

Comparative study on the clinical efficacy and quality of life of helical tomotherapy and three-dimensional conformal radiotherapy for locally advanced nasopharyngeal carcinoma

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ABSTRACT

Background: To explore the therapeutic effect of helical tomotherapy (HT) and three-dimensional conformal radiotherapy (3DCRT) on locally advanced nasopharyngeal carcinoma (NPC) and the impact on patients' quality of life. **Materials and Methods:** Retrospectively, we analyzed data from 354 patients with locally advanced NPC who were admitted to our hospital from January 2015 to January 2019. Patients were divided into 3DCRT group and HT group with distinct therapy modality. The clinical efficacy, appetite changes and adverse reactions of the 2 groups were observed, and quality of life scale (SF-36) scores and 1-, 2- and 3-year survival ratios of the 2 groups at pre-therapy and post-therapy were compared. **Results:** the HT group exhibited a markedly superior objective remission rate (ORR) compared to the 3DCRT group ($P < 0.05$), but the difference between the disease control rate (DCR) of the two groups was not statistically significant ($P > 0.05$). **Conclusion:** HT radiotherapy for patients with locally advanced NPC shows precise advantages, which can effectively improve the clinical therapeutic effect of the patients.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor that arises in the nasopharynx, making it a prevalent clinical malignancy affecting the ear, nose, and throat. (1,2). As per the data from the International Agency for Research on Cancer, about 129,000 individuals received a diagnosis of NPC in 2018, representing merely 0.7% of all reported tumor cases, and NPC is geographically endemic. NPC is very popular in East and Southeast Asia (3,4). What's more, NPC is more common in southern China, and the frequency ratio in men is greater than in women. Statistics in 2015 show that the ratio in China is about 2.5:1 (5,6). The early symptoms of NPC are atypical and the onset is relatively insidious. Most patients are already in stage III or IV when they seek treatment, and locally advanced NPC has lymph node metastasis. The recurrence rate is high and clinical treatment is difficult (7,8). Radiotherapy is often used in clinical practice. Chemotherapy is a combined treatment modality for NPC. In recent years, with advancements in radiation therapy technology, advanced techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Helical Tomotherapy (HT) have gradually been applied in the treatment of NPC. IMRT dynamically adjusts the intensity of radiation beams to achieve a more precise dose

distribution, significantly enhancing treatment effectiveness and reducing side effects. HT, on the other hand, provides a uniform dose distribution and steeper dose gradient through spiral scanning, further protecting normal tissues. Three-dimensional conformal radiation therapy (3D-CRT) is a common clinical treatment method for NPC, while helical tomotherapy (HT) has a better dose in the therapy of locally advanced NPC (9,10). 3DCRT, which utilizes a CT-guided radiation planning over therapy planning system, can adjust radiation beams according to the three-dimensional shape of the tumor to reduce damage to surrounding normal tissues. However, the precision and uniformity of dose distribution with 3DCRT still need improvement. Uniformity and steeper dose gradient can effectively protect other healthy organs and reduce adverse reactions while treating locally advanced NPC (11,12). However, there are few comparative studies on the efficacy of HT and 3D-CRT in the therapy of locally advanced NPC. The study included 354 patients with locally advanced NPC who were hospitalized at our institution between January 2015 and January 2019 as the study subjects, aiming to compare the impact of HT radiotherapy and 3DCRT on the clinical efficacy and life quality of sufferers with locally advanced NPC. The novelty of this study lies in its direct comparison of helical tomotherapy (HT) and 3DCRT in patients

with locally advanced nasopharyngeal carcinoma (NPC). Although both HT and 3DCRT have been widely used in clinical practice, there have been few studies evaluating the impact of these two technologies on the clinical efficacy and quality of life of NPC patients simultaneously. This study fills this gap and provides a deeper understanding.

