

Application of intensity-modulated radiation therapy in the treatment of nasopharyngeal carcinoma

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Abstract. The objective of the present study was to investigate the application values of the intensity-modulated radiation therapy (IMRT) and the three-dimensional conformal radiation therapy (3D-CRT) in the treatment of nasopharyngeal carcinoma (NPC). A total of 124 patients diagnosed with nasopharyngeal carcinomas were included into the study and randomly divided into the control group and the observation group, with 62 patients in each group. The 3D-CRT combined with postoperative chemotherapy were performed on the control group and the observation group received IMRT combined with postoperative chemotherapy, and then were followed up for a median duration of 25.5 months. Comparison of the survival analysis of the two groups showed no differences between them in terms of the total effective rate and effectiveness ($P>0.05$), or radiotherapy complications ($P>0.05$). In addition, no significant differences between the two groups were found in the follow-up local tumor control probability (TCP), regional lymph node control rate, distant metastasis-free rate, tumor-free survival rate, recurrence rate and overall survival rate ($P>0.05$). Furthermore, there was no difference between the two groups in the overall score of quality of life ($P>0.05$). The present study concludes that the IMRT and the 3D-CRT have almost the same short-term and long-term clinical effects in the treatment of nasopharyngeal carcinoma and both of them have high effectiveness and safety.

Introduction

The nasopharyngeal carcinoma (NPC), a disease commonly seen in southern China (1) accounts for approximately 15-30%

of all types of malignant head and neck tumors and is very susceptible to radiation therapy. The statistics (2,3) show that the local tumor control probability (TCP), regional lymph node control rate, distant metastasis-free rate, the 5-year tumor-free survival rate and the 5-year overall survival rate of intensity-modulated radiation therapy (IMRT) are approximately 85-95, 95-99, 80-88, 75-85 and 85-90%, respectively. With the development of imaging and radiotherapy technologies, the three-dimensional conformal radiotherapy (3D-CRT) has been found increasing applicable. The CT or the MRI were adopted for exact delineation of the target areas, as well as the calculation of radiation doses, fields of radiotherapy and other parameters. In addition, it also matches irradiation target areas to the shapes of tumor target areas in the three-dimensional directions and thereby to distribute radiation dose in target areas more reasonably and to reduce exposure of adjacent normal tissues to irradiation (4). The combined intracavitary brachytherapy (IBT) further improves the short-term and long-term effects of radiotherapy, and has high application values in the treatment of both primary and recurrent nasopharyngeal carcinoma (NPC) (5,6). The main aim of the present study is to analyze the application effects of the IMRT and the 3D-CRT in the treatment of nasopharyngeal carcinoma, and to provide reference for rational selection of the clinical treatment regimen.

Patients and methods

Patient data. A sample of 124 patients admitted to our hospital from January 2013 to March 2016 and was diagnosed with nasopharyngeal carcinoma pathologically, were selected. Following was the inclusion criteria: the patients without metastasis to distant organs and KPS scores ≥ 85 points, patients who had good treatment compliance and underwent required courses of treatments with complete clinical data and informed consents were obtained from them. Exclusion criteria: patients who had to terminate treatment due to the presence of radiotherapy contraindications, and serious complications of chemotherapy or radiotherapy, patients who voluntarily gave up treatment due to intolerance to chemotherapy or the presence of complications of chemotherapy, patients who could not be scored by scales or whose data could not be analyzed, patients suffering from other serious diseases, such as dysfunctions of heart, liver, lungs, kidney, brain and other organs. The study was approved by the Ethics Committee of

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Dezhou People's Hospital, and informed consents were signed by the patients and/or guardians.

The selected sample was randomly divided into the control group and the observation group according to their admission date, each group contained 62 patients. The control group included 39 males and 23 females, with an average age of 62.5 ± 14.4 years, 36 of whom were diagnosed as poorly differentiated squamous cell carcinomas, 24 were undifferentiated carcinomas, 2 were of other types of carcinomas. Furthermore, the stage I, II, III and IV of carcinomas were 4, 22, 31 and 5 respectively, and the average maximum diameter of tumors in this group was 3.3 ± 1.2 cm. The observation group was composed of 36 males and 26 females, with the average age of 61.8 ± 15.3 years, 35 of whom were diagnosed as poorly differentiated squamous cell carcinomas, 24 of undifferentiated carcinomas and 3 of other types of carcinomas. Moreover, the patients with stage I, II, III, IV of carcinomas were 5, 24, 27 and 6, respectively. The average maximum diameter of tumors in this group was 3.4 ± 1.3 cm; baseline data of the two groups were comparable.

