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Clinical observation of short-term efficacies of different hypofractionated radiation therapies after modified radical mastectomy for breast cancer

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Summary

The aims of this study were to analyze the acute and advanced responses of different hypofractionated radiation therapies (HFRT) after modified radical mastectomy for breast cancer (MRM-BC). A total of 162 patients were included into this prospective clinical Stage I-II study from October 2010 to May 2015, including 77 cases (group 42.5 Gy) and 85 cases (group 36.5 Gy). The acute and advanced side effects were analyzed according to static intensity modulation plan and Radiation Therapy Oncology Group (RTOG) classification criteria. There was no significant difference in the white blood cell reactions, acute skin reactions, and acute pharyngeal - esophageal reactions between group 42.5 Gy and 36.5 Gy, and no late complication was observed during follow-up. The median follow-up time of group 42.5Gy was 36 months and that of group 36.5 Gy was 12 months. There was no statistical significance in the local recurrence-free survival rate, disease-free survival rate, and distant metastasis rate between the two groups. There was no local recurrence or death in both groups (with the radiation field), and the local recurrence-free survival and overall survival rates of the two groups were both 100%. The incidence of acute adverse reactions and short-term efficacies of the two post-MRM-BC HFRT (42.5 Gy/16 F and 36.5 Gy/10 F) were similar, but the advanced adverse reactions and efficacies still need further observation.

Key words: Breast cancer; Modified radical mastectomy; Hypofractionated radiation therapy; Survival analysis.

Introduction

Breast cancer (BC) is one of common malignant tumors in women, with its incidence increasing annually and its mortality rate ranks second place in female malignancies in Western developed countries [1]. The incidence of BC in China also exhibits a gradually increasing trend, and new BC cases per year are about 200,000. The National Comprehensive Cancer Network (NCCN) guidelines suggest multiple reaction monitoring (MRM) for local advanced BC, as well as adjuvant chemotherapy plus postoperative adjuvant radiotherapy (AC-pAR). Eighteen randomized meta-analyses show that comprehensive treatments such as MRM or AC-pAR cannot only reduce tumor recurrence but also improve the overall survival (OS) of patients with axillary lymph node metastasis [2].

Conventional adjuvant radiotherapeutic mode is 50Gy/25 F/5W, but this model has many negative factors such as multiple hospital visit and high medical costs hypofractionated radiation therapies (HFRT) which cannot only obtain the similar or increased biological effects than conventional-dose fractionation, but also shorten therapeutic period, so it has been widely used in treating multiple tumors [3]; furthermore, it has been proven to be a safe, effective, and short-course radiotherapy mode [4]. BC tissues and tissues with normal late reactions have similar sensitivity to fractional doses, and their α/β values are approximately 4 Gy [5-7]. According to the theory of radiobiology and compared with conventional-dose fractionated mode, HPRT may be more effective; at the same time, it will not increase damages in normal late response tissues, so it can obtain higher therapeutic ratios [5].

In this study, the authors investigated and compared the acute and long-term side effects, as well as short-term efficacies, of two post-MRM-BC HFRT modes, and discussed the safety of HFRT in order to explore the best dose-fractionated model. This study was approved by the Ethics Committee of Chinese PLA General Hospital (No. S2014-001-02) and had been registered as one clinical stage I/II study (China Clinical Trials Registry No.: ChiCTR-ONRC-14004391).

Materials and Methods

The BC patients treated in the department of Radiation Oncology, the General Hospital of the People's Liberation Army, from October 2010 to May 2015 were collected, and all the patients underwent MRM and six- to eight-cycle adjuvant chemotherapy, as well as comprehensive baseline examination, before the radiotherapy.

Each patient was placed in one breast tray supinely and had

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fixed upwards their bilateral upper limbs. After recording the tray and headrest parameters, a CT scanner was used to perform normal scanning for positioning (from the lower edge of C1 until L1, layer thickness 5 mm). The images were then transferred into the Pinnacle Version 9.10 planning system for outlining the target area and surrounding normal organs referring to preoperative breast MRI and mammography. The target area and OAR outlining referred to International Commission on Radiation Units and Measurements 50 (ICRU50) [8], and the No, 62 report [9] was completed by resident physicians and revised by one chief physician; OARs covered the two lungs, skin, entire heart, esophagus within the target area, and spinal cord and healthy breast 10 cm within the target area. The PTV was identified by evenly extending CTV 6 mm outward, with its anterior boundary 3 mm to the skin and posterior boundary not exceeding the lesioned lung margin, and revised by the chief physician involved [10].