MATERIALS AND METHODS

General information

This was a retrospective study involving 354 sufferers with locally advanced NPC who were received in our hospital among the time between January 2015 and January 2019 were regarded as the study subjects. Inclusion criteria: ① Those with confirmed pathological examination for NPC, clinical stage III-IVb, Karnofsky Performance Status (KPS, KPS score is a widely used scale for assessing the general health status and functional status of cancer patients. This scoring system range from 0 to 100, where; 100 represents a patient who is fully functional, and 0 indicates a patient who is unable to carry out any activities) score ≥ 80 points; ② Patient age between 50-75 points; ③ Sufferers and families are both with good compliance, and cooperative with the test and therapy, and all signed informed consent form. Exclusion criteria: ① Those with combined serious organ dysfunction; ② Those who combined with cognitive dysfunction or neurological illness; ③ Those who combined with pernicious tumors; ④ Those who allergic to the drugs used in this research; ⑤ Those who combined with serious endocrine, digestive system or nutritional metabolism diseases. Based on distinctive therapy methods, the sufferers were divided into 3DCRT one and HT one, with 177 instances in each. It had 177 instances in the 3DCRT one, including 138 males and 39 females. The mean age was (58.47 ± 6.28) years old and the mean BMI (21.86 ± 1.28) kg/m². It had 177 instances in the HT one, with 125 men and 52 women, and the mean age was (59.34 ± 7.47) years and the mean BMI was (21.73 ± 1.35) kg/m². It had no clear distinctions in age, gender, BMI, etc. between the groups ($P > 0.05$). General Hospital of Southern Theatre Command, PLA ethics committee under (approval No. NZLLKZ2022087), approved all experimental procedures. Demographic information of patients is shown in table 1.

Table 1. General data analysis of the 2 groups [n (%)($\bar{x} \pm s$)].

grouping	n	Age (years)	Gender		BMI (kg/m ²)
			Male	Female	
3DCRT group	177	58.47±6.28	138(77.97)	39(22.03)	21.86±1.28
HT group	177	59.34±7.47	125(70.62)	52(29.38)	21.73±1.35
χ^2/t		1.186	2.500		2.500
P		0.236	0.114		0.114

Note: n: Number of patients; Age: Years; Gender: Male (M), Female (F); BMI: Body Mass; Index (kg/m²); 3DCRT: Three-Dimensional Conformal Radiotherapy; HT: Helical Tomotherapy.

Methods

Both groups of patients underwent cisplatin chemotherapy: Nuoxin (cisplatin injection) (purchased from Jiangsu Haosen Pharmaceutical Group Co., Ltd., approval number: National Medical Approval No. H20040813, specification: 6ml: 30mg) was intravenously injected on the 1st, 22nd, and 43rd days of treatment, 80mg/m²/time, once a day, while also receiving treatment such as antiemesis and kidney protection.

3DCRT group: The 3DCRT group received radiotherapy based on the CT and MRI results. The primary tumor of NPC (pGTVnx) was given a total dose of 68-70 Gy, with visible metastatic lymph nodes (pGTVnd) receiving 66-70 Gy. The high-risk clinical target area (CTV1) was treated with 60-64 Gy, and the low-risk clinical target area (CTV2) with 50-54 Gy. The treatment was delivered in single fractions of 2 Gy, five times per week. **HT Group:** Patients in the HT group were positioned supine, with the head and neck fixed using a thermoplastic head-neck-shoulder mask. CT scans were performed to define the target area and outline the organs at risk. The HT treatment plan was designed as follows:

pGTVnx: 70-74 Gy/30-33 fractions

pGTVnd: 64-70 Gy/30-33 fractions

CTV1: 60-64 Gy/30-33 fractions

CTV2: 50-56 Gy/30-33 fractions

The prescribed dose was required to cover more than 98% of the target volume, with the volume of the planning target volume (PTV) that receives >110% of the prescribed dose being less than 20%, and the volume receiving <93% of the treatment dose being less than 3%. All other sites outside the PTV were limited to <110% of the prescribed dose, while the dose to other organs at risk was limited based on the RTOG criteria. The HT radiotherapy plan was designed and validated using the HiArt Tomotherapy studio Accuray Incorporated, USA.

Observation indicators

Efficacy evaluation: It is categorized into complete remission (CR), partial response (PR), stable situation (SD), and disease progression (PD). Among them, the patient's lesions completely disappeared after treatment as CR, the diameter of the lesion shrinks by $\geq 50\%$ after treatment; the maximum diameter of the lesion shrinks by <50% after treatment; the diameter of the patient's tumor increases or new lesions appear after treatment. Among them, Objective Relief (ORR) = CR + PR, and Disease Control Rate (DCR) = CR + PR + SD.

Monitoring of appetite changes: Observe and record changes in the sufferer's appetite during therapy, divided into increasing, stable, and decreasing. The patient's daily food intake is increased by more than 100g; the patient's daily food intake is stable if the change is within 100g; the patient's daily food intake is reduced by 100g. The

above is a reduction. The increase is effective. Occurrence of adverse reactions: Closely detecting the occurrence of adverse reactions in both groups of sufferers, including bone marrow suppression, elevated transaminase, rash, salivation reaction, and gastrointestinal reaction.

Quality of life evaluation: Comparing the Scoring of Quality of Life Scale (SF-36) points between the 2 groups at pre-therapy and post-therapy, including physical, emotional, cognitive and social function dimensions, with a full points of 100. The greater the point, the greater the sufferer's life quality.