Research methods. During this study, the radiotherapy and nursing team remained the same. The control 3D-CRT combined with postoperative chemotherapies were performed on the control group together with thoroughly preoperative examinations. Patients were scanned from the top of the head to the places 2 cm under clavicular heads by 64-Slice Spiral CT scanner, manufactured by GE Healthcare, with the distance between two slices of 3 mm, and then enhanced scanning was performed. The Olympus Master (Olympus, Tokyo, Japan) and the Nucletron BV (Nucletron, Veenendaal, Netherlands) software were applied for image fusion. The clinical target volume (CTV) of the primary tumor was 8-10 mm outside the gross tumor volume (GTV), if the tumor was close to the brainstem or spinal cord, whereas the irradiation margin could be expanded by 3 mm at the minimum. Due to errors in the system and set-up, planning target volume (PTV) was determined by expanding the irradiation margin of CTV by 3 mm. Preventive irradiation may not be performed to cervical lymph drainage areas. The involved organs included brainstem, spinal cord, optic nerves, optic chiasms, temporal lobe, pituitary, temporomandibular joint, eye balls, crystalline lens and parotid gland. The tolerance doses of involved organs were determined individually according to the dose of initial radiotherapy during the planning process and in accordance with tolerance range stipulated by RTOG. RTS[®] version 2.6.4 (Holland Nucletron), that was employed for the development of treatment plans. In addition, the isocenter coplanar irradiation technique was applied in this study with the isocenter point that was located at the center of GTV-P. Then, the study was evaluated according to the isodose line of the treatment plan and dose-volume histograms, and the minimum planning dose GTV-P was considered as at least 50 Gy (single fraction was 2 Gy/1.8 Gy, 1 time per day and 5 days per week). Furthermore, 5-7 coplanar irradiation fields were designed by Elekta accelerator and multi-leaf collimator. The postoperative chemotherapy of 20 mg/m² dl DDP, 2.2 g/m² dl 5-FU and 120 mg/m² dl calcium folinate per week, a total duration of 9 cycles was given to the patients.

On the observation group, the IMRT combined with postoperative chemotherapy were performed. The preoperative CT

scanning and image reconstruction, as well as the delineation of target areas and the involved organs were the same as in the control group. The definition of target areas was based on ICRU-50 and -62 reports, i.e. nasopharyngeal carcinoma areas including locations of primary tumors (GTVnx) and cervical lymph node metastasis areas (GTVnd). Clinical target volume (CTV) was 5-10 mm larger than tumor area and planning target volume (PTV) was 3-5 mm than CTV, which were modified according to the near anatomic structure. The prescription dose of GTV was 68-70 Gy with each fraction of 2.13-2.2 Gy, and the prescription dose of CTV was 58-60 Gy with each fraction of 1.85-1.88 Gy. The multi-leaf collimator was set at static intensity-modulated mode. The target areas were re-delineated and radiotherapy regimen was developed according to the specific situations of tumors after 20-25 times of radiotherapy. Chemotherapy regimen on the observation group was the same as the one for the control group.

Observation indexes. Clinical effective rates and complications rates between the two groups after 3 months of the treatment were compared. The follow-up duration ranged from 6.0 to 45.0 months with the median time of 25.5 months. The TCP, regional lymph node control rates, distant metastasis-free rates, tumor-free survival rates, recurrence rates and overall survival rates of two groups were compared. According to the Response Evaluation Criteria in Solid Tumors (RECIST), treatment effects were divided into complete remission (CR), partial remission (PR), stable disease (SD) and disease progression (PD). The CR indicated that all target lesions disappeared and no new lesions appeared, and tumor markers were normal for at least 4 weeks. The PR suggested that the sum of maximum diameters of target lesions reduced by at least 30% for at least 4 weeks. The SD indicated that the sum of maximum diameters of target lesions was between the criteria of PR and the criteria of PD. Finally, the PD suggested that the sum of maximum diameters of target lesions increased by at least $\geq 20\%$, or absolute value increased by 5 mm or new lesions emerged. The results were recorded according to the complications and grading of RTOG/EORTC radiotherapy.

The quality of life of patients was compared in three aspects by adopting SF-36 scale, such as physical, social and psychological functions. The total scores were 100 points. The higher score indicated the better quality of life.

Statistical analysis. Statistical analysis were performed, using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software. The measurement data was expressed by the mean \pm standard deviations, and the groups were compared using independent t-tests. On the other hand, the count data were expressed by the number of cases or percentage (%), and then comparisons among groups were analyzed by the χ^2 test. Ranked data were analyzed by non-parametric rank sum test. For all statistical tests, 5% level of significance was considered.

Results

Comparisons of clinical effective rates. The results show (Table I), that there was no statistical difference between the two groups in terms of total effective rate and effectiveness ($P > 0.05$).

Table I. Comparisons of clinical effective rates [number of case (%)].

Group	No. of cases	CR	PR	SD	PD	Total effective rate
Control group	62	20	28	9	5	57 (91.9)
Observation group	62	18	27	10	7	55 (88.7)
Z/ χ^2				-0.626		0.369
P-value				0.531		0.544

Table II. Comparisons of complication rates [number of case (%)].

