Hypofractionated Versus Conventional Fractionated Radiotherapy for Patients with Triple Negative Breast Cancer: A Single Institution Randomized Trial

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Abstract: *Introduction*: Delivering hypofractionated radiotherapy schedules for patients with breast cancer is a growing interest. The current study aimed to determine whether hypofractionated radiotherapy is as effective and safe as conventional fractionated radiotherapy for patients with triple negative breast cancer, irrespective of lymph node status or surgical type.

Methods: The current study is a randomized, open-label trial. A total of 148 female participants with non-metastatic triple negative breast cancer (TNBC) were recruited from January 2019 to December 2023. Eligible participants were randomly assigned (1:1) for hypofractionated schedule or conventional radiotherapy schedule. The trial included all non-metastatic TNBC eligible to adjuvant radiotherapy due to positively involved lymph nodes or high-risk features of the primary tumor. The 3- year Loco-regional recurrence free survival (RFS) was the primary end point.

Results: At a median follow-up of 24 months, seven (5.3%) patients had developed locoregional recurrence, all of them in hypofractionated radiotherapy (RT) arm. The 3-year Loco-regional RFS rate was significantly higher in conventional RT arm compared to the hypofractionated RT arm (p <0.001). The 3-year distant metastases free survival was not significantly differed in the two groups (p =0.121). The 3-year overall survival was 90.4%, with no significant difference between the groups (p= 0.091).

Conclusion: The effectiveness of hypofractionated radiotherapy for disease control of triple-negative disease, irrespective of lymph node status or type of surgical interference remains questionable.

Keywords: Triple negative breast cancer, hypofractionated radiotherapy, conventional radiotherapy.

1. INTRODUCTION

Breast cancer (BC) is one of widely diagnosed malignancy in women. The role of adjuvant radiotherapy and its fractionation techniques is essential in BC treatment. Moderate hypofractionation schedule typically delivers 40 to 42.5 Gray over approximately three weeks with or without a boost RT dose [1, 2]. The American Society for Radiation Oncology (ASTRO) recommends hypofractionation strategy for all patients with invasive breast cancer or ductal carcinoma in situ (DCIS) to irradiate the whole breast without an additional regional lymph nodes field. Dose homogeneity of >7% should be considered and the breast tissue volume receiving >105% of the prescription dose should be minimum [3, 4].

The effectiveness of hypofractionated modalities have been established in BC. In 2002, a Canadian trial demonstrated that hypofractionated schedule was as effective as the conventional RT schedule after breast-conserving surgery (BCS). In START A and B trials, the 5-year results confirmed the equivalent effectiveness and safety of hypofractionated RT with conventional fractionated RT for most patients underwent BCS and received whole-breast RT (5, 6]. The conventional radiotherapy schedule is the standard for postmastectomy radiotherapy (PMRT). A randomized clinical trial from China suggested that a hypofractionated PMRT achieved comparable oncological outcome and similar adverse effects as conventional fractionated approach [7].

The principles of radiotherapy in TNBC are similar to other BC subtypes. TNBC represents 15% of BC and has higher grade and more aggressive features than other subtypes [8]. The effectiveness of moderate hypofractionation for cases with TNBC were discussed in several studies including a Canadian trial [9], a Chinese trial, [10] and a study from Denmark, Germany, and Norway (DBCG HYPO) [11].

Particularly, in the Canadian (OCOG) trial, the local recurrence outcome was in favor of conventional fractionated RT with hazard ratio at 1.27 for patients with basal (TNBC) disease. A subgroup analysis in this trial demonstrated that hypofractionated RT was less

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efficient in high-grade tumors. For patients with high-grade tumors, the cumulative incidence of local recurrence (LR) was 4.7% with conventional RT compared with 15.6% in the hypofractionated RT [9].

The safety of hypofractionated schedules is still controversial, particularly for patients with or without reconstruction after mastectomy; cases require regional nodal irradiation or patients with certain histological subtypes and collagen vascular disease [12, 13].