Long-term prognosis: Follow-up was conducted with telephone or outpatient follow-up, and the follow-up period will be 3 years after treatment. The deadline is January 2022. The 1-, 2-, and 3-year survival ratios of the 2 groups of sufferers will be compared.

Statistical methods

SPSS20.0 software was used to analyze the experimental data. Taking ($\bar{x} \pm s$) indicates age, BMI, life quality and other measurement data, all of which conform to normal distribution, and *t* test is used. Count data such as gender, efficacy, adverse reactions, etc. are expressed in (%), and the χ^2 test is used. The statistical results were considered statistically clear with $P < 0.05$.

RESULTS

Comparison of therapeutic effects the 2 treatment modalities

3DCRT group: Complete response (CR): 47 cases (26.55%) Partial response (PR): 90 cases (50.85%) Stable disease (SD): 30 cases (16.95%) Disease progression (PD): 10 cases (5.65%) Objective response rate (ORR): 138 cases (77.97%) Disease control rate (DCR): 167 cases (94.35%). HT group: Complete response (CR): 73 cases (41.24%) Partial response (PR): 91 cases (51.41%) Stable disease (SD): 9 cases (5.08%) Disease progression (PD): 4 cases (2.26%) Objective response rate (ORR): 164 cases (92.66%) Disease control rate (DCR): 173 cases (97.74%). The objective remission rate (ORR) of the HT group was significantly greater than that of the 3DCRT group ($P < 0.001$), whereas the difference in disease control rate (DCR) between the two groups did not reach statistical significance ($P = 0.102$) (table 2 and figure 1).

Table 2. The therapeutic efficacy compared between 2 groups of sufferers after therapy [n (%)].

grouping	n	CR	PR	SD	PD	ORR	DCR
3DCRT group	177	47 (26.55)	90 (50.85)	30 (16.95)	10 (5.65)	138 (77.97)	167 (2.677)
HT group	177	73 (41.24)	91 (51.41)	9 (5.08)	4 (2.26)	164 (92.66)	173 (97.74)
χ^2						15.238	2.677
<i>P</i>						<0.001	0.102

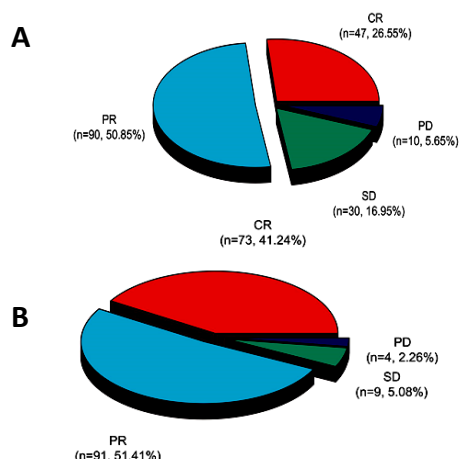


Figure 1. The therapeutic effects compared between the 2 groups of sufferers at post-therapy. Note: **A** is the efficacy classification after treatment in the 3DCRT group ; **B** is the efficacy classification after treatment in the HT group.

Comparison of the appetite changes between the 2 treatment modalities

The effective rates of appetite change in the 3DCRT and HT was 74.01% and 77.97% respectively. It had no statistically obvious distinction in the effective ratio of appetite change in the HT and the 3DCRT ($P > 0.05$) (table 3 and figure 2).

Table 3. The changes in appetite compared between the 2 groups of sufferers at post-therapy [n (%)].

grouping	n	Changes in appetite			
		Add	Stable	Reduce	Effective
3DCRT group	177	131 (74.01)	30 (16.95)	16 (9.04)	131 (74.01)
HT group	177	138 (77.97)	26 (14.69)	13 (7.34)	138 (77.97)
<i>t</i>					0.759
<i>P</i>					0.384

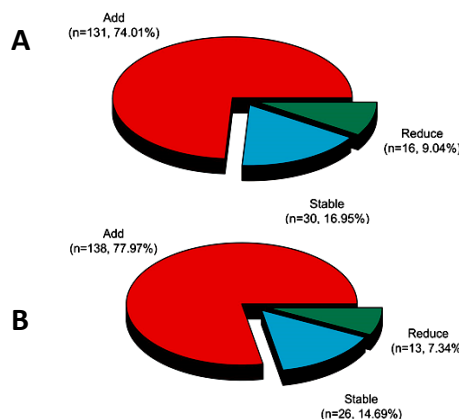


Figure 2. The changes in appetite compared between the 2 groups of sufferers after therapy. Note: **A** is the classification of appetite changes after therapy in the 3DCRT group ; **B** is the classification of appetite changes after treatment in the HT group.

