivered in five fractions per week. During HT treatment, patients perform megavoltage computerized tomography (MVCT) imaging examination at least once every week to verify patient settings. The imaging frequency is determined by the setting error of the initial daily scan. Since February 2016, MVCT image guidance has been performed before each fraction of HT treatments. CT simulation was repeated two to three times during treatment to adapt the plan to the dosimetric goals of PTVs and maintain dose limits for OARs.

Chemotherapy

Overall, 97.6% (83/85) patients received chemotherapy, including concurrent chemotherapy with or without induction chemotherapy. Those who refused chemotherapy were for personal reasons. Among these patients, 97.6% (83/85) patients received induction chemotherapy (IC), 94.1% (80/85) patients received concurrent

chemoradiotherapy (CCRT), and just 11.8%(10/85) patients received adjuvant chemotherapy (AC). Induction chemotherapy consisted of cisplatin and 5-fluorouracil (PF); cisplatin and docetaxel (TP); or a triplet of cisplatin, 5-fluorouracil, and docetaxel (TPF) every 3 weeks for two to three cycles. Concurrent chemotherapy was cisplatin weekly (40 mg/m²) or every 3 weeks (75 mg/m²) of radiotherapy. The general course was four to six cycles.

Patient Follow-Up

Acute side effects were observed weekly, and peak toxicity was recorded. Acute and late side effects were defined and classified according to the Common toxicity criteria: version 2.0 [15]. One month after the end of radiotherapy, the efficacy was evaluated by MRI. Patients were followed up after treatment completion every 3 months for the first 2 years, 3-6 months for the third and fifth years, and 1 year thereafter. The follow-up of the primary tumor was assessed by nasopharyngoscope at each visit. MRI scans, bone scans, chest X-rays, and liver ultrasound examinations were performed every 6 months for the first 2 years,

Statistical Analysis

All of the data were analyzed using SPSS 23.0 software. The follow-up duration was calculated from the first day of therapy to the day of death or last examination. The probabilities of progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. OS was defined as the time from the date of diagnosis to the date of death from any causes or the last follow-up. PFS was defined as the period of time from the start of treatment or diagnosis to the first recurrence or distant turn, or death, or the last follow-up date.

Results

Dosimetry Analysis

Eighty-two patients completed radiotherapy; three of them were interrupted because of severe pulmonary infection. The trial flowchart is shown in Figure 1. Of these, one was in the CCRT group, one was in the IC group, and one was in the simple radiotherapy group. The delivered doses to OARs basically met the established constraints. The

Table 2. The Actual Exposure Doses of Targets and Parts of Organs at Risk

PTVs	Ds (cc)	V95% (ave)	Dmin (Gy)	Dmax (Gy)	Dmean (Gy)	V110%	MMR
PGTVnx	70-74	72.60	70.29	73.92	71.42	3.21	1.05
PGTVnd-L	70-74	70.29	69.96	71.94	70.07	2.24	1.03
PGTVnd-R	70-74	70.29	69.96	71.94	70.12	2.13	1.03
PTV1	60-64	60.06	59.4	62.70	61.04	3.76	1.06
PTV2	50-56	50.96	50.4	53.2	52.35	3.64	1.06

Note: Ds represents the standard dose.V95%(ave), Dmax, Dmean, and Dmin refer to the 95% of PTV volume received dose, and the values of the average dose, maximum dose, mean dose, and minimum dose, respectively. Maximum/minimum ratio (MMR): The volume differences in the target areas and OARs contoured independently by different physicians or the range of relative differences in the dosimetry parameters of the treatment plan due to the delineation differences were described using the PTV and OAR volume as well as the MMR of the dose parameters corresponding to these volumes. The MMR is expressed by the following equation: $MMR = X_{max}/X_{min}$, where X_{max} and X_{min} are the maximum and minimum values of the evaluated parameters, respectively. MMR reflects the largest difference in the delineation by different planning. The closer the value is to 1, the better the MMR value.

actual exposure doses of PGTV and PTV are presented in Table 2. The mean dose to left and right parotid gland was less than 30 Gy. The mean doses to oral cavity and larynx-esophagus-trachea were less than 45 Gy. The maximum dose to brainstem and spinal cord was less than 54 Gy and 40 Gy, respectively. Here are two dose distribution pictures for patients with large locally advanced (LA)-NPC targets (Figure 2).

