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Post-mastectomy hypofractionated versus conventionally fractionated radiation therapy for patients receiving immediate breast reconstruction: Subgroup analysis of a phase III randomized trial

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Introduction

Post-mastectomy radiation therapy (PMRT) has been proved to improve loco-regional control, and disease-free survival (DFS) for patients with large tumors and/or positive axillary nodes [1,2]. Despite the oncological benefits, numerous studies have shown that PMRT using conventional fractionation confers negative impact on reconstructed breasts in the setting of immediate breast reconstruction (IBR) [3–6]. As compared to conventionally fractionated (CF)- PMRT, a moderately hypofractionated (HF)- regimen is demonstrated to provide equivalent disease control for patients with high-risk breast cancer in a randomized phase 3 trial [7,8]. However, patients who had IBR were excluded from the trial [7]. Currently, it's of great interest to know whether hypofractionation for PMRT instead of conventional fractionation compromises the safety of reconstructed breasts. Several studies have explored the use of HF-PMRT and showed preliminary feasibility [9–12], however, data on the reconstruction complications following HF-PMRT for patients undergoing IBR remains limited.

We initiated a phase III randomized trial comparing HF- with CF-PMRT to the chest wall and regional nodes, and allowed to enroll patients with various types of IBR. Here we report the complications of the reconstructed subgroup.

Materials and methods

Study design and participants

This study is a part of the randomized, non-inferiority, open-label, phase III trial (FDRT-BC008), which is registered at ClinicalTrials.org, number NCT03856372, with patients recruited from a single academic hospital (Fudan University Shanghai Cancer Center) in Shanghai, China. Patients were eligible to be included if they were women aged 18–70 years; had histologically proven invasive breast cancer, underwent mastectomy with negative margins and standard axillary dissection (≥10 lymph nodes); had 1–3 positive axillary lymph nodes with at least one clinical or pathological factor predicted for an increased risk of locoregional recurrence, including a younger age, histological grade 3, tumor size measuring 3–5 cm, 2–3 positive nodes, and negative hormone receptor, or had ≥4 positive nodes; and had no contraindications to adjuvant systemic therapy and radiotherapy. Immediate implant-based reconstruction with either direct placement of a permanent implant (PI) (i.e., single-stage DTI) or a temporary tissue expander (TE) followed by later placement of a PI (i.e., two-stage TE/I), or autologous tissue (AT) reconstruction was allowed. Patients were excluded if they were male, had bilateral breast cancer, presented with metastasis to supraclavicular region, internal mammary, or distant organs, had previous thoracic or regional nodal irradiation, had previous or concurrent other malignancies except for non-melanoma skin cancer, were pregnant, received neoadjuvant systemic therapy, or had serious non-malignant

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diseases, such as active collagen vascular disease or other comorbidities that precluded radiotherapy. The clinical staging work-up included physical examinations and diagnostic imaging studies to exclude local–regional and distant disease. All patients provided written informed consent for treatment and use of their data for research purposes before enrollment. The study protocol was approved by the institutional ethical committee.

Randomization and masking

Eligible participants were randomly allocated (1:1) to either HF- or CF-PMRT group according to a computer-generated randomization sequence. Before randomization, patients were stratified by primary tumor (T) stage (T1-2 vs. T3-4), nodal (N) stage (N1 vs. N2-3), molecular subtype (HR+/HER2- vs. HR+/HER2+ vs. HR−/HER2+ vs. HR−/HER2−); and patients who underwent IBR were stratified according to the type of breast reconstruction irradiated (AT vs. PI vs. TE) at randomization, but modification was made according to other stratification factors. Patients and clinicians were unmasked to treatment allocation. The study scheme is shown in Fig. 1.

Procedures

At computed tomography (CT) simulation, each patient was placed supine on a breast board with both arms fully abducted and head secured. CT scans were acquired with a slice thickness of 5 mm from upper neck to upper abdomen. The clinical target volume (CTV) for the ipsilateral chest wall and regional lymph nodes areas, including interpectoral space (Rotter's nodes), infraclavicular region, supraclavicular region, and internal mammary nodes (IMNs), was contoured per the ESTRO contouring guideline [13,14]. The planning target volume (PTV) was created by expanding a 5 mm margin to the CTV. In the setting of TE/I, PMRT was given to fully inflated TEs according to our clinical practice. A simple intensity-modulated RT (IMRT) plan was designed using Pinnacle or Eclipse treatment planning system (TPS). The prescribed dose to the PTV was 42.56 Gy in 16 fractions (2.67 Gy per fraction) for HF-PMRT group, and 50 Gy in 25 fractions (2 Gy per fraction) for CF-PMRT group. A mastectomy scar boost was allowed for patients with T4 disease or close margins. Planning objectives included achieving a homogeneous dose throughout the target volume with the requirement that the maximum dose in the target be no greater than 110 % of the prescribed dose, and minimizing radiation to normal tissues per our institutional guidelines. The treatment was performed using Elekta or Varian linear accelerators daily from Monday to Friday. A 3 mm tissue-equivalent bolus over the entire chest wall was used up to 60 % of the total prescribed dose.

