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Similar Outcomes of Standard Radiotherapy and Hypofractionated Radiotherapy Following Breast-Conserving Surgery

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Adjuvant radiation therapy is commonly administered to breast cancer patients who received breast-conserving surgery. However, lengthy treatment times of standard radiotherapy pose certain challenges. Here, we performed a prospective controlled study comparing standard radiation to hypofractionated radiotherapy in terms of efficacy and outcome.

Material/Methods: Eighty breast cancer patients (tumor stage pT1-2N0-1M0) who had undergone breast-conservation surgery were randomly divided into 2 groups (40 patients/group). The experimental group received 43.2 Gy to the whole breast in 18 fractions for 24 days with a concomitant boost (50.4 Gy) to the tumor bed. The control group received 45 Gy to the whole breast in 25 fractions for 44 days with a boost to the tumor bed of 59 Gy. Survival, locoregional recurrence, adverse effects, and aesthetic results were all considered for analysis.

Results: The following criteria were included as part of study follow-up: local control, survival, adverse skin reactions, cosmetic outcome, and hematological toxicity. At a median follow-up of 27 months (follow-up rate 100%), there were no statistical differences in any of the categories between the 2 groups. The 2-year survival rate of both groups was 100% without any locoregional recurrence. Although there was some skin toxicity, these instances were not severe and they cleared on their own within 6 weeks. The most common problems encountered by patients were breast fibrosis and altered pigmentation.

Conclusions: A shortened whole-breast hypofractionated irradiation schedule with a concomitant boost is as effective as standard radiation and may be a reasonable alternative following breast conservation surgery.

MeSH Keywords: Breast • Radiation • Radiotherapy, Computer-Assisted

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Background

Breast cancer is one of the most common cancers affecting women worldwide and a primary cause of cancer-related death in women [1]. Despite high morbidity and mortality, breast cancer death rates have actually declined over recent years. This is most likely the result of earlier detection and improved therapies. Therapeutic options for breast cancer include both targeted (e.g., anti-estrogens and HER2 antagonists) and non-targeted therapies (e.g., radiation therapy) [2]. The choice of therapy and surgical approach largely depends on the tumor characteristics [3]. If diagnosed at an early stage, breast conservation surgery can often be performed; this involves surgical removal of the cancer cells with minimal disturbance of normal breast tissue [4]. Breast-conserving surgery usually includes either lumpectomy or partial mastectomy. Following surgery, patients often receive adjuvant radiation therapy, which helps kill any remaining cancerous cells that may not have been removed during the operation. To date, an optimal fractionation schedule for breast irradiation has not been universally accepted, and many studies have examined the benefits and drawbacks of various treatment regimens [5–8].

Previous studies have shown that breast-conserving surgery in conjunction with irradiation has a similar outcome as a radical operations such as a full mastectomy [9]. The current standard for radiation treatment involves whole-breast tangential irradiation with a subsequent boost to the tumor bed; this has been proven to decrease locoregional recurrence [10]. However, this standard regimen occurs over a long period of time and can potentially interfere with post-operative chemotherapy treatment. Specifically, standard radiation treatment following breast-conserving surgery for early-stage disease typically occurs over the course of 6–7 weeks. Previous work has shown that breast cancer has a low α/β ratio (3–4 Gy) and that hypofractionated radiation therapy (>2 Gy/fraction) may be effective without significantly increasing adverse effects [11,12]. Additionally, a shorter regimen could also reduce medical costs. Interestingly, a study showed that implementation of a cost-minimization strategy was effective on a patient-by-patient basis and significantly reduced medical expenses [13]. Here, we further examine the influence of radiotherapy scheduling on patients undergoing breast conservation surgery. Specifically, we examined whether there were any outcome differences between early-stage breast cancer patients receiving standard radiotherapy compared to those receiving whole-breast hypofractionated irradiation with a concomitant boost.

Material and methods

Study design

We performed a phase II randomized controlled study in a single-blinded manner. Patients met the inclusion criteria were enrolled the study in the Department of Radiation Oncology, Tianjin Medical University Cancer Institute and Hospital between January 2011 and December 2011. Patients were randomly divided into an experimental group (24-day group) and a control group (44-day group) using a random number table. Written informed consent was obtained from all patients and the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital approved the study protocol.

Study patients

Patients were enrolled in the study if they met the following inclusion criteria: patients were diagnosed at an early disease stage (pT1-2N0-1M0) and underwent breast-conserving surgery. All patients were 18 years of age or older, with a Karnofsky performance status (KPS) score greater than or equal to 70. Silver clips were used to denote tumor volume and help localize radiation, which had to be administered within 1 month of surgery.

Patients who met any of the following exclusion criteria were not enrolled in the study: any patient who had received radiation therapy in the ipsilateral breast, chest wall, lung, or lymph nodes was excluded from the study. Additionally, women diagnosed with either inflammatory breast cancer or bilateral breast cancer or who had received prior breast-conserving surgery or breast reconstruction surgery were excluded. Finally, those who experienced breast cancer recurrence were prevented from enrolling in the study.