Comparison of adverse reactions between the 2 treatment modalities

Bone marrow suppression: 3DCRT group: 36 cases (20.34%) HT group: 30 cases (16.95%); Elevated transaminases: 3DCRT group: 63 cases (35.59%) HT group: 57 cases (32.20%); Skin rash: 3DCRT group: 58 cases (32.77%) HT group: 43 cases

(24.29%); Gastrointestinal reactions: 3DCRT group: 29 cases (16.38%) HT group: 24 cases (13.56%); Salivary gland reactions: 3DCRT group: 42 cases (23.73%). HT group: 25 cases (14.12%). There was no statistically significant variance in the incidence of myelosuppression, transaminase elevation, rash, and

gastrointestinal reaction adverse reactions between the HT group and the 3DCRT group ($P>0.05$). The occurrence of salivary reactions in the HT group was notably reduced compared to the 3DCRT group, with a statistically significant difference ($P<0.05$). (table 4, figures 3-7).

Table 4. The adverse reactions compared between 2 groups of sufferers during therapy [n (%)].

grouping	n	Bone marrow suppression	Elevated transaminase	Rash	Gastrointestinal reactions	Salivation reaction
3DCRT group	177	36 (20.34)	63 (35.59)	58 (32.77)	29 (16.38)	42 (23.73)
HT group	177	30 (16.95)	57 (32.20)	43 (24.29)	24 (13.56)	25 (14.12)
χ^2		0.671	0.454	3.117	0.555	5.320
<i>P</i>		0.413	0.501	0.077	0.456	0.021

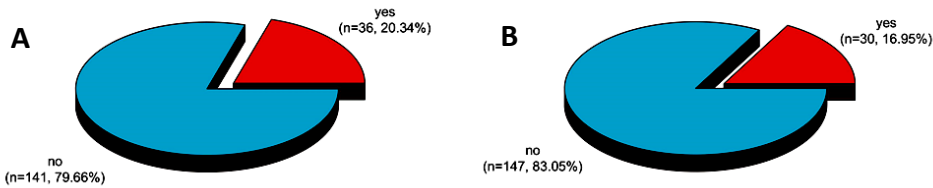


Figure 3. Comparison of the occurrence of bone marrow suppression in the two groups of patients. Note: **A** represents the incidence of bone marrow suppression in the 3DCRT group, while **B** represents the occurrence of bone marrow suppression in the HT.

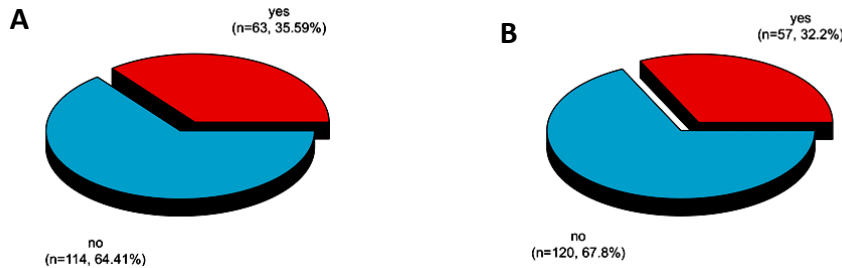


Figure 4. Comparison of the occurrence of elevated transaminase levels in the two groups of patients. Note: **A** is the occurrence of elevated transaminase in the 3DCRT group; **B** is the occurrence of elevated transaminase in the HT group.

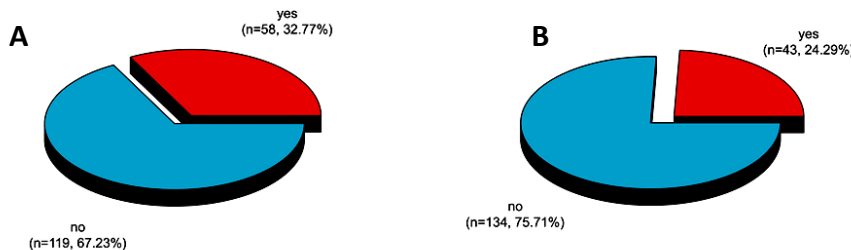


Figure 5. Comparison of the occurrence of rash or salivation reaction between the two groups of patients. Note: **A** is the occurrence of rash or salivation reaction in the 3DCRT group; **B** is the occurrence of rash or salivation reaction in the HT group.