2. PATIENT AND METHODS

This current study is an open-label randomized study without stratification. A total of 148 female participants with non-metastatic TNBC were recruited from January 2019 to December 2023. Eligible participants were randomly assigned (1:1) for hypofractionated schedule or conventional RT schedule (odd number for hypo fractionated RT and even number for conventional fractionated RT). Seventeen participants were omitted from the study (9 patients received adjuvant RT in other institutions, 5 didn't continue the entire course of RT, and the remaining 2 lost the follow up), 131 participants were finally included (Figure **1**). This study was approved by the research ethics committee, faculty of medicine, Tanta university (code number: 36264PR915/10/24). An informed consent was signed by the participants before the study.

2.1. Inclusion and Exclusion Criteria

Eligible criteria were female patients aged ≥ 18 years, who had a Karnofsky performance score of 60% or higher; triple negative invasive breast cancer treated with CBS or mastectomy and axillary dissection with negative margins. Less than 8 months between radiotherapy and surgery is considered for eligibility.

The study included all non-metastatic TNBC eligible to adjuvant RT due to positively involved LN or high-risk features of the primary tumor (T3 or T4 lesions and T2 disease with limited axillary dissection and have other negative prognostic factors, such as lymph vascular invasion or high-grade tumor). Our study included TNBC patients irrespective of lymph node status or type of surgical interference.

Exclusion criteria included hormone receptor positive BC, bilateral BC, distant metastasis, previous irradiation, breast reconstruction, previous or concurrent malignancies or active collagen vascular disease.

2.2. Pretreatment Evaluation

The participants were evaluated by medical history, clinical examination, adequate pre-operative imaging studies (bilateral breast mammogram and MRI if indicated), and pathological examination for accurate diagnosis, staging, and treatment planning. Laboratory investigations (Renal functions, liver functions and complete blood count) were done to all participants.

2.3. Treatment Details

Conventional RT Arm

A dose of 50 Gy in 25 fractions of 2 Gy/fx daily over 5 weeks (from Saturday to Wednesday) was delivered.

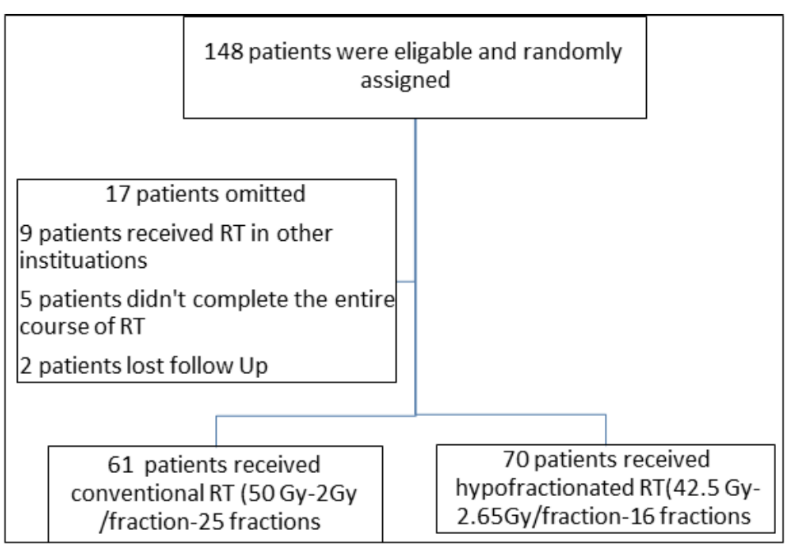

Figure 1: Trial design and randomization.

Hypofractionated RT Arm

A dose of 42.5 Gy in 16 fractions of 2.65 Gy/ fx from Saturday to Wednesday over 3 weeks was delivered. A dose of 42·5 Gy is biologically equal to 50 Gy in 25 fractions relying on the α/β ratio of the breast (4·0 Gy).