Treatment regimens

Patients had undergone various treatment modalities based on their presentation and tumor characteristics. Here, we outline the primary treatment regimens used for all patients in the study.

Surgery

Breast-conserving surgery was performed by surgical excision of the primary tumor, with a 2–3 cm margin of macroscopically normal tissue and an axillary dissection. Dissection of axillary lymph nodes was dependent on sentinel lymph node biopsy. When the sentinel node biopsy was positive, the axillary lymph nodes were dissected; in all other cases, no dissection of axillary lymph nodes was performed. The dissection of axillary lymph nodes was conducted at either a level I–II or a level I–III, depending on the patient's risk level. During surgery, silver clips were placed to mark the tumor perimeter.

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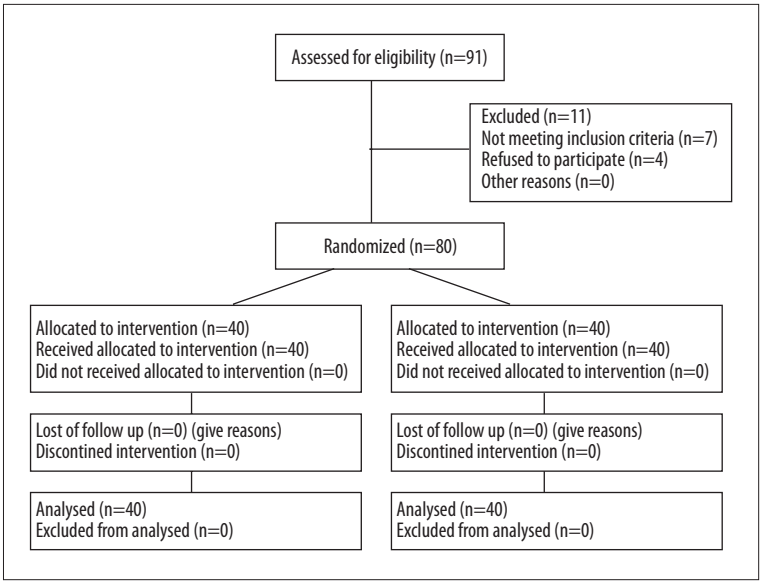

Figure 1. Flowchart of patient grouping.

Chemotherapy

Patients received postoperative chemotherapy if they were axillary lymph node positive or if they were axillary lymph node negative but at a high risk of recurrence (i.e. <35 years old with a tumor diameter ≥2 cm, a histological grade of II–III, signs of vascular invasion, HER-2 positive, ER/PR negative). Chemotherapy was administered over 6 cycles. The first cycle of chemotherapy was performed 2 weeks after breast conversation surgery. This was followed by irradiation for 3 weeks and then additional rounds of chemotherapy. A 2-drug chemotherapy regimen was used in this study – either pharmorubicin combined with cyclophosphamide or pharmorubicin combined with paclitaxel. There was no difference in the proportion of different chemotherapy regimens between the 2 groups.

Radiotherapy

Radiotherapy was started within 1 month of surgery and 3 weeks after the first cycle of chemotherapy. Patients in experimental group underwent 24 days of whole-breast 2-field tangent radiotherapy of 43.2 Gy in 18 fractions (dose/fraction=2.4 Gy) with a concomitant boost to the tumor bed of 50.4 Gy in 18 fractions (dose/fraction=0.4 Gy). Those in control group underwent 44 days of whole-breast 2-field tangent radiotherapy of 45 Gy in 25 fractions with a dose/fraction of 1.8 Gy and a subsequent boost to the tumor bed of 59 Gy in 7 fractions (dose/fraction=2 Gy). Irradiation was administered to the entire breast tissue and to lymph nodes between the pectoral muscles and lymphatic drainage area of the pectoral wall under the breast. We used 6 MV of X-ray, which was 95% of the prescribed isodose X-ray. The irradiated range of the tumor bed was 1–2 cm outside of the silver clip. The photon beam energy was set between 6 and 9 MV based on tumor bed depth.

Endocrine therapy

Patients with tumors that were hormone receptor-positive (ER & PR) received endocrine therapy after chemotherapy. Premenopausal women received tamoxifen, while postmenopausal patients received third-generation aromatase inhibitors.

Follow-up and endpoint outcomes

Patients were followed until September 2013. Specifically, follow-up was performed immediately at the end of radiation and 6 weeks, 6 months, 12 months, and 24 months after this time. Follow-up observations included a review of patient medical history, physical examination, bilateral breast anteroposterior X-ray examination, chest radiography, mammography, and breast ultrasound. The study's primary endpoint was locoregional recurrence. Secondary endpoints included acute skin reactions, advanced skin reactions, aesthetic outcome, and hematological toxicity. Locoregional recurrence was defined as the area of the breast and the supraclavicular lymph drainage area within the radiation field; definite diagnosis was confirmed by both clinical and imaging examinations [14]. Skin adverse reactions (levels I–4) were assessed according to American acute and late radiation tumor tissue radiation injury grading standards. Aesthetic results, including breast edema, skin sag, fibrosis, telangiectasia, scarring, pigmentation, breast size, nipple level, and bilateral symmetry were graded as "excellent", "good", "fair", or "poor" according to guidelines established by the Joint Center for Radiation Therapy (JCRT) and as previously described [15].