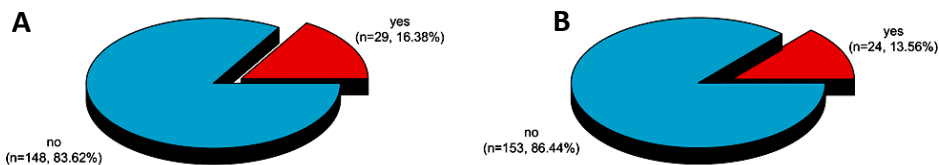


Figure 6. The gastrointestinal reactions compared between the 2 groups of sufferers. Note: **A** denotes the occurrence of gastrointestinal reactions in the 3DCRT group, whereas **B** signifies the occurrence of gastrointestinal reactions in the HT group.

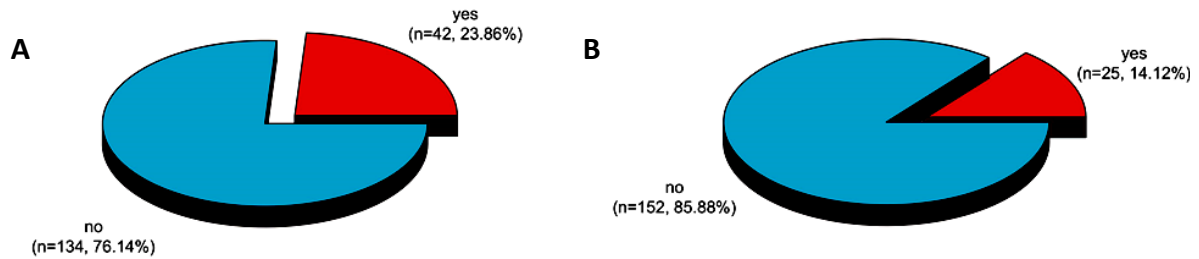


Figure 7. Comparison of the occurrence of salivary reaction between the two groups of patients. Note: **A** is the occurrence of salivary reaction in the 3DCRT group; **B** is the occurrence of salivary reaction in the HT group.

Comparison of the quality of life between the 2 treatment modalities

3DCRT group: Before treatment: Physical function: 50.16±6.29 Emotional function: 52.22±6.04 Cognitive function: 63.16±8.21 Social function: 31.46±3.18 After treatment: Physical function: 75.15±6.29 Emotional function: 71.75±5.20 Cognitive function: 82.44±6.16 Social function: 63.23±6.74. HT group: Before treatment: Physical function: 49.88±6.21 Emotional function: 52.01±6.29 Cognitive function: 62.88±6.34 Social function: 31.99±5.20 After treatment: Physical function: 87.46±8.23 Emotional function: 86.51±8.10 Cognitive function: 90.22±6.39 Social function: 75.11±5.15. There was no statistically clear distinction between the physical, emotional, cognitive and social function dimension

scores between the 2 groups before and after treatment ($P > 0.05$); and the points of every dimension in the HT group were clearly greater than the 3DCRT group, statistically significant ($P < 0.05$) (table 5, figures 8 and 9).

Comparison of long-term survival rates between the 2 groups

The 1, 2, and 3-year survival ratios of the 3DCRT group was 82.49%, 75.14%, and 61.02%, respectively. The 1, 2, and 3-year survival ratios of the HT group was 91.53%, 84.75%, and 75.71%, respectively. The survival rate was clearly greater than the 3DCRT group, statistically significant ($P < 0.05$) (table 6, figures 10-12).

Table 5. The life quality compared between 2 groups of sufferers at pre-therapy and post-therapy ($\bar{x} \pm s$).

time	grouping	n	Somatic function	Emotional function	Cognitive function	Social function
Before treatment	3DCRT group	177	50.16±6.29	52.22±6.04	63.16±8.21	31.46±3.18
	HT group	177	49.88±6.21	52.01±6.29	62.88±6.34	31.99±5.20
t			0.425	0.310	0.355	1.147
P			0.671	0.756	0.723	0.252
After treatment	3DCRT group	177	75.15±6.29 ^a	71.75±5.20 ^a	82.44±6.16 ^a	63.23±6.74 ^a
	HT group	177	87.46±8.23 ^a	86.51±8.10 ^a	90.22±6.39 ^a	75.11±5.15 ^a
t			15.811	20.401	11.662	18.633
P			<0.001	<0.001	<0.001	<0.001

Note: Compare to before therapy at the same time, a $P < 0.05$.