Acute and Late Side Effects

Most patients have no severe acute and late side toxicities that affect treatment. Acute radiation-related side effects were mainly of grade 1 or 2 in skin reaction, mucositis, dysphagia, leucopenia, and anemia. Grade 3 toxicities were noted in four cases (4.9%) for skin, two (2.4%) for mucosa, eight (9.8%) for leucopenia, three (3.7%) for anemia, and one (1.2%) for thrombocytopenia. Grade 4 leukopenia was observed in 4 patients (4.9%), all of which were in the IC plus CCRT group.

Late radiation-related side effects were mainly of xerostomia and lower incidence of hearing and visual loss. Twenty-seven patients suffered from grade 1 to 2 hearing loss, and four cases had grade 3 hearing loss, which needs hearing aid assistance. No one has grade 4 late toxic reaction. Three patients reported a diminished sense of

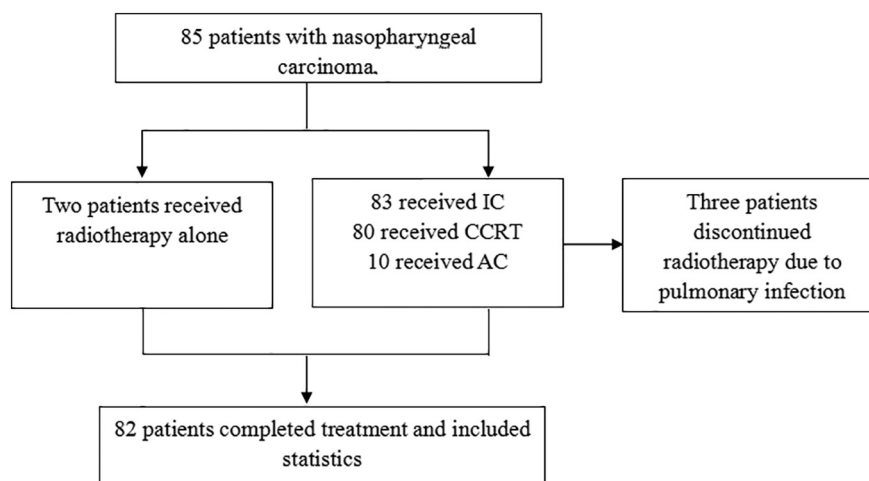


Figure 1. The trial flowchart is shown.IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy, CCRT; AC, adjuvant chemotherapy.