The prescription PTV doses of the two groups were 42.5 Gy/16 F and 36.5 Gy/10 F, respectively; at least 95% of the target volume was to be covered under the prescription dose, and <5% target volume mad to receive 110% of the prescription dose. The limit dosage of involved organs in group 42.5 Gy were designed as: lesioned lung V20 < 25%, healthy lung V5 < 15%, heart V30 < 10%, and healthy breast Dmax < 6 Gy. The limit dosage of involved organs in group 36.5 Gy were designed as: lesioned lung V16 < 20%, healthy lung V5 < 10%, heart V24 < 10%, and healthy breast Dmax < 5 Gy. After defining the prescription dose and limit dosage of involved organs, the images were transmitted into the Pinnacle Version workstation, and the treatment protocols were designed and verified by radiotherapists. The two groups were designed with intensity-modulated radiation therapy (IMRT) plans; chest group was given the four-field IMRT plan, and chest+supraclavicular group was given the five-field IMRT plan (all the plans were approved by the chief physician). Cone beam computed tomography (CBCT) scanning was performed before each treatment, which was firstly automatically registered according to the bony structure, followed by manual fine registration targeting the chest ± supraclavicular region according to the soft tissue structure, in order to better match the pre-treatment real-time image with the planned image. The treatment was implemented after the position errors were recorded by radio- therapists. No patient's treatment plan was revised during treatment.

The acute adverse reactions were defined as the side effects appeared from the beginning of radiotherapy within 90 days after the end of radiotherapy, and those appeared 90 days after the end of radiotherapy were defined as the late adverse reactions. All the patients were re-examined with chest CT, ultrasound of neck and supraclavicular fossa, ultrasound of breast and armpit, abdominal B ultrasound/CT, pelvic ultrasound/CT, and bone scan once every three months after radiotherapy, and once every six months two years after radiotherapy. The acute and late adverse reactions were evaluated according to the RTOG criteria (Table 1).

Statistical analysis was performed using the SPSS Statistics 22 statistical package. The matching property of basic information between the two groups was analyzed by the paired *t*-test, the rank-sum test, the exact test, or the χ^2 test. The incidence of acute adverse events was measured by the χ^2 test or the exact test; the single-factor analysis was used to exclude the variables that had relatively weaker correlation with the occurrence of acute and late responses ($p < 0.15$), and the logistic regression equation was used for further correlation analysis, with a $p < 0.05$ identified as statistical significance.

The primary end-point events of follow-up referred to clinical recurrence, including: local recurrence, regional lymph node metastasis, and distant metastasis. SPSS Statistics 22 was used for the analysis; the survival analysis used the Kaplan-Meier survival curve, with a $p < 0.05$ identified as statistical significance.

Results

The patients were enrolled in accordance with their admission sequence and the total 162 patients were grouped into Group 42.5 Gy (77 cases, from October 2010 to August 2013) and Group 36.5 Gy (85 cases, from September 2013 to May 2015). The basic situations of the patients are shown in Table 2; the intragroup difference showed good matching while no statistical significance.

Sixty-three patients (81.8%) in group 42.5 Gy and 51 patients (60.0%) in group 36.5 Gy showed no leukopenia. The incidence of grades I/II leukopenia in the two groups were 7.8% and 28.2% and 7.8% and 4.7%, respectively; group 36.5 Gy did not appear with grade IV leukopenia, while group 42.5 Gy had two cases of grade IV leukopenia. Forty-two patients (31.2%) in group 42.5 Gy and 49 patients (57.6%) in group 36.5 Gy did not show acute skin reactions.

Three patients (3.9%) in group 42.5 Gy had grade II skin reactions, while no patient in the two groups had serious grades III/IV acute skin reactions. Twenty-one patients (27.3%) in group 42.5 Gy and 14 patients (16.5%) in group 36.5 Gy had grade I pharyngeal-esophageal reactions. The two groups had two cases of grade II pharyngeal-esophageal reactions, respectively. There was no significant difference in the incidence of leukopenia, skin, or pharyngeal-esophageal reactions between the two groups. The acute reactions of the two groups are shown in Table 3.

The patients were further sub-grouped, according to whether the supraclavicular region was radiated, into subgroup C (chest) and S (chest + supra-clavicle), and the incidence of acute adverse reactions are shown in Table 4.