Group	No. of cases	Skin and nasopharyngeal ulcer	Cranial nerve injury	Difficulty in opening mouth	Hearing loss	Xerostomia	Total complication rate
Control group	62	2	1	1	1	2	7 (11.3)
Observation group	62	2	1	0	1	2	6 (9.7)
χ^2							0.086
P-value							0.769

Table III. Comparisons of follow-up survival indexes [number of case (%)].

Group	No. of cases	TCP	Regional lymph node control rate	Distant metastasis-free rate	Tumor-free survival rate	Recurrence rate	Overall survival rate
Control group	62	55 (88.7)	5 (91.9)	50 (80.6)	45 (72.6)	6 (9.7)	60 (96.8)
Observation group	62	54 (87.1)	58 (93.5)	51 (82.3)	44 (71.0)	4 (6.5)	60 (96.8)
χ^2		0.076	0.000	0.053	0.040	0.435	0.000
P-value		0.783	1.000	0.817	0.842	0.510	1.000

Comparisons of complication rates. There was no statistical significant difference between the two groups regarding the radiotherapy complications ($P>0.05$) (Table II).

Comparisons of follow-up survival indexes. For follow-up survival indexes, the χ^2 test was performed and the results show (Table III) that there were no statistically significant differences between the two groups regarding TCP, regional lymph node control rate, distant metastasis-free rate, tumor-free survival rate, recurrence rate and overall survival rate ($P>0.05$).

Comparison of quality of life. The total scores of quality of life of the control group and the observation group were 82.5 ± 13.4 and 84.2 ± 15.6 at average, respectively. Based on two sample t-tests, no statistical difference between the two groups was found ($t=0.213$, $P=0.768$).

Discussion

Previously, Lai *et al* (7) studied 1,276 patients with nasopharyngeal carcinoma who were treated with the IMRT and two-dimensional conventional radiation therapy (2D-CRT), respectively, and found that the IMRT achieved much

better results than the 2D-CRT in 5-year local recurrence-free survival rate, lymph node recurrence-free survival rate, distant metastasis-free rate and disease-free survival rate. Moreover, Petsuksiri *et al* (8) conducted a study and found that IMRT induced less complication of inner ear dose-limiting sensorineural hearing loss than 2D-CRT did. The study conducted by Fang *et al* (9) on 203 patients with diagnosis of nasopharyngeal carcinoma and treated with 3D-CRT ($n=93$) and IMRT ($n=110$), respectively, showed that 3-year local tumor control probability, distant metastasis-free survival rate and overall survival rate of patients from IMRT group were not lower than those of patients from 3D-CRT group. A further study (10) showed that IMRT treated with multi-target processing technology achieved higher distribution uniformity of radiation dose to patients of all stages than 3D-CRT combined with IBT. In addition, IMRT treated with multi-target processing technology had better tumor coverage to patients with locally advanced tumors, improved their TCP and GTV dose while not exceeding tolerance doses of important tissues and structures (11). Moreover, a meta-analysis (12) proposed that the single mode of hyperfractionated radiotherapy improved overall survival periods of patients, but it only reduced planned total radiation doses of accelerated radiotherapy, especially of split-course

radiotherapy or hyperfractionated accelerated radiotherapy without improving overall survival rates.

Multivariate analysis in this context showed (13) that the delineation of IMRT target areas, dose distribution volumes of normal tissue structures and imaging technology reflecting tissue structures of target areas were the key factors influencing the local and the regional control rate, radiotherapy complications at the advanced stage and the quality of life of patients with nasopharyngeal carcinoma. Although IMRT improves local tumor control possibility and recurrence-free survival rate, however, it cannot increase overall survival rate significantly (14), which needs to be investigated further. In addition, the criterion of the delineation of IMRT target areas (15), and the relationship between the volume-dose distributions of the important tissues surrounding the target areas with the response of patients who have advanced cancer to radiotherapy (16) as well as the impact of reduced doses to tissue surrounding target areas on the local and the regional control rates, recurrence and metastasis (17) still need further verification. The present study shows that IMRT and 3D-CRT have almost the same short-term and long-term clinical effects in the treatment of nasopharyngeal carcinoma and both of them have high effectiveness and safety.

Local residues or recurrence and distant metastasis are important risk factors impacting long-term survival prognosis of patients (18). The re-irradiation, especially of re-intensity-modulated radiotherapy or stereotactic radiotherapy has certain application values (19). Popovtzer *et al* (20) conducted a retrospective study on 66 patients with recurrent head and neck squamous cell carcinomas where all of them had gone through 3D-CRT and IMRT with the average dose of re-irradiation of 68 Gy. It was found that 47 cases experienced local failures, furthermore, all of which occurred in 95% isodose regions of re-irradiation tumor target areas (RGTV) suggesting that it was very important to increase local residual or recurrent radiation doses and precisely locate radiotherapy target areas. Further clinical study based on larger sample size are still needed in order to determine the advantages and disadvantages of 3D-CRT and IMRT re-irradiation.

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