2.4. Radiotherapy Field

The planned target volumes for breast and lymph nodal levels were based on the RTOG guideline- 2016 [14]. For women treated with BCS, we administered whole-breast RT (WBRT). The participants who received neoadjuvant therapy were included even if they achieved a complete remission. A boost dose to the tumor bed was offered to minimize the risk of in-breast tumor recurrence. Regional nodal RT was offered for participants with involved lymph nodes and high-risk features.

The target volume for WBRT extended to the lateral border of the sternum medially and to the mid-axillary line laterally. The field extended 1 cm beyond the palpable breast tissue. The caudal extent of the field is approximately 1 cm below the inframammary fold in the intact breast. The head of the clavicle is the cranial end of RT field.

For Patients treated with mastectomy, we delivered PMRT to chest wall and regional nodes (mainly supraclavicular and infraclavicular node). For patients with complete axillary dissection, axilla irradiation was omitted. Similar to the intact breast, tangential photon fields were conducted to the chest wall with considerations regarding the underlying volume of heart and lungs.

2.5. RT Technique

Virtual simulation and multiple RT fields are required for 3-Dimensional Conformal RT to conduct proper dose of RT to the target volume while sparing organs at risk. For accurate virtual simulation, immobilization of the patient is essential to minimize movements. Radiopaque catheters are applied to delineate the borders of the RT field and the scars. Thin CT images with 3 mm thickness through the treatment volume were done. Eclipse treatment planning system v18.1. with 6 MeV photon beam was used.

2.6. Systemic Treatment

The neoadjuvant or adjuvant chemotherapy protocols included, dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) and 5 fluorouracil, anthracycline and cyclophosphamide (FAC).

2.7. Follow up

During the RT course, all patients were evaluated once weekly for acute radiation toxicity. The participants were monitored every 3 months during the first year, followed by biannual assessment for 3 to 5 years. Acute adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. Late RT toxicity was scaled with the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.

2.8. Clinical End Points

Loco-regional RFS was the primary endpoint and defined as time interval from randomization to documented local or regional recurrence or death from any cause, whichever occurred first.

Overall survival (OS), distant metastases free survival (DMFS), and acute and late adverse events were the secondary points. The OS is defined as death from any cause from the time of randomization until the end of follow-up. The DMFS is the time from randomization till distant metastasis or death.

2.9. Statistical Analysis

This trial aimed to evaluate whether hypofractionated RT is as efficacious and safe as conventional RT. A total of 148 patients underwent randomization in a 1:1 ratio. Seventeen patients were excluded. This final sample size of 131 participants. Kaplan–Meier curves were used to estimate the survival outcomes and log-rank tests were used to compare the two treatment groups. Cox proportional-hazards model was used to calculate the hazard ratios and 95% confidence intervals. All statistical tests were two sided, and p value $<0·05$ was significant [15].

We performed an interaction analysis to evaluate the effect of the experimental clinicopathological characteristics and treatment modalities were compared using the chi-square test for numeric categorical variables.

3. RESULTS

Between January 2019 to December 2023, 131 women with non-metastatic TNBC were randomly

Table 1: Baseline Characteristics

Characters	Conventional RT (61 Case)		Hypo Fractionated RT (70 case)		P Value
	no	%	no	%	
Age					
>51	22	36.1	41	58.6	0.010
<51	39	63.9	29	41.4	
Menopausal status					
Premenopausal	37	60.7	27	38.6	0.012
Postmenopausal	24	39.3	43	61.4	
Histopathological types					
IDC	55	90.2	63	90	0.890
ILC	4	6.6	5	7.1	
Medullary	2	3.3	2	2.9	
Family history					
No	49	80.3	64	91.4	0.066
Yes	12	19.7	6	8.6	
Parity					
Nullipara	6	9.8	9	11.5	0.588
Multipara	55	90.2	61	87.1	
T stage					
T1	5	8.2	9	12.9	0.483
T2	48	78.7	48	68.6	
T3	4	6.6	9	12.9	
T4	4	6.6	4	5.7	
N stage					
N0	14	23	22	31.4	0.465
N1	30	49.2	25	35.7	
N2	13	21.3	17	24.3	
N3	4	6.6	6	8.6	
Stage					
IA	2	3.3	2	2.9	0.209
IIA	12	19.7	18	25.7	
IIB	26	42.6	22	31.4	
IIIA	10	16.4	18	25.7	
IIIB	9	14.8	4	5.7	
IIIC	2	3.3	6	8.6	
Grade					
G1	0	0	1	1.4	0.140
G2	54	88.5	53	75.7	
G3	7	11.5	16	22.9	
LVI					
YES	26	42.6	23	32.9	0.404
NO	27	44.3	33	47.1	
Unknown	8	13.1	14	20	
Type of surgery					
CBS	26	44.1	28	40	0.641
MRM	33	55.9	42	60	
Induction chemotherapy					
NO	51	83.6	50	71.4	0.098
Yes	10	16.4	20	28.6	