In Group 42.5 Gy, 35 patients (88.5%) in subgroup C and 32 patients (76.2%) in subgroup S did not have leukopenia, respectively. Subgroup C had two cases of grade II leukopenia (both patients with concurrent chemotherapy). Twelve patients in the two subgroups did not have acute skin reactions, respectively; two patients (5.7%) in subgroup C and one patient (2.4%) in subgroup S had grade II skin reactions. The incidence of leukopenia in subgroup S was higher than subgroup C (28.3% and 11.4%, respectively), but the difference was not statistically significant. The same results were also found in acute skin response between the two subgroups [subgroup S (71.4%) and C (65.7%)], and there was no statistically significant difference between the two groups. Subgroup C had no patient with pharyngeal-esophageal reactions, 20 patients (47.6%) in subgroup S did not have pharyngeal esophageal reactions, but 21 patients (50%) and one patient (2.4%) in subgroup S had grades I and II pharyngeal-esophageal reactions, respectively.

In Group 36.5 Gy, 32 patients (64.0%) in subgroup C and 19 patients (54.3%) in subgroup S did not have leukope-

Table 1. — *Evaluation criteria of RTOG radioactive responses*

Organ	Standards of RTOG Acute Radiation Injuries				
	Level 0	Level 1	Level 2	Level 3	Level 4
Skin	N/A	Follicle-like dark red spots / dry peeling / sweating decrease	Tenderness or bright red spots/ flake wet peeling / moderate edema	Fused wet peeling and depressive edema except for outside skin folds	Ulcers, bleeding, or necrosis
Pharynx and esophagus	N/A	Mild dysphagia or swallowing pain / requires narcotic analgesics/ requires liquid diet	Continuous hoarseness but can produce sounds / Implicated earache, sore throat, flaky fibrous exudation or mild laryngeal edema, while doesn't require anesthetic / cough, and requires antitussive	low talking sounds / Implicated earache and sore throat, and requires anesthetic / fused fibrous exudation, obvious laryngeal edema	Significant dyspnea, wheezing, hemoptysis /requires tracheotomy or intubation
Lungs	N/A	Mild dry cough or breathing difficulties when being tired	Persistent cough and requires narcotic antitussive/ slight activities can cause breathing difficulties while no breathing difficulty when resting	Severe cough, ineffective to narcotic antitussive, or occurs breathing difficulties during resting / has clinical or imaging evidence of acute radiation pneumonia /requires intermittent oxygenation or steroid therapy	Severe respiratory insufficiency / requires persistent oxygenation or assisted ventilation
Heart	N/A	Asymptomatic but with objective evidence of ECG changes; or has pericardial abnormalities while no other evidence of heart disease	Symptomatic, combined with ECG changes and imaging findings of congestive heart failure, or pericardial diseases / requires no special treatment	Congestive heart failure, angina pectoris, pericardial disease, may require antiepileptic	Congestive heart failure, angina pectoris, pericardial disease, arrhythmia, ineffective to non-surgical treatment
WBC ×1000	≥4.0	3.0-4.0	2.0-3.0	1.0-2.0	<1.0
Platelet ×1000	>100	75-100	50-75	25-50	<25 or autogenous hemorrhage
Neutrophil ×1000	≥1.9	1.5-1.9	1.0-1.5	0.5-1.0	<0.5 or septicaemia
neutrophil GM%	>11	9.5-11	7.5-9.5	5.0-7.5	----

Organ	Advanced radioactive injury criteria					
	Level 0	Level 1	Level 2	Level 3	Level 4	Level 5
Skin	n/a	Slight atrophy, pigmentation / slightly hair loss	Flaky atrophy / moderate telangiectasia / total hair loss	Significant atrophy / significant telangiectasia	Ulcer	Directly died of advanced cancer
Esophagus	N/A	Mild fibrosis / mild difficulty when swallowing solid food while without swallowing pain	Can't intake normal solid food / can eat semi-solid food / may have signs of expansion	Severe fibrosis / can only eat fluid food/ may have swallowing pain / requires expand	Necrosis / perforation / fistula	
Lung	N/A	Asymptomatic or mild symptoms (dry cough); slight imaging performance	Moderate symptomatic fibrosis or pneumonia (severe cough); low fever, imaging changes	Severe symptomatic fibrosis or pneumonia; dense imaging changes	Severe respiratory insufficiency / continuous oxygenation / auxiliary oxygenation	
Heart	N/A	Asymptomatic or mild symptoms of transient T wave inversion and ST segment changes, sinus tachycardia> 110 (resting)	Mild labor angina; mild pericarditis; normal heart size while with persistent abnormal T wave and ST changes; low QRS	Severe angina pectoris; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; normal ECG	Pericardial tamponade / severe heart failure / severe constrictive pericarditis	
Bone	N/A	Asymptomatic, no growth stagnation; bone mineral density decrease	Moderate pain or tenderness; growth stagnation; irregular bone sclerosis	Severe pain or tenderness; complete bone growth stagnation; dense bone sclerosis	Spontaneous necrotic fracture	

