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Efficacy and safety of hypofractionated radiotherapy and conventional fractionated radiotherapy in the treatment of early breast cancer patients after breast-conserving surgery

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► ***Original article***

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ABSTRACT

Background: To compare the efficacy as well as safety of hypofractionated radiotherapy (HFRT) with conventional fractionated radiotherapy (CFRT) for the treatment of early breast cancer (EBC) patients after breast-conserving surgery (BCS). ***Materials and Methods:*** Clinical data of 126 early breast cancer patients diagnosed and treated in our hospital from March 2021 to June 2023 were retrospectively analyzed. Patients were divided into HFRT group and CFRT group. The CFRT group accepted conventional segment radiotherapy. The HFRT group accepted hypofractionated radiotherapy. The clinical effect, breast beauty effect, incidence of adverse reactions, duration of hospital stay, local recurrence as well as distant metastasis in two groups were compared. ***Results:*** The HFRT and CFRT group showed no statistical difference in total response rate, breast beauty effect, length of hospital stay, local recurrence and distant metastasis rate ($P>0.05$). The incidence of bone marrow suppression, acute skin adverse reactions and radiation pneumonia in the HFRT group was lower than that in the CFRT group ($P<0.05$). The advanced skin adverse reactions were not statistically different between groups ($P>0.05$). ***Conclusion:*** Conventional radiotherapy and hypofractionated radiotherapy have similar clinical efficacy and safety for early breast cancer patients after BCS, while hypofractionated radiotherapy with the advantages of less radiotherapy times, short course of treatment and higher safety is valuable for clinical treatment.

INTRODUCTION

Breast cancer is the most prevalent malignancy among females and the fifth cause of cancer-related death in China [1]. With the gradual promotion and application of early breast cancer screening in China, the detection rate of early breast cancer is increasing in recent years [2]. The early diagnosis and effective treatment significantly affects the prognosis of breast cancer patients [3]. In clinical practice, surgical intervention has been continuously and massively changed, which shifts from radical surgery to more patient-satisfying breast-conserving surgery (BCS). BCS can not only preserve the beauty of the breast, but also present similar therapeutic effect as modified radical surgery, and the quality of life of patients is significantly improved [4], and better than those receiving mastectomy [5]. Radiation therapy is considered as the standard treatment after breast conserving surgery [6]. Currently, the most commonly used radiotherapy scheme is to deliver 50 Gray (Gy) to the affected side of the whole breast, conventional division 1.8-2.0 Gy/times, 5 times per week, and then local supplement of 10-16 Gy in the tumor bed area, which is called conventional radiotherapy [7]. However, due to the long course of conventional radiotherapy, the economic burden of patients increases, and multiple radiotherapy affects the life quality of patients, and reduces the confidence for continuous treatment [8].

With the deepening of radiobiology research and the rapid development of radiotherapy technology, the hypofractionated radiotherapy (HFRT) mode which can shorten the course of treatment has attracted increasing attention [9]. Under the premise that the relative biological dose is equivalent to that of conventional fractioned radiotherapy, the dose of each fractioned radiotherapy is increased (>2 Gy/F), while the total dose of irradiation is reduced, so that the course of treatment can be shortened. The results of relevant studies indicate that the α/β value of breast tissue is about 4 Gy, which is equivalent to the late response tissue and is more sensitive to dose segmentation [10]. From the perspective of radiobiology, hypofractionated radiotherapy mode (>2 Gy/F) may be more effective for breast cancer [11]. The efficacy as well as safety of HFRT in early breast cancer patients is worth of our deep concern. In recent years, relevant clinical trials have shown that compared with conventional fractionated radiotherapy, the outcomes and cosmetic effect of hypofractionated radiotherapy on early breast cancer

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patients after breast conservation surgery are comparable. The radiotherapy response of normal tissues is not aggravated, and is even less severe than that of conventional fractionated radiotherapy [12]. Additionally, hypofractionated radiotherapy is indicated with more favorable survival outcomes and less adverse events relative to the conventional fractionated radiotherapy, suggesting its value for early breast cancer treatment in clinic [12].

Therefore, our study aimed to compare the efficacy as well as safety of HFRT with CFRT in treating early breast cancer patients after BCS. The findings of our work might provide novel clues for the formulation of treatment plans for early breast cancer patients.

MATERIALS AND METHODS

General data

Clinical data of 126 early breast cancer patients diagnosed and accepted therapy in our hospital from March 2021 to June 2023 were retrospectively analyzed. Patients were separated into HFRT group and CFRT group, with 63 cases in each group, according to postoperative radiotherapy methods. The general information of patients was provided in table 1. No significant difference was found in the general data between groups (P>0.05), indicating comparability. Inclusion criteria: (1) All were confirmed by pathological examination; (2) All patients conformed to the diagnostic criteria for early breast cancer; (3) The time of radiotherapy was 1 month after surgery. Exclusion criteria: (1) Serious medical system disease; (2) with a history of other tumors; (3) with distant metastasis.