According to international guidelines, adjuvant chemotherapy was given to all patients, hormonal therapy was given to HR-positive patients, anti-HER2 targeted therapy was given to patients with HER2 positive disease. PMRT was delivered 2–4 weeks after completion of adjuvant chemotherapy, while no concomitant administration was allowed.

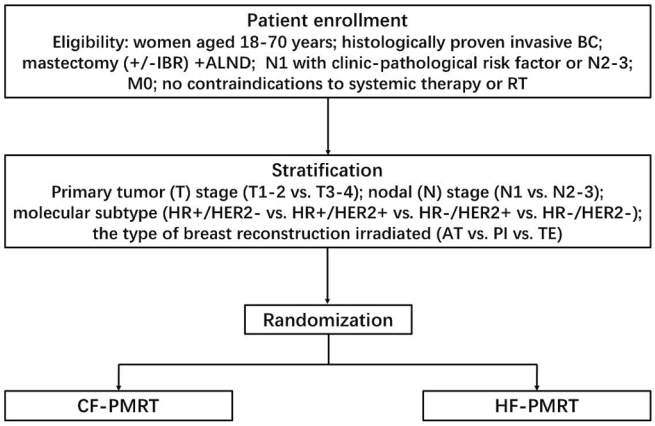

Fig. 1. Study scheme.

Outcomes

The primary endpoint was loco-regional recurrence (LRR), and the secondary endpoints included distant metastasis (DM), disease-free survival (DFS), overall survival (OS), acute/late normal tissue effects, reconstruction complications, and implant-related complications.

Specifically, reconstruction complications include surgical site infection, wound dehiscence, skin necrosis, fat necrosis, and seroma or hematoma requiring surgical intervention such as debridement, suture and washout; whereas implant-related complications include implant rupture or exposure, capsular contracture (CC), implant removal, and conversion to AT reconstruction, while focusing on reconstruction failure (RF) and CC. For RF, two endpoints were considered: "definitive RF" was defined as implant removal without replacement or salvage reconstruction, and "total RF" was defined as implant removal regardless of the replacement or salvage reconstruction. The CC was assessed using the Baker scale [15,16].

Statistical analysis

The primary hypothesis of this trial was that 5-year LRR with HF-PMRT is non-inferior to that with CF-PMRT. 5-year LRR in the CF group was assumed to be 7 % on the basis of pervious results in similar patient groups. A maximum loss of efficacy of 4 % in the HF group was accepted; that is, HF-PMRT would be considered non-inferior to CF-PMRT if 5-year LRR in the HF group did not exceed 11 %, with a non-inferiority margin of 4 % (equivalent to a hazard ratio [HR] of $<$1.88). Under assumed LRR rates and guarding against 5 % ineligibility or loss to follow-up, we expected a final target accrual of 1494 patients to provide at least 80 % power, with a one-sided significance level of 0.05. The choices of the statistical significance and power were made to provide an appropriate compromise between feasibility and statistical rigour. The accrual will terminate until the sample size is reached, and the termination time does not depend on the number of patients undergoing IBR enrolled.

For the reconstructed subgroup, patient characteristics were described as medians and ranges for continuous variables, and as frequencies and percentages for categorical variables using descriptive method. Patients were divided into 2 groups according to the fractionation of PMRT, and stratified according to the type of reconstruction irradiated. Between the study groups, comparisons were done using the Pearson's chi-square test or Fisher's exact test for categorical variables. Nonparametric estimates of the LRR, DFS, and RF were estimated using the Kaplan-Meier method, and the log-rank test was applied to assess differences between groups. A p-value of less than 0.05 was considered statistically significant. All the analyses were performed using the statistical software SPSS 25.0.