Table 2. — *Basic conditions of two groups.*

Clinical features	42.5 Gy		36.5 Gy		*p*
	Chest (n=35)	Chest+supra-clavicle (n=42)	Chest (n=50)	Chest+supra-clavicle (n=35)	
Age (years)					0.694
Range	35-68	30-77	27-65	25-63	
Median age	50	50	50	50	
T staging					0.458
T1	19 (54.3%)	22 (52.4%)	23 (46.0%)	8 (22.9%)	
T2	14 (40.0%)	18 (42.9%)	25 (50.0%)	24 (68.5%)	
T3	2 (5.7%)	2 (4.7%)	2 (4%)	3 (8.6%)	
N staging					0.345
N0	2 (5.7%)	0 (0%)	2 (4%)	0 (0%)	
N1	33 (94.3%)	0 (0%)	48 (96.0%)	0 (0%)	
N2	0 (0%)	32 (76.2%)	0 (0%)	26 (74.3%)	
N3	0 (0%)	10 (23.8%)	0 (0%)	9 (25.7%)	
TNM staging					0.209
IIa	20 (57.1%)	1 (2.4%)	23 (46.0%)	0 (0%)	
IIb	15 (42.9%)	2 (4.7%)	27 (54.0%)	2 (5.7%)	
IIIa	0 (0%)	28 (66.7%)	0 (0%)	21 (60.0%)	
IIIb	0 (0%)	1 (2.4%)	0 (0%)	3 (8.6%)	
IIIc	0 (0%)	10 (23.8%)	0 (0%)	9 (25.7%)	
Pathological staging				0.567	
I	1 (2.86%)	1 (2.4%)	3 (6.0%)	1 (2.9%)	
II	24 (25.4%)	29 (69.0%)	40 (80.0%)	22 (62.9%)	
III	10 (28.6%)	12 (28.6%)	7 (14.0%)	12 (34.2%)	
Site					0.332
Left	18 (51.4%)	27 (64.3%)	29 (58.0%)	19 (54.3%)	
Right	17 (48.6%)	15 (36.7%)	21 (42.0%)	16 (45.7%)	
ER, PR, Her-2					0.221
(- - -)	4 (11.4%)	3 (7.1%)	3 (6.0%)	2 (5.7%)	
(- -)	5 (14.3%)	15 (35.7%)	12 (24.0%)	6 (17.1%)	
(-)	11 (31.4%)	6 (14.3%)	9 (18.0%)	4 (11.4%)	
Endocrine therapy					0.214
Yes	27 (60.3%)	30 (60.3%)	35 (70.0%)	26 (74.3%)	
No	8 (39.7%)	12 (39.7%)	15 (30.0%)	9 (25.7%)	
Chemotherapeutical plan chemotherapy			0.683		
AC-T	28 (80.0%)	33 (78.6%)	36 (72.0%)	28 (80.0%)	
AC-TH	7 (20.0%)	9 (21.4%)	14 (28.0%)	7 (20.0%)	

Table 3. — *Comparison of acute reactions between two groups.*

Acute reactions	36.5 Gy (n=85)	42.5 Gy (n=77)	*p*
WBC			0.067
0	51 (60.0%)	63 (81.8%)	
I	24 (28.2%)	6 (7.8%)	
II	4 (4.7%)	6 (7.8%)	
III	6 (7.1%)	0 (0%)	
IV	0 (0%)	2 (2.6%)	
Skin reactions			0.061
0	49 (57.6%)	24 (31.2%)	
I	36 (42.4%)	50 (64.9%)	
II	0 (0%)	3 (3.9%)	
Pharyngeal-esophageal reactions			0.133
0	70 (82.3%)	55 (71.4%)	
I	14 (16.5%)	21 (27.3%)	
II	1 (1.2%)	1 (1.3%)	