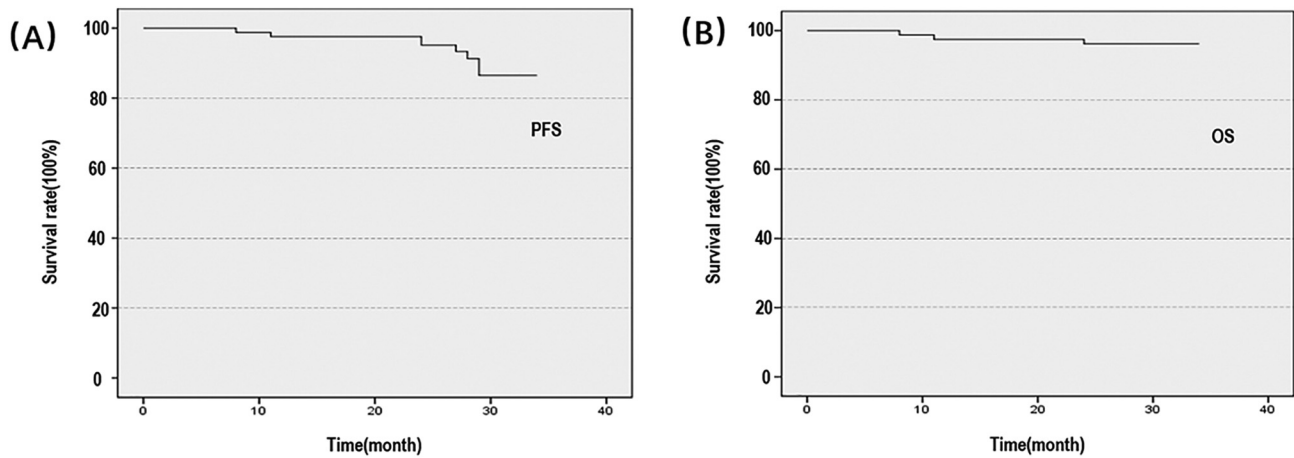


Figure 2. The delineation of tumor volume: the red line indicates gross target volume (GTV); the green line indicates clinical target volumes (CTV); different dose distribution areas use different color identification.

taste. Grade 3 xerostomia toxicities were noted in five cases, 16 cases had varying degrees of otitis media, and no one needed surgical treatment. As time passed, the xerostomia gradually recovered. Distributions of acute and late toxicity are shown in Table 3.

Patterns of Failure

At a median follow-up of 27 months, eight patients had recurred locally, one patient had neck node recurrence, and three patients had distant metastases; the specific data were shown in Table 4. Metastases occurred to bone, lung, and liver. Kaplan-Meier (K-M) analysis resulted in a 2-year estimate of PFS, local relapse-free survival, nodal relapse-free survival, distant metastases-free survival, and OS rate of 90%, 96.3%, 98.8%, 96.3%, and 96.3%, respectively (Figure 3). Prognostic related univariate analysis was shown in Table 5 and Table 6; age was related to 2-year PFS ($P < .05$), and treatment was related to 2-year OS and 2-year PFS ($P < .05$). Two patients with stage IVa, who underwent complete IC + CCRT treatment, died of local recurrence; they did not choose further treatment after relapse. Another local relapse patient is currently undergoing chemotherapy and now is stable. Another patient died because of nasopharyngeal fatal bleeding, which did not pass away in time.

Discussion

Radiotherapy is the main treatment for nasopharyngeal carcinoma. The dose in the target area is directly related to the local control of the tumor, and the difficulty of radiotherapy was in delivering high doses of radiation to the target structures while sparing adjacent bystander

healthy tissues. A 10-year follow-up showed that IMRT demonstrated an improved ultimate therapeutic ratio compared with 2DRT in patients with NPC, with significant improvement of OS and decrease in most late toxicities and noncancer death [16]. However, patients with advanced stage have lower benefit from IMRT than those with early stage. This may be due to the fact that the vast majority of LA-NPCs present with intracranial invasion or extensive erosion of the skull base, while considering protecting the surrounding normal tissue so as not to increase the target dose. Therefore, LA-NPC patients with intensity-modulated radiotherapy are in trouble. HT as a new dynamic intensity-modulated radiotherapy technology also has the advantage of improving dose distribution. Lee et al. [17] by comparing 20 conventional NPC accelerators with IMRT and HT found that the dose curve of the latter target is steeper, the target area has better conformity and dose uniformity, and it is more conducive to the protection of organs such as the parotid gland, spinal cord, and brain stem. Between these, the specific application and clinical results of HT in LA-NPC patients are still worth exploring, and our center has conducted a corresponding retrospective study.