Table 1. Clinical characteristics of patients.

Characteristics	HFRT (N=63)	CFRT group (N=63)	P
Age (years)	41.85±4.13 (37-47)	41.78±4.16 (35-46)	0.925
Histological types			0.957
Infiltrating ductal carcinoma	45	46	
Intraductal carcinoma	11	11	
Mucous carcinoma	7	6	
T stage			0.853
T1	23	22	
T2	40	41	
N stage			0.857
N0	35	36	
N1	28	27	

N, number; T, tumor; N, node.

Conventional segment radiotherapy group

Intensity modulated radiotherapy (IMRT) was adopted using the linear accelerators (Varian Medical Systems, USA), and the radiotherapy dose in tumor bed area and whole breast was 60.2 Gray (Gy) and 50 Gy, respectively, and totally 60.2 Gy/50 Gy/28 f, 5 times a week, 1 course of treatment per week, for a total of 6 courses of treatment (figure 1A).

Hypofractionated radiotherapy group

First, the IMRT simultaneous dosing technique was adopted, and the whole breast radiotherapy dose was 42.6 Gy / 16 f, and then the 9 mV electron wire was added to the tumor bed area. The dose was set as 10 Gy/ 4 f, 5 times a week, 1 course of treatment per week, for a total of 6 courses of treatment (figure 1B).

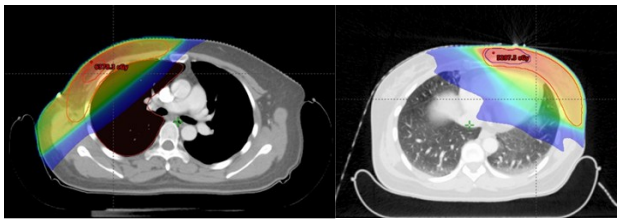

Figure 1. Representative images of HFRT and CFRT in breast cancer patients after breast-conserving surgery. **(A)** The breast cancer patient received the HFRT after breast-conserving surgery. **(B)** The breast cancer patient received the CFRT after breast-conserving surgery.

Observation indicators

(1) Clinical efficacy. Complete remission: the tumor lesion disappeared after treatment; Partial remission: the tumor lesion diameter decreased by more than 30% following treatment; Stable: the tumor lesion diameter decreased but did not meet the criteria of partial remission following treatment; Progressive: the tumor lesion diameter increased by more than 20% following treatment. Total response rate = complete response rate + partial response rate + stable rate.

(2) Breast beauty effect. Excellent: After treatment, the texture, size and shape of the breasts of patients were similar to that of the healthy breast or had slight differences, and the horizontal distance between 2 nipples was less than 2.0 cm; Good: After treatment, both sides of the patient breasts were asymmetrical, but not obvious. The appearance of the affected side was slightly different from that of the healthy side, and the horizontal distance between 2 nipples was less than 3.0 cm; General: After treatment, the patient suffered from severe breast deformation, which was significantly different from the healthy breast, but it was acceptable, and the two nipples were more than 3.0 cm apart. Poor: The patient could not accept the affected breast after treatment. Excellent and good rate = (excellent + good)/total cases ×100%.

(3) The incidence of adverse reactions, including bone marrow suppression, acute skin adverse reactions, advanced skin adverse reactions and radiation pneumonia, was evaluated using the acute radiation injury grading criteria formulated by the American Cancer Radiation Therapy Collaboration Group and the advanced radiation injury grading criteria formulated by the European Organization for Research and Treatment of Cancer.

(4) The length of hospital stay was compared between two groups.

[DOI: 10.61186/ijrr.23.1.163]

(5) The follow-up lasted for 6 months after treatment, and local recurrence as well as distant metastasis in 2 groups was compared.

Statistical analysis

SPSS statistical software (Version 20.0, SPSS Inc., USA) was adopted for data analyses. Measurement data were shown as the (x±s) and compared by t test. Statistical data were exhibited as [n (%)], and were analyzed by χ^2 test. P<0.05 indicated statistical significance.

RESULTS

Clinical efficacy of HFRT and CFRT in early breast cancer patients

For patients in the hypofractionated radiotherapy group, there were 32 complete remission cases (50.79%), 20 partial remission cases (31.75%), 6 stable cases (9.52%) and 5 progressive cases (7.94%). For those in the conventional segment radiotherapy group, there were 29 complete remission cases (46.03%), 19 partial remission cases (30.16%), 8 stable cases (12.7%) and 7 progressive cases (11.11%). The total response rate of the hypofractionated radiotherapy group was 82.54%, and was higher than that of the conventional segment radiotherapy group was 76.19%, with no statistical difference between HFRT and CFRT groups (P>0.05, table 2).