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; RT, radiotherapy; LVI, lymphovascular invasion; CBC, conservative breast surgery; MRM, modified radical mastectomy.

recruited to receive hypofractionated RT (n=70) or conventional fractionated RT (n=61), irrespective of stage, grade, or use of systemic therapy.

The Patient clinicopathological features and treatment were well equalized between the two groups except for premenopausal patients and those less than

51years old who were higher in conventional arm compared to hypofractionated arm (Table **1**).

The median age was 51 years (range 18-75). Fifty-five (90.2%) patients in conventional RT group and 63 (90%) patients in hypofractionated RT group had invasive ductal carcinoma. Locally advanced disease (stage IIb and III) was reported in 97 patients in both groups [47 (77%) patients in conventional versus 50 (71.4%) patients in hypofractionated arm]. Axillary LN positively involved in 95 patients in both groups [47 (77%) patients in conventional arm vs. 48 (68.6) patients in hypofractionated arm]. Seventy-five patients underwent mastectomy in both groups (33 (55.9%) patients in conventional arm vs. 42 (60%) patients in hypofractionated arm. Thirty patients received neoadjuvant chemotherapy in both groups [10 (16.4%) patients in conventional arm vs. 20 (28.6%) patients in hypofractionated arm].

3.1. Loco-Regional RFS

During 24-months of median follow up, seven patients (5.3%) out of 131 developed LR, all of them in the hypofractionated arm. Five patients out of 7 had progressed recurrence in chest wall or ipsilateral breast and the remaining two in regional nodes.

The 3- year Loco-regional RFS rate was 100% for patients who received conventional RT and 80.2% with hypofractionated RT. There was significant difference in locoregional RFS between hypofractionated arm and conventional arm [HR 2.296, 95%CI (1.54: 6.55), *p* <0.001] (Figure **2**). The univariate analysis demonstrated a significant correlation between Locoregional recurrence and higher tumor grade [HR 3.863, 95%CI (1.53:3.73), *p* =0.012] (Table **2**). There was no significant difference between the two treatment groups regarding other prognostic factors. Multivariate analysis confirmed that radiotherapy fractionation is an independent variable for local relapse (*p* = 0.020).

3.2. Distant Metastases Free Survival

Forty-one (31.3%) patients developed distant metastases. Liver and lung were the most prominent sites of metastases. The 3-year DMFS rate for all patients was 59.4%. The 3-year DMFS was 70.6% [95%CI (40.5-49.6)] for conventional RT, and 49.7% [95%CI (30.1- 43)] for hypofractionated RT. The DMFS was not significantly differ in both arms (*p* =0.121) (Figure **3**).

3.3. Overall Survival

Elven (8.5%) cases died (6 in conventional RT arm and 5 in hypofractionated RT arm). The 3-year OS was 90.4% for all participants. The 3-year OS rate was 88.9% (95% CI 58.9-64.3) for the conventional RT and 82.3% (95% CI 47-58.3) for the hypo fractionated RT. The difference between the two groups was non-significant (*p*= 0.091) (Figure **4**).