Results

Patients

From Sep 2018 to July 2022, a total of 1494 patients were enrolled onto the trial. Among them, 136 patients received IBR, including 22 with AT reconstruction, 27 with DTI, and 87 with TE/I at the time of mastectomy. Before randomization, 4 patients with TE had completed substitute of PI.

After randomization, three patients including one with PI and two with TE withdrew informed consent before receiving PMRT, and were excluded from analysis. The final cohort consisted of 133 patients,

including 22 with AT irradiated, 30 with PI irradiated, and 81 with TE irradiated. AT reconstruction included the transverse rectus abdominis muscle (TRAM) (n = 3), the latissimus dorsi (LD) muscle (n = 13), and the deep inferior epigastric perforators (DIEP) (n = 6) flaps. All implants including TE or PI were positioned posterior to major pectoral muscle.

Of the final patient cohort, 67 patients were assigned to CF group, including 11 with AT, 15 with PI, and 41 with TE; and 66 patients assigned to the HF group, including 11 with AT, 15 with PI, and 40 with TE. Table 1 compares patient and treatment-related characteristics between groups. The two groups of irradiated patients were well-balanced with similar age, menopausal status, and laterality distribution, and no significant differences in tumor size, histology, grade, nodal, or hormonal receptor status. Overall, most patients were young, premenopausal women with pathologically staged T1-2N1-2 disease. All patients received recommended adjuvant systemic therapy.

Disease control and survival

The median follow-up time was 38.1 (range: 21.2–63.4) months and 39.5 (range: 22.6–65.8) months for CF group and HF group, respectively. In the CF group, one patient developed supraclavicular recurrence with concomitant DM to liver, and one had DM to lung only; whereas in the HF group, none experienced any recurrence. The 3-year LRR was 3.6 % in the CF group versus 0 % in the HF group (p = 0.285). The 3-year DFS was 95 % in the CF group and 100 % in the HF group (p = 0.145). Until the last follow-up, two patients had died of breast cancer in the CF group. The 3-year OS was 97.5 % in the CF group, compared with 100 % in the HF group (p = 0.142).

Table 1
Patient and treatment-related characteristics (n = 133).

Variables	Value		p-value
	CF (n = 67)	HF (n = 66)	
Age (years), median (range)	38 (26–69)	39 (27–57)	0.799
Menopausal status			
Pre-	62 (92.5 %)	62 (93.9 %)	0.935
Peri-	1 (1.5 %)	1 (1.5 %)	
Post-	4 (6.0 %)	3 (4.5 %)	
Side			
Left	33 (49.3 %)	35 (53.0 %)	0.663
Right	34 (50.7 %)	31 (47.0 %)	
Histology			
IDC	61 (91.0 %)	62 (93.9 %)	0.261
ILC	6 (9.0 %)	2 (3.0 %)	
Others	0 (0)	2 (3.0 %)	
Histological grade			
G2	38 (56.7 %)	31 (47.0 %)	0.516
G3	26 (38.8 %)	32 (48.5 %)	
Unknown	3 (4.5 %)	3 (4.5 %)	
Primary tumor (T) stage			
T1	21 (31.3 %)	17 (25.8 %)	0.759
T2	41 (61.2 %)	43 (65.2 %)	
T3	5 (7.5 %)	6 (9.1 %)	
Nodal (N) stage			
N1	37 (55.2 %)	37 (56.1 %)	0.548
N2	20 (29.9 %)	23 (34.8 %)	
N3	10 (14.9 %)	6 (9.1 %)	
Molecular subtype			
HR+/HER2−	42 (62.7 %)	42 (63.6 %)	0.329
HR+/HER2+	10 (14.9 %)	14 (21.2 %)	
HR−/HER2+	8 (11.9 %)	8 (12.1 %)	
HR−/HER2−	7 (10.4 %)	2 (3.0 %)	
Type of mastectomy			
SSM	58 (86.6 %)	60 (90.9 %)	0.605
NSM	9 (13.4 %)	6 (9.1 %)	
Type of reconstruction irradiated			
AT	11 (9.8 %)	11 (9.8 %)	0.914
PI	15 (22.5 %)	15 (22.5 %)	
TE	41 (60.9 %)	40 (60.9 %)	
Adjuvant systemic therapy			
Hormonal therapy	52 (77.6 %)	56 (84.8 %)	0.286
Chemotherapy	67 (100 %)	66 (100 %)	1.000
Anti-HER2 therapy	18 (26.9 %)	22 (33.3 %)	0.416

Abbreviations: IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; SSM: skin-sparing mastectomy; NSM: nipple-sparing mastectomy; AT: autologous tissue; PI: permanent implant; TE: temporary expander; CF: conventional fractionation; HF: hypofractionation.