Breast beauty effect in two groups of patients

The breast beauty in two groups of patients after treatment was evaluated. For patients in the hypofractionated radiotherapy group, 30 cases presented excellent beauty effect, 21 cases showed good beauty effect, 9 cases showed general effect and 3 cases showed poor effect. For those in the conventional segment radiotherapy group, 28 cases presented excellent beauty effect, 17 cases showed good beauty effect, 12 cases showed general effect and 6 cases showed poor effect. The breast beauty effect of the hypofractionated radiotherapy group was 80.95%, and was higher relative to the conventional segment radiotherapy group (71.43%), while no statistical difference was found between the HFRT and CFRT groups (P>0.05, table 3).

Incidence of adverse reactions in two groups of patients

There were 23 bone marrow suppression cases (36.51%), 30 cases with acute skin adverse reactions (47.62%), 5 cases with advanced skin adverse reactions (7.94%) and 2 cases with radiation pneumonia (3.17%) in the HFRT group. For patients who received CFRT, there were 35 cases showed bone marrow suppression (55.56%), 45 cases showed acute skin adverse reactions (71.43%), 6 cases showed advanced skin adverse reactions (9.52%) and 12 cases showed radiation pneumonia (19.05%). The incidence of bone marrow suppression, acute skin adverse reactions and radiation pneumonia in the hypofractionated radiotherapy group was lower relative to the conventional segment radiotherapy group (P<0.05). No difference was found in advanced skin adverse reactions between the two groups (P>0.05, table 4).

Table 2. Clinical outcomes in two groups of breast cancer patients.

Groups	N	Complete remission	Partial remission	Stable	Progressive	Total response rate
Hypofractionated radiotherapy group	63	32	20	6	5	52 (82.54%)
Conventional segment radiotherapy group	63	29	19	8	7	48 (76.19%)
χ^2						0.78
P						0.38

N, number.

Table 3. Effects of HFRT and CFRT on breast beauty in two groups of breast cancer patients.

Groups	N	Excellent	Good	General	Poor	Excellent and good rate
Hypofractionated radiotherapy group	63	30	21	9	3	51 (80.95%)
Conventional segment radiotherapy group	63	28	17	12	6	45 (71.43%)
χ^2						1.58
P						0.21

N, number; HFRT, hypofractionated radiotherapy; CFRT, conventional fractionated radiotherapy.

Table 4. Incidence of adverse reactions after HFRT or CFRT in two groups of breast cancer patients.

Groups	N	Bone marrow suppression	Acute skin adverse reactions	Advanced skin adverse reactions	Radiation pneumonia
Hypofractionated radiotherapy group	63	23 (36.51%)	30 (47.62%)	5 (7.94%)	2 (3.17%)
Conventional segment radiotherapy group	63	35 (55.56%)	45 (71.43%)	6 (9.52%)	12 (19.05%)
χ^2		4.60	7.41	0.10	8.04
P		0.03	0.01	0.75	<0.01

N, number; HFRT, hypofractionated radiotherapy; CFRT, conventional fractionated radiotherapy.

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Length of hospital stay in two groups of breast cancer patients

The duration of patient hospital stay was 24.62±2.46 days in the HFRT group and 25.09±2.56 days in the CFRT group. Although patients receiving HFRT showed relative shorter hospital stay, there was no statistical difference between the two groups (P>0.05, figure 2).

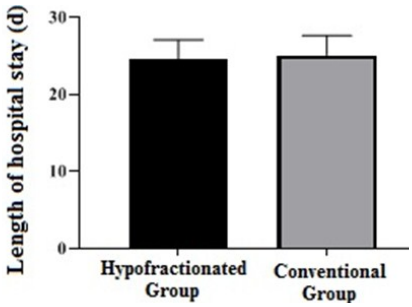

Figure 2. Length of hospital stay of breast cancer patients in both groups.

Local recurrence and distant metastasis rate in two groups of patients

As shown in table 5, in the HFRT group, 2 patients (3.17%) showed local recurrence and 4 patients (6.35%) showed distant metastasis. For patients who received CFRT, there were 3 local recurrence cases (4.76%) and 6 distant metastasis cases (9.52%). No statistical difference was found in local recurrence as well as distant metastasis between the two groups (P>0.05, table 5).

Table 5. Local recurrence and distant metastasis rate in breast cancer patients in both groups.

Groups	N	Local recurrence	Distant metastasis
Hypofractionated radiotherapy group	63	2 (3.17%)	4 (6.35%)
Conventional segment radiotherapy group	63	3 (4.76%)	6 (9.52%)
χ^2		0.21	0.43
P		0.65	0.51

N, number.