In our study, due to the widespread presence of solid tumors, excessive lymph node volume, and intracranial invasion in patients with LA-NPC patients, dose limitation became more difficult. Fortunately, compared with previous radiotherapy methods, HT has less damage to the OARs, such as brain stem, parotid gland, optic nerve, and cochlea. During follow-up after treatment, the incidence of grade 3 xerostomia was only 6%, and the grade 3 hearing loss was just 5%. No serious grade 4 toxicity and side effects occurred, and the quality of life of patients improved significantly, reflecting a low long-term toxicity and side reaction. In the past studies, the protective effect of IMRT on parotid function has been well established,

Table 3. Acute and Late Toxicity (RTOG Grading Criteria)

Toxicities	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxicities					
Mucositis	54	25	11	2	0
Skin reaction	13	42	23	4	0
Dysphagia	70	8	4	0	0
Leucopenia	9	31	30	8	4
Anemia	32	35	11	3	0
Thrombocytopenia	62	14	5	1	0
Late toxicities					
Xerostomia	13	45	20	5	0
Hearing loss	51	21	6	4	0
Vision loss	71	8	3	0	0

Table 4. Distributions of Failure Cases

Patterns of Failure	Alive	Died	Total
Local recurrence	1 (12.5%)	2 (25.0%)	3 (37.5%)
Nodal recurrence	1 (12.5%)	0 (0%)	1 (12.5%)
Distant metastasis	3 (37.5%)	0 (0%)	3 (37.5%)
Pharyngeal bleeding	0 (0%)	1 (12.5%)	1 (12.5%)
Total (n, %)	5 (62.5%)	3 (37.5%)	8 (100%)

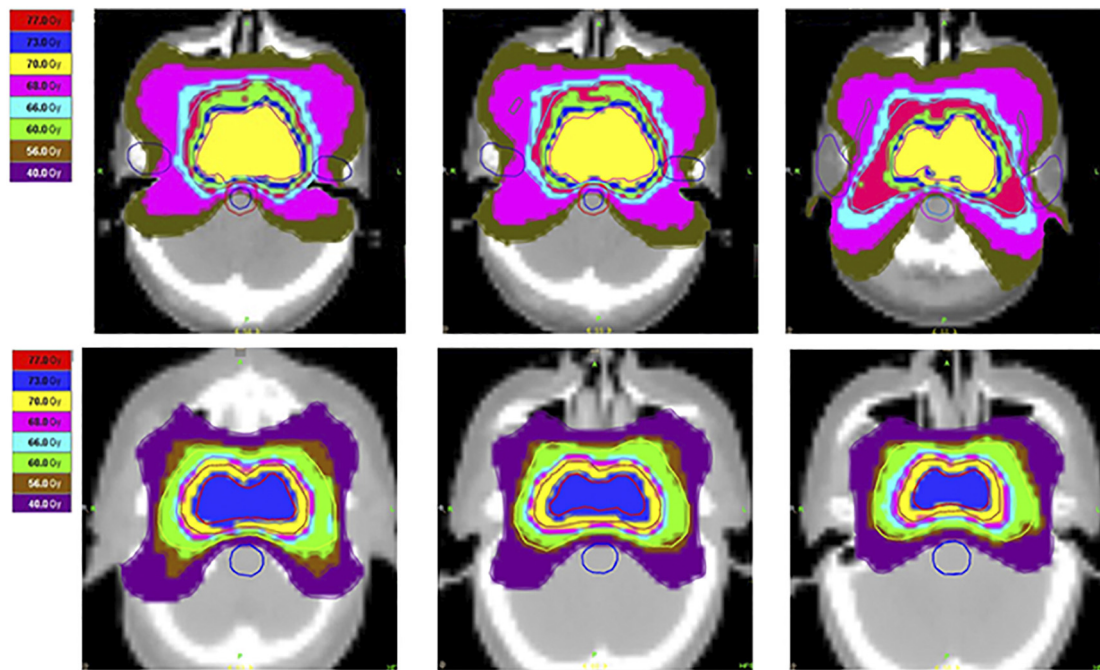


Figure 3. Kaplan-Meier estimates of survival curves. (A) PFS and (B) OS rates. All patients were followed up for more than 2 years.

especially in early NPC; its protective effect on parotid function has been confirmed in clinical randomized controlled studies [18,19]. In one of the prospective studies, Pow et al. [18] compared the effects of IMRT and conventional radiotherapy on parotid function after early nasopharyngeal carcinoma treatment. At 12 months postradiotherapy, IMRT group had recovered better than conventional radiology group. Not only that, but Nguyen et al. [20] have found that HT can significantly reduce the exposure dose of the cochlea without sacrificing the target dose distribution of patients with LA-NPC.