nia, respectively. Subgroup C and S had 5 (10.0%) and 1 (2.8%) case of grade III leukopenia. Thirty patients in the two subgroups did not have acute skin reactions nor grade II or higher skin reactions, respectively. Although the incidence of leukopenia in subgroup S was higher than subgroup C (45.7% and 36.0%, respectively), the difference was not statistically significant. The same results were also found in acute skin response between the two subgroups (subgroup S (71.4%) and C (65.7%)), and there was no statistically significant difference between the two groups. Subgroup C had no patient with pharyngeal-esophageal reactions, 21 patients (60.0%) in subgroup S did not have pharyngeal-esophageal reactions, but 14 patients (40%) in subgroup S did not have grade I pharyngeal-esophageal reactions, but the difference was not statistically significant.

In this study, the acute lung reactions were mainly of

Table 4. — *Comparison of acute toxicity between subgroups of groups 42.5 Gy and 36.5 Gy.*

Acute toxicity	Group 42.5 Gy			Group 36.5 Gy		
	C (n=35)	S (n=42)	*p*	C (n=50)	S (n=35)	*p*
WBC			0.1414			0.1657
0	31 (88.5%)	32 (76.2%)		32 (64.0%)	19 (54.3%)	
I	3 (8.6%)	3 (7.1%)		12 (24.0%)	12 (34.3%)	
II	1 (2.9%)	5 (11.9%)		1 (2.0%)	3 (8.6%)	
III				5 (10.0%)	1 (2.8%)	
IV	0 (0%)	2 (4.8%)				
Skin reactions			0.6111			0.6590
0	12 (34.3%)	12 (28.6%)		30 (60.0%)	19 (54.3%)	
I	21 (60.0%)	29 (69.0%)		20 (40.0%)	16 (45.7%)	
II	2 (5.7%)	1 (2.4%)				
Pharyngeal-esophageal reactions		<0.0001			<0.0001	
0	35 (100%)	20 (47.6%)		50 (100%)	21 (60.0%)	
I	0 (0%)	21 (50.0%)		0 (0%)	14 (40.0%)	
II	0 (0%)	1 (2.4%)				

Table 5. — *Single-factor analysis of acute toxicity-related factors.*

Factor	WBC (*p*)	Skin reactions (*p*)	Pharyngeal-esophageal reactions (*p*)	Lung (*p*)
Age	0.769	0.823	0.904	0.823
T staging	0.650	0.243	0.531	0.243
N staging	0.209	0.529	<0.001	0.529
TNM staging	0.238	0.745	<0.001	0.745
Pathological staging	0.450	0.652	0.169	0.652
ER	0.164	0.111	0.108	0.161
Endocrine therapy	0.369	0.376	0.123	0.376
Chemotherapy protocol	0.061	0.572	0.496	0.572

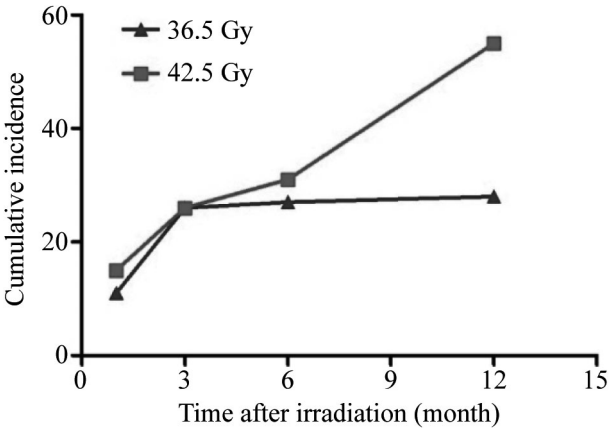

Figure 1. — Changes of lung reactions over time.

Table 6. — *Logistic regression analysis of acute toxicity-related factors.*

Pharyngeal-esophageal reactions	RR	95% CI	*p*
N staging	0.946	0.896-0.998	0.043
TNM staging	2.167	0.750-6.265	0.153

grade I, and no grade II/III lung reactions occurred. Three months after the end of radiotherapy, 15 patients in group 42.5 Gy (19.5%) and group 36.5 Gy (17.6%), respectively, revealed local radioactive fibrosis by chest CT, which appeared as cloudy or patching shadows close to the lesioned lung, but no patient showed clinical symptoms (such as cough, fever, breathing difficulty, etc.).