DISCUSSION

Breast-conserving surgery is considered as the first choice for early breast cancer patients due to its advantages of less intraoperative trauma, good postoperative aesthetic outcomes and high compliance [13]. Substantial literature has confirmed that radiotherapy after breast-conserving surgery can effectively increase the survival time of patients and reduce the risk of recurrence and metastasis [14]. The traditional conventional breast fractionated radiotherapy scheme means that each irradiation is 2.0 Gy, five times a week, and the total dose is 50 Gy, which can effectively control the tumor without increasing the acute radiation reaction, so as to effectively protect the normal tissue, and is widely applied in clinical practice [15]. However, due to the 6-7 weeks long treatment course and the low utilization rate of equipment, the cost of radiotherapy is easy to increase, and patient compliance and confidence of radiotherapy decrease, and the risk of local metastasis as well as recurrence increases [16].

Hypofractionated radiotherapy refers to irradiation 2 or more times a day, each dose is less than the conventional dose, the total dose is the same as the conventional dose, but the course of treatment is shortened [17]. The advantage is that it can overcome the accelerated regrowth of living stem cells of breast cancer in conventional fractionated radiotherapy, and can effectively control the rapid proliferation of breast cancer without increasing the adverse reaction of radiation [18]. On the one hand, the relative biological total dose is similar to conventional radiotherapy, and on the other hand, the single irradiation dose is increased to more than 2.0 Gy [19]. In the field of radiobiology, compared with conventional segmentation radiotherapy, large segmentation radiotherapy may be more capable of killing breast cancer cells, with greater radiological advantages [20].

Studies by foreign scholars have shown that early breast cancer patients can obtain good clinical benefits via the hypofractionated radiotherapy program, which is related to the potential doubling time of breast tumor cells (α/β value of breast tissue is about 4 Gy higher than the average value of tumor cells [21]. The α/β value of tumor cells and normal early-reaction tissues is about 8 to 10 Gy, while the α/β value of normal late-reaction tissues is only 2 to 3 Gy. The smaller α/β value indicates that the sensitivity of tissue response to single dose change is higher, and the degree of response increases with the increase of single dose [22]. However, the lower α/β value of breast tumor cells makes it possible to obtain better therapeutic effect by hypofractionated radiotherapy [23]. Multiple clinical reports have confirmed that the sensitivity of fractionated radiotherapy for breast cancer tissue is similar to that of normal breast tissue, and the same equivalent biological dose does not increase the damage of normal breast tissue, while the fractionated dose of >2 Gy is more beneficial to the breast cancer patients after surgery [24].

Clinical trials have also revealed that the HFRT shows similar efficacy and toxicities with CFRT for early or high-risk breast cancer patients [11, 25]. The adverse reaction incidence of hypofractionated radiotherapy was also not statistically different with that of the conventional fractionated radiotherapy [26, 27]. Consistently, in our study, the outcomes displayed no significant difference in total response rate (table 2), breast beauty effect (table 3), length of hospital stay (figure 2), local recurrence, as well as distant metastasis rate (table 5) between the two groups, indicating that hypofractionated radiotherapy had similar clinical efficacy with conventional

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radiotherapy, which was similar to previous studies [28, 29]. Besides, the incidence of adverse events such as bone marrow suppression, acute skin adverse reactions, and radiation pneumonia in the hypofractionated radiotherapy group presented lower relative to the conventional segment radiotherapy group. No significant difference in advanced skin adverse reactions between 2 groups (table 4). We not only revealed the safety of hypofractionated radiotherapy consistent to the previous findings, but also indicated the similar aesthetic outcomes as well as the hospital stay of patients. Moreover, the recurrence rate showed no statistical difference between the two treatment modalities, which was in line with the previous conclusions that hypofractionated radiotherapy is safe and cost-effective and shows similar clinical effects to conventional segment radiotherapy [21]. All these outcomes suggested that hypofractionated radiotherapy could lessen the occurrence of adverse reactions and had higher safety, which was in accordance with a previous study [30].

In conclusion, conventional radiotherapy and hypofractionated radiotherapy have similar clinical efficacy and safety for early breast cancer patients after BCS, while hypofractionated radiotherapy has the advantages of less radiotherapy times, short course of treatment and higher safety. However, due to the short follow-up time of this study and the insufficient sample size, the conclusions require to be confirmed by more and larger clinical studies.

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***Ethical consideration*:** This study was approved by the Ethics Committee of Pingxiang People's Hospital (approval number: SW-2022R155-HS02, March 02, 2022).

***Author contribution*:** J.T., conceptualized the study and wrote the original draft. X.X., M.C., L.L., Z.Z. collected the data and reviewed and edited the manuscript. All authors conducted the data analysis and approved the final version of the manuscript.

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