3.4. Toxicity

After radiotherapy, acute and late toxicity in both arms were reported in Table **3**. Death due to grade 4

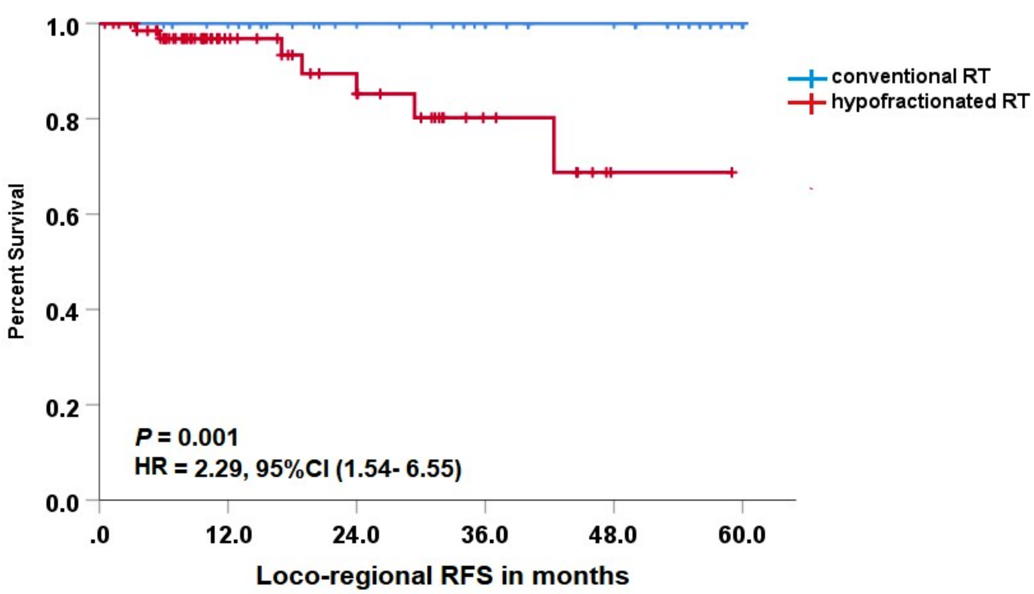

Figure 2: Kaplan myer analysis of loco-regional RFS curves for 131 patients received hypofractionated RT and conventional RT.

Table 2: Univariate and Multivariate Analysis for Locoregional RFS.

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P	HR (95%CI)	P
Age	1.02 (2.27: 4.60)	0.978	-	-
Menopausal status	1.445 (0.32:6.49)	0.631	-	-
OCP	0.903 (0.36: 2.21)	0.821	-	-
Family history	1.418 (0.27: 7.34)	0.677	-	-
Parity	0.865 (0.10: 7.26)	0.894	-	-
T stage	1.853 (0.63:5.40)	0.259	-	-
N stage	1.154 (0.51: 2.59)	0.729	-	-
Overall stage	1.306 (0.71:2.38)	0.383	-	-
Grade	3.863 (1.53:3.73)	0.012*	3.942(0.854-8.19)	0.268
LVI	2.674 (0.90:7.91)	0.075	-	-
Type of surgery	1.607 (0.31:8.31)	0.572	-	-
RT schedule	2.296 (1.54: 6.55)	0.001*	9.152(1.022-8.197)	0.020*
Induction chemotherapy	2.265 (0.425:12.06)	0.338	-	-

Abbreviations: RT, radiotherapy; LVI, lymphovascular invasion; CBC, conservative breast surgery; MRM, modified radical mastectomy.