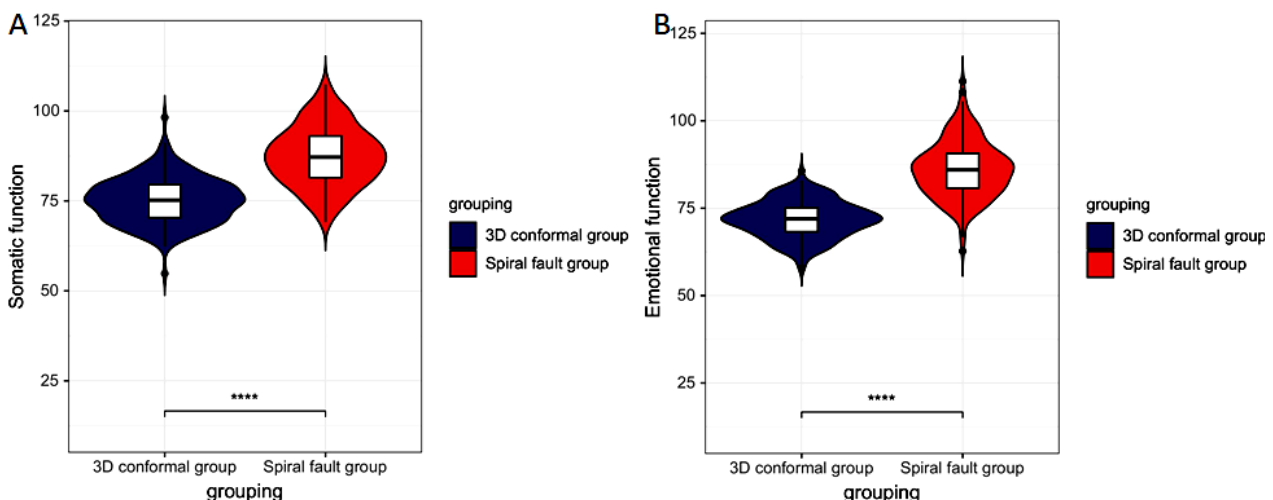


Figure 8. The physical and emotional functions compared between the 2 groups of sufferers after therapy. Note: **A** is the comparison of the physical function of the 2 groups of sufferers at post-therapy; **B** is the comparison of the emotional function of the 2 groups of sufferers at post-therapy.

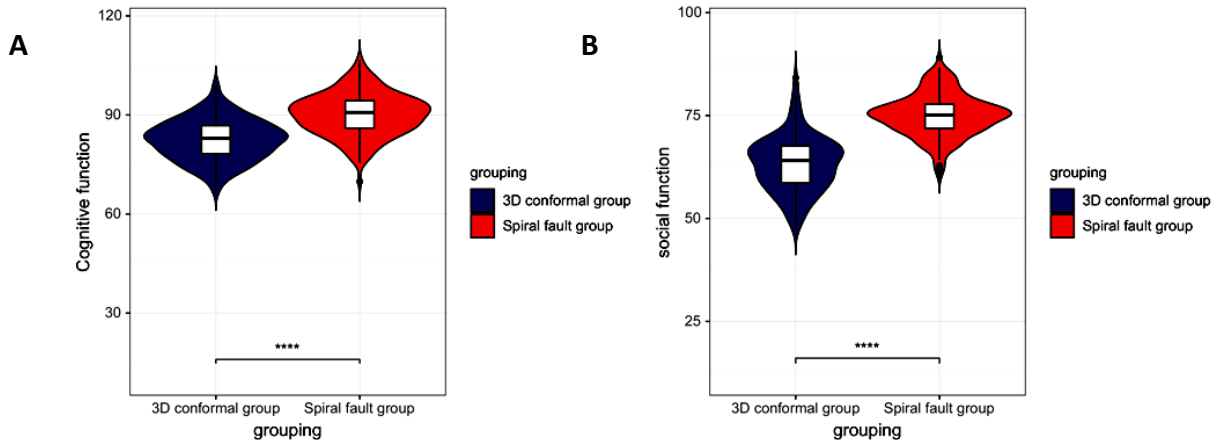


Figure 9. Comparison of cognitive function and social function between the 2 groups of sufferers after therapy. Note: **A** is the comparison of the cognitive functions of the 2 groups of sufferers after therapy; **B** is the comparison of the social functions of the 2 groups of sufferers after therapy.

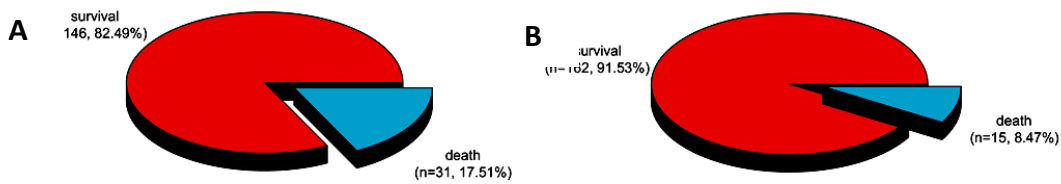


Figure 10. Comparison of 1-year survival ratios between the 2 groups of sufferers. Note: **A** is the 1-year survival ratio of the 3DCRT one; **B** is the 1-year survival ratio of the HT one.