Complications

The median follow-up for assessment of reconstruction complications was 38.1 (range: 21.2–65.8) months for the whole cohort; and the median time to occurrence for any type of reconstruction complication was 5.8 (range: 1.6–14.8) months and 4.6 (range: 2.2–11.7) months after initiation of PMRT in the HF and CF groups, respectively (p = 0.69). Table 2 shows the absolute incidence of reconstruction complications per reconstruction type. The reconstruction complication is more common for patients with TE irradiated, then for patients with PI irradiated, and uncommon for patients with AT irradiated. No significant differences were found between HF and CF groups, for any of the reconstruction types.

Table 3 compares the implant-related complications. Among patients with PI irradiated, 13.3 % in the CF group versus 6.7 % in the HF group had implant removed due to surgical site infection or wound dehiscence. None of them received salvage reconstruction. The 3- year definitive RF rate was 7.1 % in both groups. The CC was the most common complication related to implant; Baker grade III was observed in 33.3 % of the CF group versus 26.6 % of the HF group, and Baker grade IV in 6.7 % of each group.

Until the last follow-up, among patients with TE irradiated, 85.4 % (n = 35) in the CF group and 90 % (n = 36) in the HF group completed replacement of TE with PI. The median time from completion of PMRT to replacement was 8.2 (range: 3.1–25.2) months in the CF group, and 7.6 (range: 3.9–21.4) months in the HF group. Of the remaining patients who did not complete replacement, 5 in the CF group versus 2 in the HF group switched to AT reconstruction due to thinning of mastectomy flaps with high risk of PI exposure; 1 in the CF group and 2 in the HF group had TE removed due to infection, without salvage AT reconstruction. Of the patients who completed replacement, two in each group had PI removed due to wound dehiscence. Overall, 19.5 % (n = 8) in the CF group versus 15.0 % (n = 6) in the HF group experienced total RF; correspondingly, the 3-year rate of total RF was 19.6 % and 15.9 % (p = 0.26), respectively; whereas 7.3 % (n = 3) in the CF group, compared to 10.0 % (n = 4) in the HF group experienced definitive RF, correspondingly, the 3-year rate of definitive RF was 7.3 % and 10.1 % (p = 0.19), respectively.

The CC was equally common among patients with TE irradiated; Baker grade III was observed in 26.8 % in the CF group versus 22.5 % in the HF group, and Baker grade IV was in 9.8 % in CF group versus 7.5 % in the HF group. There was no significant difference between CF and HF groups for any implant complication.

Discussion

This subgroup analysis focused on the reconstruction and implant-related complications of patients who received HF-PMRT relative to CF-PMRT in the setting of various types of IBR. Compared with delayed reconstruction, IBR involves a reconstruction of breast mound at the same time of mastectomy, and has some potential advantages, including improved physical self-image satisfaction, quality of life, and overall mental health [17]. However, in the setting of PMRT after IBR, the irradiation of a reconstructed breast will be inevitable, and leads to an increased rates of complications, which might vary with the type of reconstructions [3–6,12,17]. We therefore stratified enrolled patients according to the type of reconstruction. For the entire cohort, two-stage TE/I was the most commonly used technique, followed by single-stage DTI, and AT reconstructions. On the whole, the incidence of

Table 2
Reconstruction complications per reconstruction type.

	AT			PI			TE		
	CF (n = 11)	HF (n = 11)	p-value	CF (n = 15)	HF (n = 15)	p-value	CF (n = 41)	HF (n = 40)	p-value
Infection	0	0		2 (13.3 %)	0	0.483	6 (14.6 %)	4 (10.0 %)	0.526
Wound dehiscence	0	0		0	1 (6.7 %)	1.000	3 (7.5 %)	3 (7.5 %)	0.975
Fat necrosis	0	1 (9.0 %)	1.000	0	0		0	0	
Skin necrosis	1 (9.0 %)	0	1.000	0	0		0	0	
Seroma or hematoma	0	0		0	0		0	0	

Abbreviations as above in Table 1.

Table 3
Implant-related complications.