Table 5 shows the results of the single-factor analysis and logistic regression. The related factors included the age, tumor grade, T staging, ER status, N staging, endocrine therapy, TNM staging, and chemotherapy protocols, etc. The single-factor analysis showed that the chemotherapy protocol was associated with leukopenia, the ER status was associated with skin reactions, and the T staging and TNM staging were associated with pharyngeal-esophageal reactions. The results of the logistic regression obtained after substituting the related single factors into showed that only N staging was positively correlated with pharyngeal-esophageal reactions: the later the N staging, the more severe pharyngeal-esophageal reactions, but the correlation was weak with the RR close to 1 (0.946) (Table 6).

The single-factor analysis did not reveal factors associated with acute lung reactions. The incidence of adverse pulmonary reactions in group 36.5 Gy did not increase with the post-radiotherapy period, but the incidence of adverse pulmonary reactions in group 42.5G significantly increased with the post-radiotherapy period (Figure 1).

Due to short follow-up duration, no other late adverse reaction was observed, except for lung injury, in the two groups during the follow-up period (such as skin fibrosis, heart damage, or rib fracture, etc.).

No patient in both groups exhibited local recurrence

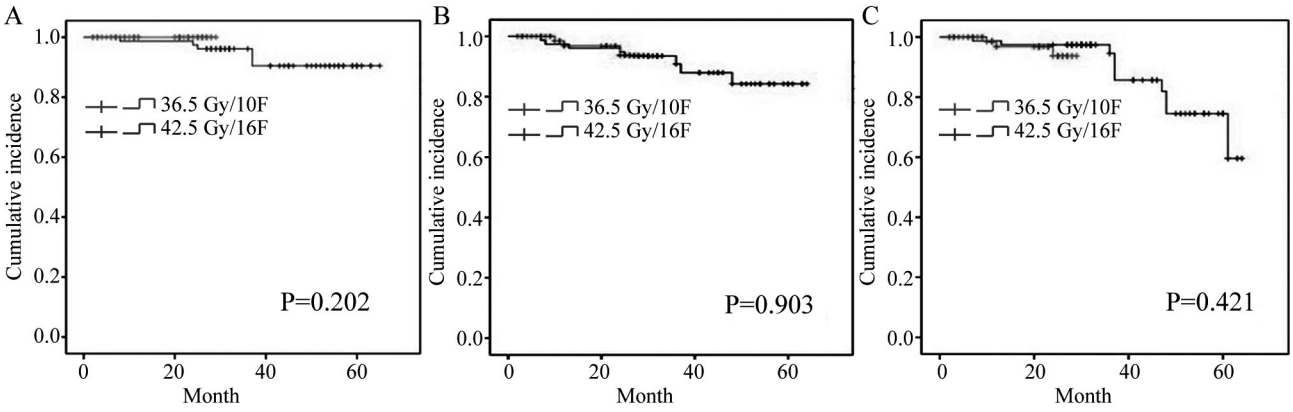

Figure 2. — A: Local recurrence-free survival rates; B: Disease-free survival rates; C: Distant metastasis-free survival rates.

(within the radiation field) nor died, and the local recurrence-free survival and overall survival rates of two groups were both 100%. In group 42.5 Gy: the median follow-up time was 36 (26-61) months, the two- and three-year local recurrence-free survival rates were 97.4% and 90.5%, the two-, three-, and four-year disease-free survival rates were 94.8%, 87.9%, and 84.3%, and the two-, three-, and five-year distant metastasis-free survival rates were 94.5%, 74.5%, and 59.6%. In group 36.5 Gy: the median follow-up time was 12 months (5-24 months due to short admission time), the one-year local recurrence-free survival rate was 100%, the one- and two-year disease-free survival rates were 96.8% and 93.7%, and the one- and two-year distant metastasis-free survival rates were 96.8% and 93.7%. The differences between the two groups showed no statistical insignificance (Figure 2).

Discussion

HFRT increases the dose of single irradiation (>2 Gy/time), while the total irradiation dose is reduced and the treatment time is shortened, but the bio-effect dose is equal to or greater than conventional fractionated radiotherapy [11, 12]. In recent years, it has been widely used in lung cancer, hepatocellular carcinoma, or prostate cancer; the effect is not inferior to conventional fractionated radiotherapy, and the adverse reactions are not increased, so HFRT may become one safe and efficient postoperative adjuvant radiotherapeutic mode [13-16]. Cytokinetic studies have shown that BC tissues have a potential doubling time higher than average, which supports HFRT for BC in theory [17]. At the same time, clinical studies also reveal that post-MRM-BC HFRT does not increase radiotherapy injury in late reaction tissues [18, 19].