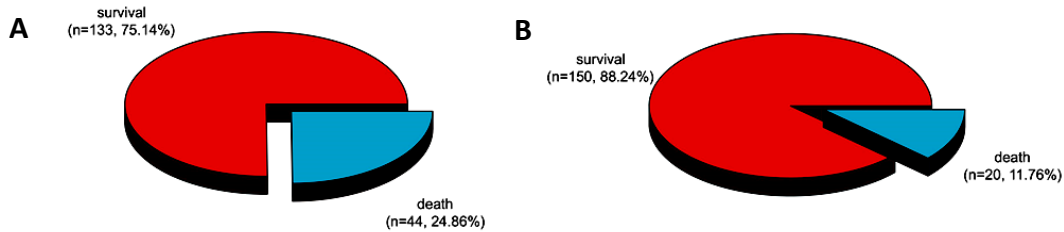


Figure 11. Comparison of 2-year survival ratios between the 2 groups of sufferers. Note: **A** is the 2-year survival ratio of the 3DCRT one; **B** is the 2-year survival ratio of the HT one.

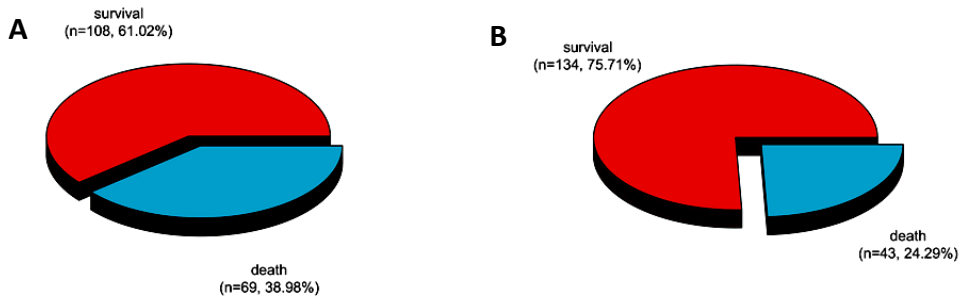


Figure 12. Comparison of 3-year survival ratios between the 2 groups of sufferers. Note: **A** is the 3-year survival ratio of the 3DCRT one; **B** is the 3-year survival ratio of the HT one.

Table 6. The long-term survival rates compared between the 2 groups of sufferers [n (%)].

grouping	n	1 year survival	2 years survival	3 years survival
3DCRT group	177	146 (82.49)	133 (75.14)	108 (61.02)
HT group	177	162 (91.53)	150 (84.75)	134 (75.71)
χ^2		6.396	5.092	8.829
P		0.011	0.024	0.003

DISCUSSION

NPC refers to a malignant tumor that occurs on the top or side wall of the nasopharyngeal cavity. The specific pathogenesis is not yet fully understood, but most studies believe that the occurrence of NPC is caused by Epstein-Barr virus infection, genetic and

environmental factors (such as drinking and smoking) caused by the interaction between (13, 14). NPC is one of the usual malignant tumors in southern China, and its early symptoms are not clear. Most sufferers are already in the advanced stage when they seek treatment. The treatment is difficult and the prognosis is poor, which seriously threatens the

life safety and life quality of the Chinese people (15, 16).

Combination therapy with radiotherapy and chemotherapy is the first-line therapy option for NPC. For chemotherapy, cisplatin is often used, which has a certain degree of safety and can assist in improving the effect of radiotherapy (17, 18). 3DCRT is a common clinical radiotherapy method, but the irradiation range selected for 3DCRT treatment is relatively large, and the dose distribution within the irradiation area is relatively uniform. Therefore, other healthy organs are damaged during treatment, and the therapeutic effect is reduced (19, 20). HT is an emerging intensity-modulated radiotherapy technology in recent years. It not only has better metrology advantages in intensity-modulated radiotherapy and protects normal tissues to the maximum extent (21, 22), but also allows tumor tissues to receive higher and more uniform radiation doses. Breaking through the limitations of traditional accelerators, it achieves 360-degree full-angle focusing under CT guidance, thereby giving a more precise and efficient treatment dose to tumor tissue, while protecting healthy tissue and reducing the risk of adverse reactions (23, 24). Comparison in this research showed that the objective response ratio in the HT one was clearly greater than the ORR in the 3DCRT one, but it had no statistically clear distinction in DCR between the 2 groups. It shows that HT can improve the therapeutic effect of locally advanced NPC to a certain extent. The reason is that HT treatment can better achieve the uniformity of dose distribution in the target area and effectively increase the steepness of the dose gradient in the target area, so it is more prominent in improving the therapeutic effect. Although radiotherapy can effectively kill tumor cells, it also has a certain impact on normal tissue leading to toxic reactions, which not only increases the patient's pain and may affect subsequent treatment and the therapeutic effect (25, 26). This study showed that the difference between the effective rate of appetite change in the HT group and the effective rate of appetite change in the 3DCRT group was not statistically significant. Moreover, the difference in the incidence of myelosuppression, aminotransferase elevation, rash and gastrointestinal reactions between the HT group and the 3DCRT group was not statistically significant. The incidence of salivary reactions in the HT group was significantly lower than that of the 3DCRT group. While HT treatment has lower toxicity and side effects on patients, it can reduce the occurrence of salivary reactions, has certain advantages in salivary gland protection, and has higher safety.