	PI			TE		
	CF (n = 15)	HF (n = 15)	p-value	CF (n = 41)	HF (n = 40)	p-value
Implant rupture	0	0		1 (2.4 %)	0	1.000
Implant exposure	0	1 (6.7 %)	1.000	2 (4.8 %)	1 (2.5 %)	1.000
CC						
Baker grade III	5 (33.3 %)	4 (26.7 %)	0.705	11 (26.8 %)	9 (22.5 %)	0.530
Baker grade IV	1 (6.7 %)	1 (6.7 %)		4 (9.8 %)	3 (7.5 %)	
TE removal	–	–		6 (14.6 %)	4 (10.0 %)	0.737
PI removal	2 (13.3 %)	1 (6.7 %)	1.000	2 (4.8 %)	2 (5.0 %)	1.000
Conversion to AT	0	0		5 (12.1 %)	2 (5.0 %)	0.675

Abbreviations: CC: capsular contracture; as above in Table 1.

reconstruction complications is demonstrated to be higher for patients with TE irradiated, then for patients with PI irradiated, and the lowest for patients with AT irradiated, which is in line with the findings of previous studies [5,18].

Previous studies have demonstrated the superiority of AT reconstruction over implant-based reconstruction, such as lower rates of reconstruction complications, better satisfaction with the cosmetic outcome, etc. [17,19,20], even in the setting of PMRT [5,21]. In this study, a total of 22 patients with AT irradiated were included. Owing to the small number of TRAM, LD, and DIEP flaps, we put all types of autologous flaps together as autologous approach. Among them, the reconstruction complications were rare, and did not significantly increase with altered fractionations. This finding confirms that hypofractionated PMRT is technically safe for autologous approach, and therefore represents a viable option for patients who underwent immediate AT reconstruction.

Notwithstanding the advantages of autologous approach, extra burden caused by the longer operation time, hospital stay, and recovery time, as well as morbidity at donor site might preclude some patients from receiving AT reconstruction [22]. However, single-stage DTI allows for completion of all surgeries in one setting with comparable rates of complications to AT reconstruction [5], and therefore is commonly adopted by many patients. In the current study, 30 patients with PI irradiated in total were included, and no significant difference in the rates of any complications was observed between HF- and CF-PMRT groups, which indicates that HF-PMRT is as safe as CF-PMRT for patients with PI irradiated. However, up to 40 % of patients from both PMRT groups developed Baker grade III-IV CC. Similarly, as Sinnott et al. [16] reported, in the setting of CF-PMRT, Baker grade III or IV CC occurred in 43.5 % of patients undergoing subpectoral implant-based reconstruction, which is 12 times greater than that of patients who underwent prepectoral reconstruction. Whereas in the setting of HF-PMRT, Rojas et al. [12] observed a rate of 14.3 % of Baker IV CC in patients undergoing subpectoral DTI reconstruction, which is higher compared to our finding. In contrast, Naoum et al. [5] reported a much lower rate (7 %) of CC after CF-PMRT to single-stage DTI reconstruction. Notably, in Naoum's study, only surgical intervention to release the capsule was used to define CC and no grading was provided, which was quite different from the definition of CC graded with the Baker scale in other studies. The development of CC might be associated with patient-specific characteristics (e.g., body mass index, BMI), the thickness of mastectomy flaps, prosthesis type, prosthesis position (prepectoral vs. subprectoral), surgical techniques, and RT techniques (e.g., radiation dose and fractionations, dose homogeneity, the use of bolus, and boost to the chest wall), etc. [5,16,23,24]. To reduce the occurrence of severe CC and improve the cosmetic outcome, comprehensive measures, such as the use of acellular dermal matrix (ADM), prepectoral placement, improved dose homogeneity, selective use of bolus, and omission of chest wall boost, should be considered.

The validity of two-stage TE/I reconstruction is being questioned for some reasons, such as the need for a longer journey to complete reconstruction, more surgeries, and higher rates of complications and reconstruction failure as compared to DTI [4]. Also, the debate about optimal timing for PMRT to the TE or PI after expander replacement is ongoing [25]. However, two-stage TE/I approach is still commonly used, since it allows corrective measures to be taken at the time of TE replacement for PI, which represents an opportunity to address implant displacement or breast asymmetry. In this subgroup analysis, patients with TE irradiated constituted 60 % of the entire cohort. Similarly, Baker grade III-IV CC was the most common complication, which occurred in around 30 % of patients with TE irradiated. In addition, up to 10 % of them developed absolute RF. No significant increase of any complications related to implant was observed with the altered fractionations of PMRT, which suggests that it's feasible to use hypofractionation for PMRT in patients undergoing two-stage TE/I reconstruction.