Combined with our results, it is sufficient to prove that HT has a unique advantage in protecting OAR tissue while ensuring the target dose, which not only helps patients to successfully complete the treatment but also reduces the long-term side effects of patients with radiotherapy.

We also found that the acute toxicity of NPC affecting treatment during radiotherapy and chemotherapy was mainly caused by chemotherapy which induced hematological toxicity. The higher the number of chemotherapy cycles, the more severe the toxic reaction, and the severe leukopenia during treatment tends to lead to low immune function and serious infection, affecting the patient's overall treatment. In our study, 97.6% (83/85) patients received chemotherapy, including concurrent chemotherapy with or without induction chemotherapy. Three patients (3/85) discontinued treatment due to severe pulmonary infection which could not be effectively controlled. And then the 3 patients quit the group. Whether induction chemotherapy could increase the incidence of toxic reactions during CCRT remains a question. In the study of Hui [21] and Fountzilias [22], severe thrombocytopenia occurred in the Fountzilias study, and there were no statistically significant differences

Table 5. Log-Rank Test for Univariate Analysis

Factor	Number (%)	2-Year OS		2-Year PFS	
		χ^2	P	χ^2	P
Age (y)		3.75	.53	4.03	.45
≤50	45 (54.9%)				
>50	37 (45.1%)				
Gender		0.06	.93	0.13	.91
Male	59 (71.9%)				
Female	26 (28.1%)				
T stage		4.58	.21	7.06	.07
T1	7 (8.5%)				
T2	22 (26.8%)				
T3	23 (28.1%)				
T4	30 (36.6%)				
N stage		0.45	.93	2.95	.40
N0	3 (3.7%)				
N1	6 (7.3%)				
N2	53 (64.6%)				
N3	20 (24.4%)				
AJCC stage		0.18	.91	2.65	.92
III	35 (42.7%)				
IVa	47 (57.3%)				
Treatment		96.36	.00	81.26	.00
AC + RT	4 (4.9%)				
AC + CCRT	68 (82.9%)				
AC + CCRT + IC	9 (11%)				
RT alone	1 (1.2%)				

Table 6. Log-Rank Test for Multivariable Analysis

Factor	Number (%)	2-Year OS			2-Year PFS		
		χ^2	95% CI	P	χ^2	95% CI	P
T stage		1.13	0.334-3.826	.84	0.598	0.264-1.354	.22
T1	7 (8.5%)						
T2	22 (26.8%)						
T3	23 (28.1%)						
T4	30 (36.6%)						
Treatment		0.91	0.016-0.521	.07	0.048	0.11-0.208	.00
AC + RT	4 (4.9%)						
AC + CCRT	68 (82.9%)						
AC + CCRT + IC	9 (11%)						
RT alone	1 (1.2%)						

in other adverse events in these two studies. Ou Yang's [23] meta-analysis compared adverse reactions during CCRT. The results also showed that the severe thrombocytopenia during CCRT in the neoadjuvant group was higher than that in the control group, and the other adverse reactions were similar. In Chen et al. [24], among the 205 patients who received adjuvant chemotherapy, 69% (141/205) of patients delayed treatment due to adverse reactions caused by chemotherapy, 49% (100/205) of patients had reduced chemotherapy dose due to hematologic adverse reactions and mucositis, and 42% (87/205) of the main adverse reactions of patients were concentrated in grades 3-4. Compared with our study, among the 82 patients who received chemotherapy, there were 8 patients of leukopenia in grade 3 hematologic toxicity, 3 patients of anemia, 1 patient of thrombocytopenia, and grade 4 leukopenia reduction rate was 9.6% (8/82). All patients were treated symptomatically, and the hematologic parameters returned to normal after treatment; therefore, no patient discontinued treatment because of serious chemotherapy adverse reactions. It can be seen that the incidence of chemotherapy-related adverse reactions in the patients enrolled in the center is low, which may be related to the small number of patients enrolled and the fewer cycles of chemotherapy. However, timely intervention in related symptomatic treatment and HT radiotherapy reducing side effects may be one of the reasons, and it deserves further exploration.