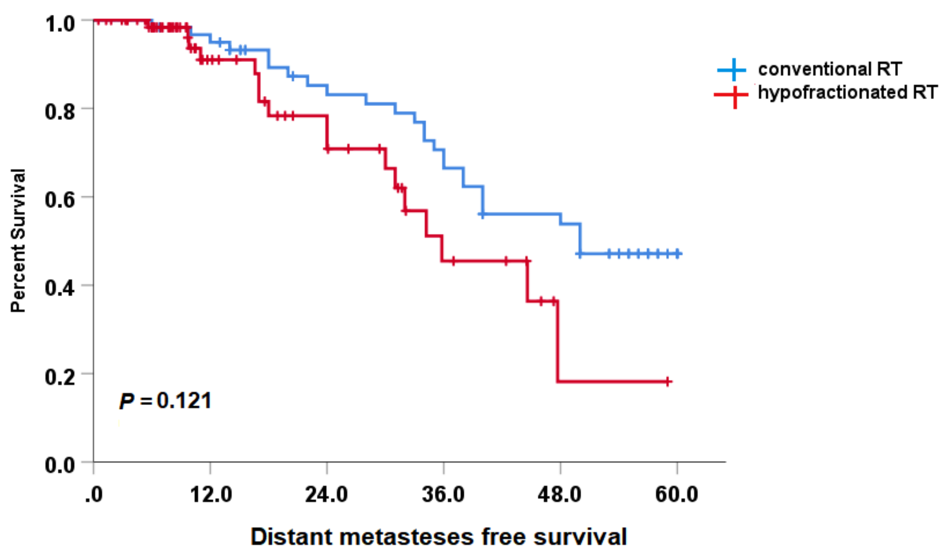

Figure 3: Kaplan myer analysis of DMFS curves for 131 patients received hypofractionated RT and conventional RT.

adverse effects was not observed. The difference between groups in the incidence of acute skin toxicity or pneumonitis was non-significant (p=0.847 and p=0.790 respectively). Late toxicity of the skin, lymphedema and lung fibrosis was numerically higher in the hypofractionated arm. Most late toxicity was grade 1-2 with no statistical significance between the groups.

4. DISCUSSION

Hypofractionated RT is recognized as an efficient strategy for BC treatment. The current work aims to assess the efficacy of moderately hypofractionated technique for patients with TNBC. Data about the effectiveness of moderate hypofractionation for cases with TNBC were discussed in several studies including a Canadian trial where 125 women randomized to moderate hypofractionation or conventional fractionation [9], a Chinese trial, where 77 patients randomized [10] and a study from Denmark, Germany, and Norway (DBCG HYPO) where188 patients randomized [11].

In the Canadian trial, LR with conventional fractionated RT was better than moderately hypofractionated RT in patients with TNBC [hazard ratio at 1.27, but with a very wide 95% CI (0.21–7.58)]

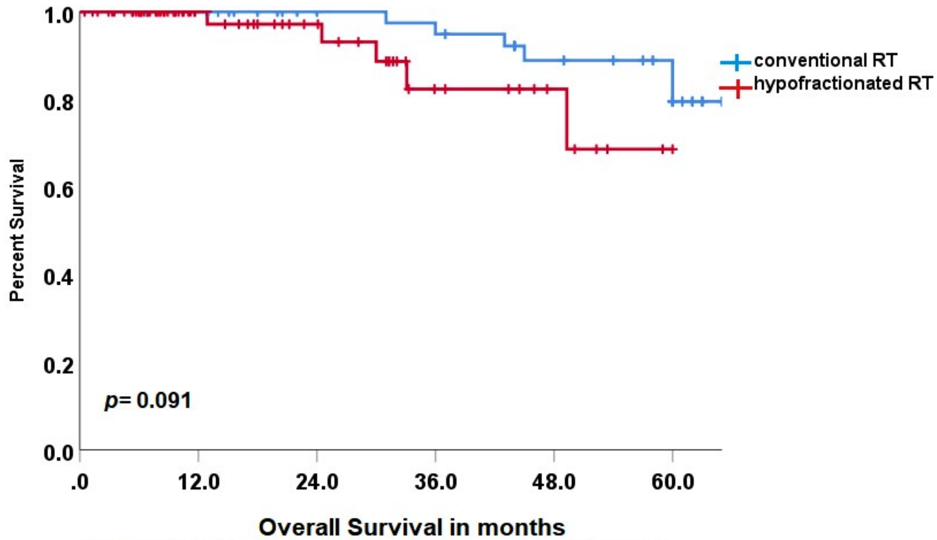

Figure 4: Kaplan myer analysis of OS curves for 131 patients received hypofractionated RT and conventional RT.