The UK conducted a series of studies in 1986, and the results obtained from a total of 5,000 patients revealed that the two HFRT modes of 41.6 Gy/13 F (3.2 Gy/F) and 40 Gy/15F (2.67 Gy/F) are feasible, and their efficacies and adverse reactions are the same to those in conventional dose-fractionated modes, but they can significantly reduce treatment times [20].

Presently, multi-centric studies abroad have shown that HFRT is safe and feasible for breast-conserving surgery in early BC. One of the most famous is the British START study [18, 21, 22]. The most famous START Study A (the UK) enrolled a total of 2,236 patients and randomly grouped them for two HFRT modes (39 Gy/13 F/5W and 41.6 Gy/13 F/5W) and one conventional fractionated mode (50 Gy/25 F/5W), the results showed that the five-year local LR rates were 5.2%, 3.5%, and 3.6% ($p > 0.05$), and the ten-year LR rates were 8.8%, 6.3%, and 7.4% ($p > 0.05$). The START Study B also enrolled a total of 2,215 patients and randomly grouped them for one HFRT mode (40 Gy/15 F/3W) and one conventional fractionated mode (50 Gy/25 F/5W), and the five-year RRFSs were 97.8% and 96.7% ($p > 0.05$), together with the ten-year RRFSs as 95.7% and 94.5% ($p > 0.05$). The probabilities of radiotherapy-associated adverse events in group 39 Gy/13 F/5W (START A) and group 40 Gy/15 F/3W (START B) were significantly lower than that in Group 50 Gy/25 F/5W, while group 41.6 Gy/13 F/5W and 50 Gy/25 F/5W in START Study A showed no significant difference in the radiotherapy-related adverse reactions. The rates of skin appearance changes in group 39 Gy/13 F/5W (START A) and group 40 Gy/15 F/3W (START B) were significantly lower than group 50 Gy/25 F/5W, while the rates of skin appearance changes in group 41.6 Gy/13 F/5W and 50 Gy/25 F/5W (START A) showed no statistical significance. A prospective study in France enrolled a total of 84 patients from 2000 to 2012, and group HFRT (23 Gy/ 4F/17 d) had two cases (4%) of grade-III fatigue, 32 cases (38%) of grade-I skin reactions, and 63 cases (75%) with a good cosmetic effect [23]. One Canadian author [24] compared the cosmetic effect of 612 patients with 50 Gy/25 F/5W with 622 patients with 42.5 Gy/16 F/4W applied after breast-conserving surgery, and the ideal cosmetic effect in the two

groups was 71.3% and 69.8%, respectively. Ciammella *et al*. [25] applied HFRT 40.05 Gy/15 F/3W (2.67 Gy/F, 5 F/W) to treat patients with early BC after their breast conserving surgery, among whom the tumor bed of 55 patients was supplemented with 9 Gy/3 F. At the end of the radiotherapy, 35 patients (about 16%) did not have acute reactions, and the rates of grades-I and II acute reactions were 68% and 15%, respectively. The median follow-up time was 34 months (the shortest observation time was ≥ 8 months); the rates of grades I and II late acute reactions were 18% and 1%, respectively. No serious late skin reaction occurred, but the rates of late grade 0-I, II, and III breast fibrosis were 98.1%, 1.4%, and 0.5%, respectively; 93% of the patients achieved a subjective and an objective good or favorable cosmetic effect. Therefore, it can be seen that HFRT after BC, breast- conserving surgery can achieve the same clinical effect to conventional fractionated modes, while it does not increase the acute and long-term side effects; furthermore, it also can significantly shorten the treatment course and reduce the treatment cost, so it can be used as an alternative postoperative radiotherapy program.

At present, international studies regarding post-MRM HFRT are less. Ko *et al*. [26] observed 131 patients with 40 Gy/16 F (5 F/W) for chest radiotherapy (the median follow-up time was 5.3 years); the acute skin reaction predominantly were of grade I, the rate of grade II was 10.7%, and no grade III reactions occurred. Budach *et al*. [27] retrospectively analyzed four randomized studies (a total of 7,095 patients) with the main end-point of observation as ipsilateral BC recurrence, as well as their adverse reactions, and found that compared with the patients undergoing conventional fractionated radiotherapy, the HFRT mode (40 Gy/15 F) is safe and reliable for most patients requiring postoperative adjuvant radiotherapy for BC, but whether HFRT can be conducted in young patients (< 40 years), after neoadjuvant chemotherapy, or for regional lymph nodes still needs further data support.