With the continuous advancement of diagnostic and therapeutic techniques, the efficacy of nasopharyngeal carcinoma has increased dramatically. However, for patients with locally advanced stage, although radiotherapy technology significantly improves local control, distant metastasis control was still not ideal and has become a major problem affecting patient survival. The causes of recurrence and metastasis of NPC were multifaceted, including biological characteristics (such as insensitivity of tumor clonal cell populations), clinical stage, and treatment techniques. In this study, we found that 2-year estimates of PFS and OS rate were highly similar between VMAT and IMRT plans. This result is consistent with the findings reported by Chen et al. [25]. Chen B. B. et al. also revealed that 2-year estimates of PFS and OS rate were 90% and 92.4% in IMRT group and 95% and 97.5% in VMAT group, respectively. Compared with ordinary radiotherapy and three-dimensional conformal RT, both of them not only improve the survival benefit but also reduce the damage after radiotherapy. In our study, three patients had distant metastases, one patient had lymph node metastasis, and 2 patients had local recurrence. Patients with liver metastases were treated with radiofrequency ablation, patients with bone metastases were treated with local radiotherapy, and patients with cervical lymph node metastases were treated with surgical resected. These patients were currently in good condition. But for retreatment after recurrence of NPC, there are still many problems. Chemotherapy for recurrent NPC can reduce tumor burden, prolong the interval between recurrent radiotherapy, and even has the hope to control distant metastasis, but the efficacy of these relapsed patients has an unfavorable survival [26,27]. Radiation therapy is still the main way of retreatment of recurrent NPC. The first principle was to protect the vital organs and tissues around the maximum while killing the tumor to the greatest extent. When the two cannot be combined, the latter should be the most important. Because the blood supply to the mucosa after the first-pass radiotherapy is poor, the patient's immune function is also reduced a lot, so the interval between the routine reradiation and the first-pass radiotherapy was usually more than 1 year [28-30]. Hence, in our study, 66% (2/3) of LR-NPC

patients died because of no intervention therapy; only one recent relapse received chemotherapy. Specific efficacy has not been evaluated.

Of course, this study still has certain limitations. Our center introduced HT units in 2015; the number of patients enrolled appears to be small. At the same time, because the current follow-up time is only more than 2 years, the long-term survival data have not yet been drawn, and the specific treatment benefits still need further observation. However, this study was still the retrospective analysis of NPC patients into the group which was more standardized, the source area and age distribution is relatively uniform, and all patients have received standardized treatment. Next, we will collect more patient data and will perform a paired analysis with IMRT to further compare the strengths and weaknesses of both.

Conclusion

HT achieves promising disease control and OS in the treatment of locally advanced NPC patients. Even with IC + CCRT + AC multicycle chemotherapy, slight acute and late side effects usually occur, and the incidence of acute hematologic toxicity is still lower. The incidence of grade 4 leukopenia was only 5%, and the incidence of grade 3 xerostomia after radiotherapy was only 6%. Besides, in LA-NPC patients' treatment, HT treatment seems to be similar to IMRT in local control and patient survival but may have partial advantages in dose distribution and quality of life, and good clinical efficacy while providing patients with higher quality of life, and it needed further paired analysis and long-term follow-up observations to be confirmed.

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Disclosure Statement

None.

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