Up to now, most literature related to IBR and PMRT dealt with conventional fractionated schedules [5,16,21,23,25,26]. In contrast, just a few studies have evaluated the safety of moderately hypofractionated PMRT regimens in the setting of IBR [9–12,27]. Whitfield et al. [9] delivered PMRT using a standard UK scheme of 40 Gy in 15 fractions over 3 weeks to 42 implant-based IBRs in 41 patients, and reported a crude rate of 19.5 % developing severe CC, which required revisional surgery. Khan et al. [10] prospectively evaluated the safety of a dose of 36.63 Gy in 11 fractions to the chest wall and regional nodes plus an optional boost to mastectomy scar in 67 patients. Among them, 41 had chest wall reconstructions. After a median follow-up of 32 months, the total rate of implant loss or failure was 24 %, the unplanned surgical correction rate was 8 %, and the total complication rate of 32 %, which was comparable to historic controls. On the basis of these data, a phase III prospective, randomized trial (Alliance A221505) is designed to test the safety of a hypofractionated schedule for patients with IBR when directly compared with conventional fractionation. Rojas et al. [12]

retrospectively investigated the RF in patients receiving implant-based IBR and hypofractionated PMRT with a dose of 40.05 Gy/15 fractions to the chest wall and infra/supraclavicular nodal region. With a median follow-up 4.2 years, 12.9 % of patients in the irradiated TE/I group underwent major revisional surgery, and 35.6 % underwent minor revisional surgery; whereas in the irradiated DTI group, 6.7 % of patients underwent major revisional surgery and 31.1 % underwent minor revisional surgery. The findings from the above-mentioned studies preliminarily confirm the safety of HF-PMRT in patients undergoing implant-based reconstruction. However, it's obvious that the outcomes are heterogeneous, which might be ascribed to the differences in study period, study design, patient selection, surgical techniques, radiation techniques, and the definition of complications.

Whereas Wong et al. [27] performed a prospective, randomized study of Radiation Fractionation Patient Outcomes After Breast Reconstruction (FABREC) to compare HF with 42.56 Gy in 16 fractions and CF with 50 Gy in 25 fractions for patients undergoing implant-based reconstruction, and found a lower absolute risk of chest wall toxic effects, which were defined as any grade 3 or higher adverse event in the ipsilateral chest wall area after PMRT began (infection, delayed wound healing, TE or implant removal, or unplanned surgical intervention), in both arms than that previously reported. Although PMRT regimens utilized in the current subgroup were essentially the same as in FABREC trial, the rate of complication seems to higher in comparison with Wong's finding. Potential factors contributing to the reduced risk of chest wall toxic effects in FABREC trial might include prepectoral placement of device, more frequent use of sentinel lymph node biopsy, smaller number of lymph nodes removed, and improvements in surgical technique, etc. Despite the existing differences between the FABREC trial and our study, the findings consistently show that hypofractionation for PMRT instead of conventional fractionation does not compromise the safety of implant-based reconstruction. These data therefore add to the increasing experience with the use of HF-PMRT after immediate implant-based reconstruction for breast cancer.

Despite the prospective nature of this study, we acknowledge that there are some potential limitations. First, the small sample size of this subgroup might lower the statistical power. Hence, we are looking forward to more robust evidence from phase III randomized trials with large sample size. Second, since the severity of capsular contracture evolves with time, the small number of Baker grade IV capsular contracture might be associated with a relatively short follow-up of this study. We will update the reconstructive outcome after a longer follow-up time.

Conclusions

The preliminary results of this subgroup analysis indicates that the incidence of reconstruction complications is demonstrated to be higher for patients with TE irradiated, then for patients with PI irradiated, and the lowest for patients with AT irradiated, however, the use of hypofractionation for PMRT in patients with any type of IBR does not seem to increase complications as compared to conventional fractionation, which needs to be further confirmed by large prospective randomized studies.

Author contributions

Conception and design: Jinli Ma, Collection and assembly of data: Xiaomeng Zhang, Xiaofang Wang, Yajuan Chu, Data analysis and interpretation: Xiaomeng Zhang, Xiaofang Wang, Yajuan Chu, and Jinli Ma, Manuscript writing: All authors, Final approval of manuscript: All authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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