With the rapid development of medical technology in recent years, the overall efficacy of NPC has gradually increased, but the therapeutic effect for locally advanced NPC is still unsatisfactory (27, 28). A study by Arslan SA *et al.* (29) found that 2 years after treatment for NPC patients, the rates of local-regional

progression-free survival, disease-free survival, distant metastasis-free survival, and overall survival were all 83%, 69%, 86% and 71% separately. 13 patients relapsed (19.4%), of which 6 patients (8.9%) local recurrence, which indicates that NPC patients have poor long-term prognosis. Therefore, long-term follow-up assessment of prognosis is also a crucial factor in evaluating the effectiveness of treatment methods. Comparison of this study showed that the scores of each dimension in the 2 groups were clearly greater after therapy. This shows that HT treatment can effectively improve the life quality of sufferers with locally advanced NPC, which may be related to the steepness of the dose gradient of HT treatment, less impact on other tissues, and high proportion of ORR (24, 30). In addition, results show that the 1, 2, and 3-year survival ratios of the 3DCRT one was 82.49%, 75.14%, and 61.02%, respectively, while, 1, 2, and 3-year survival ratios of the HT one was 91.53%, 84.75%, and 75.71%, respectively, 2- and 3-year survival ratios were clearly greater than the 3DCRT one. This shows that HT has better long-term effects, which is similar to the outcomes of the research by You R *et al.* (31). This study thought that HT treatment can significantly reduce the incidence of serious late complications and have the improvement on the overall survival ratio in sufferers with locally advanced recurrent NPC.

Limitations: Although our study had a relatively large sample size, it was limited to patients from a single center, which may not fully represent a broader patient population. Future studies should consider multi-center, large-sample clinical trials to validate our results. Our follow-up period was 3 years, which, while sufficient to evaluate short-term and medium-term outcomes, may not be adequate to fully assess long-term effects. Future research should consider extending the follow-up period to better understand the long-term impact of different treatment methods. This study only compared two treatment methods, HT and 3DCRT, without considering other potential treatment modalities such as intensity-modulated radiation therapy (IMRT). Future research could explore comparisons among different radiation therapy technologies to provide more comprehensive treatment recommendations.

Prospects: With the continuous advancement of radiation therapy technology, future research can explore new radiation therapy techniques, to further enhance treatment effectiveness and reduce side effects. Future studies can explore personalized treatment strategies based on specific patient characteristics, such as genomics and biomarkers, to improve treatment outcomes and reduce unnecessary treatment burdens.

In summary, HT radiotherapy for patients with locally advanced NPC shows precise advantages which can effectively improve the clinical therapeutic

effect of patients, prolong their survival, and help to improve the quality of life of patients. HT treatment has lower toxic side effects on patients, reduce the occurrence of salivary reactions, and has certain advantages in salivary gland protection, and HT treatment for patients with locally advanced NPC has a certain degree of safety. However, since the sample source of this experiment are all patients in our hospital, the results of this study should be validated with larger cohorts from other centers.

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Conflicts of interests: All authors disclose that they have no financial or non-financial conflicts of interest associated with this study.

Ethical consideration: This research was approved by General Hospital of Southern Theatre Command, PLA ethics committee under (approval No.NZLLKZ2022087). All methods are reported in accordance with Declaration of Helsinki. All participants signed informed consent prior to participation in the study.

Author contribution: YJ.W : Study design, data collection, data analysis, writing, and manuscript revision; YJ.W., YZ.H and WB.L.: Study design, data analysis, review, and manuscript revision; XM.L., YJ.C., L.N.S and JH.Z. : Data collection, review, and manuscript revision. All authors: Study design, review, and final approval of the manuscript.

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