In this study, most patients were not observed with severe acute adverse reactions during treatment, and there was no statistical significance in the incidence of acute adverse reactions between the two groups; 81.8% and 60.0% of the patients in group 42.5 Gy and 36.5 Gy did not have leukopenia, respectively, and only two cases in group 42.5 Gy had grade IV leukopenia. The retrospective analysis of the medical records of these two patients revealed that they were given docetaxel simultaneously in the eighth cycle of the radiotherapy, so leukopenia is mainly considered the side-effect of this chemotherapy. The serious adverse reactions in rare cases cannot be considered as the result of HFRT. Only three patients in group 42.5 Gy had grade II skin reactions, while no patient in the two groups had grade III~IV acute skin reactions. The incidence of grade I acute pharyngeal-esophageal reactions in groups 42.5 Gy and 36.5 Gy was 27.3% and 16.5%, respectively, and only one patient in the two groups, respectively, had grade II pharyngeal-esophageal reactions.

Through analyzing the results between the two subgroups, it can be seen that the two patients in group 42.5 Gy with grade IV leukopenia were both in subgroup S. In addition, the incidence of leukopenia in subgroup S was higher than Subgroup C (28.3% *vs.* 11.4%, but the difference was not statistically significant). Besides the radiation range of subgroup S was larger than that in subgroup C, the esophagus of the patients in subgroup S was also radiated by a certain dose can be one possible reason, which resulted in acute pharyngeal-esophageal reactions (subgroup C had no case of acute pharyngeal-esophageal reactions), and caused the adverse impact on patients' eating, nutritional status, and leukopenia. Similar results were also found in acute skin reactions (71.4% in subgroup S and 65.7% in subgroup C). Although there was no significant difference between the two groups, grade II acute skin reactions more occurred in subgroup S. The possible explanation may be that the radiotherapy tolerance of chest skin is superior to the supraclavicular skin. Similar results were also observed in subgroup 36.5 Gy, and the reasons may be the same to group 42.5 Gy.

Compared with clinical HFRT trials in most BC cases [27-29], the incidence of adverse reactions in this study is relatively low. The possible reasons may be: (1) the authors performed image-guided radiation therapy (IGRT) to correct the positioning error before each treatment, and because the extending margin of CTV-PTV is smaller, it can reduce the dose and exposure volume that may endanger lesioned organs, (2) pre-treatment image-guiding reduces the dose and volume against lesioned lung and heart, and (3) this study used IMRT, which also reduces the dose and volume against lesioned organs. Studies about HFRT againstage I/II BC normally use 3D-CRT techniques, and the incidences of acute skin and hematologic reactions reported are mostly within 55~65% and 50~60%, respectively, but grades III~IV adverse reactions are less [30-32]. Compared with 3D-CRT, IMRT undoubtedly has a better target fit, so in order to improve the local control rate, some clinical trials have used IMRT to give higher prescription doses, and although their adverse reactions did not decrease compared to conventional fractionated radiotherapy, the incidence of serious side effects was lower and within tolerable ranges [33-35]. There have been a wide variety of dose-fractionation modes reported in clinical trial designs, but no consensus has been achieved on the best dose-fractionation mode for post-MRM adjuvant radiotherapy. This study compared the two HFRT modes, aiming to explore the most effective and safe dose-fractionation mode, and it can be seen from the current results that the two modes both exhibited good tolerance.

Shortcomings of this study are: (1) the authors mainly observed the treatment safety, but the sample size is small so this study lacks convincing analysis toward the survival status and (2) the follow-up time is short; the present au-

thors' next study will further expand the sample size and extend the follow-up time for more accurate results, and (3) no group with conventional fractionated radiotherapy was set, and in our further studies, we should consider grouping the patients into such for further comparison.

Conclusions

The short-term observation of this study shows that post-MRM-BC HFRT cannot only significantly shorten the radiotherapy time and save patients' time and economic expenses, but also save social medical resources and costs; furthermore, its efficacies and adverse reactions are equivalent to the data of conventional fractionated radiotherapies conducted in the present center and reported in literatures, suggesting that HFRT can be one mode for MRM-BC. The present center will further assess its late adverse effects and efficacies.

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