Table 3: Acute and Late Toxicity after Radiotherapy

Acute Toxicity	Conventional RT		Hypofractionated RT		P
	No	%	No	%	
Skin					
G1-2	51	83.6	60	85.7	0.847
G3	4	6.6	3	4.3	
Pneumonitis					
G1	7	11.5	10	14.3	0.790
G2	1	1.6	2	2.9	
G3	00	0	0	0	
Late toxicity					
Skin					
G1-2	10	16.4	15	22.1	0.442
G3	0	0	1	1.5	
Lymphedema					
G1-2	8	13.1	14	20.6	0.321
G3	1	1.6	3	4.4	
Lung fibrosis					
G1-2	6	9.8	12	17.6	0.201
G3	0	0	0	0	

[9]. In 10-year follow-up, the cumulative incidence of LR was higher in hypofractionated RT arm compared to conventional RT arm. Our findings were similar to the Canadian trial regarding to increase risk of LR in hyofractionated arm (seven patients (5.3%) out of 131 developed locoregional recurrence, all of them in the hypofractionated arm).

In the Chinese study, the results were nearly similar in both arms: one patient out of 37 in hypofractionated RT arm and 1 out of 40 in conventional RT arm had LR (and 2/38 and 3/40 had locoregional recurrence) [10]. Among 188 participants in the DBCG HYPO trial, the locoregional recurrences were not significantly different in conventional RT arm nor hypofractionated radiotherapy arm [11]. Both trials included TNBC patients who underwent conservative breast surgery, while our study recruited TNBC patients irrespective of axillary node status or type of primary surgery.

The contributing factor that may impact the high incidence of LR in the hypofractionated arm in our trial is the aggressive heterogeneous biology of TNBC and BRCA1association [16]. At the cellular level, the impact of decreased proliferation on DNA synthesis-based cell was significantly obvious in conventional RT at day 25 contrary to hypofractionated RT at day 15. This observation is consistent with the clinical practice that tumor remission can't be hastened by the accelerated dose of hypofractionated RT [17].

In the current study, the 3- year Loco-regional RFS was significantly better in conventional RT arm versus hypofractionated RT arm (HR 2.296, 95% CI (1.54: 6.55), $p<0.001$). Our findings were aligned with those from a considerable observational study including patients with TNBC received whole breast irradiation, the 5- year freedom from local recurrence (FFLC) was 94.4% in conventional RT arm compared to 93.6% in hypofractionated arm, with no significant difference ($p=0.89$) and the 5- year RFS was 88.4 and 87.8 in the conventional arm and hypofractionated arm respectively [18].

The 3-year OS was not significantly differed in both arms (88.9% versus 82.3% in conventional RT and hypofractionated RT respectively). The 3-year DMFS rate was 59.4%, the difference was non-significant in both arms. Our results were consistent with other hypofractionated trials [10,11,18].

In our study, the difference in the occurrence of acute skin toxicity and pneumonitis was non-significant in hypofractionated RT group and conventional RT group ($p=0.847$ and $p=0.790$ respectively). Late toxicity of skin, lymphedema and lung fibrosis were numerically higher in the hypofractionated arm with no significant difference. Our results were comparable with previous hypofractionated RT studies [5-7].

Our results reflected a single institution study with relatively short follow-up interval. More comprehensive trials with subgroup analysis are essential to set up definite role of hypofractionated RT in TNBC based on nodal status, tumor grade and primary surgical interference.

5. CONCLUSION

The efficacy of hypofractionated RT is well-established in BC, but the effectiveness of hypofractionated radiotherapy in achieving disease control in TNBC without considering lymph node status or surgical type is still controversial [19,20].

DECLARATION OF INTERESTS

No conflict of interest.

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AGREEMENT TO PUBLICATION

All authors have confirmed this article for publication.

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