Statistical analyses

Kaplan-Meier analysis was used to calculate survival rate and locoregional recurrence. Log-rank tests were performed to

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Table 1. Clinical characteristics of 80 breast cancer patients enrolled in the study.

Clinical material	24 days group (40 cases)	44 days group (40 cases)	Statistics	P value
Mean age	49.28±10.71 (38.57, 59.98)	49.3±11.55 (37.76, 60.85)	–0.01	0.99
Median age	48	48	0.00	0.97
T value				
T1	32	33	0.08	0.78
T2	9	32		
Lymph node				
N0	31	8	0.08	0.79
N1	9	32		
Pathological type				
Invasive ductal carcinoma	35	38	1.46	0.48
Intraductal carcinoma	2	1		
Mucinous carcinoma	3	1		
Estrogen receptor				
Positive	11	10	0.07	0.80
Negative	29	30		
Progesterone receptor				
Positive	12	13	0.06	0.81
Negative	28	27		
HER2 receptor				
Positive	8	10	0.29	0.59
Negative	32	30		
Systemic therapy				
Chemotherapy	13	14	0.21	0.90
Endocrine therapy	18	16		

compare differences between groups. Data for comparability, adverse reactions, and aesthetic outcomes in the 2 groups were compared and analyzed by chi-square test. All statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). P values <0.05 were considered statistically significant.

Results

In total, 80 patients met the inclusion criteria and were enrolled in the study (experimental group, n=40; control group, n=40) (Figure 1). The clinical characteristics between the 2 groups were similar, and detailed information is provided in Table 1.

At a median follow-up of 27 months (range: 20–32 months), the follow-up rate was 100%. The 2-year survival rate of both groups was also 100%, and there was no locoregional recurrence. Adverse skin reactions (levels 1–2) experienced by patients in the 2 groups were similar. Importantly, all acute skin reactions underwent spontaneous remission after 6 weeks. No skin toxicities higher than grade 3 were detected in any patient during the follow-up period. Patients in both groups experienced overall good aesthetic results; the only problems

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Table 2. Comparison of adverse reactions between stage I–II breast cancer patients (80 cases) receiving one of two treatment regimens.

Adverse reaction	24 day group	44 day group	Statistics	P value
Acute skin reaction(0–1 level)	82.5%	77.5%	0.31	0.58
Acute skin reaction (II levels)	17.5%	22.5%	0.31	0.58
Advanced reaction of 1 level skin and subcutaneous tissue	22.5%	20%	0.08	0.79
Good cosmetic affect	67.5%	72.5%	0.24	0.63
Neutropenia (1–2 levels)	12.5%	10%	0.13	0.72
platelet decline (1 level)	2.5%	5%	0.35	0.56

encountered were breast fibrosis and alteration in pigmentation in both groups (3 cases in experimental group and 2 cases in control group for breast fibrosis, 7 cases in both of the 2 groups for alteration in pigmentation). Finally, we did not detect any significant differences in hematological toxicity (i.e., neutropenia, levels 1-2 or platelet decline, level 1). Overall, there were no statistically significant differences in any of the examined categories between the 2 groups (Table 2).

Discussion

In this study, we examined whether there were any outcome differences between early-stage breast cancer patients receiving standard radiotherapy compared to those receiving whole-breast hypofractionated irradiation with a concomitant boost. We found that there were no significant differences between the 2 regimens in any of the examined outcomes. Thus, a shortened whole-breast hypofractionated irradiation schedule with a concomitant boost is as effective as standard radiation and may be a reasonable alternative following breast conservation surgery

An earlier study by Whelan et al. showed that a significant portion of early-stage breast cancer patients could benefit from accelerated, hypofractionated whole-breast irradiation (AH-WBI) [16,17]. They found that AH-WBI (42.5 Gy in 16 fractions over 22 days) was not inferior to standard radiation (50 Gy in 25 fractions over 35 days) in terms of acute skin reactions, local recurrence within 10 years, or cosmetic outcome. However, subgroup analysis showed that, compared with standard radiation treatment, AH-WBI had a lower efficiency in high-histological grade patients; the locoregional recurrence over 10 years in patients undergoing AH-WBI compared to those receiving standard radiation treatment was 15.6% and 4.7%, respectively (P=0.01). In 2012, the British Columbia Cancer Center observed a total of 1335 early breast cancer patients with Grade 3 disease (T1–T2, N0, M0) and compared the local relapse rates between hypofractionated radiotherapy and conventionally fractionated schedules [18]; 252 patients underwent conventional fractionation of 45–50 Gy in 25 fractions, and 1083 patients received a hypofractionated schedule of 42.5–44 Gy in 16 fractions. The 10-year cumulative incidence of local relapse was 6.9% in the hypofractionated group and 6.2% in the conventionally fractionated group (p=0.99). The data show that the hypofractionated schedule was no worse than conventional fractionation, even for histologic grade 3 breast tumors. Importantly, these results are not consistent with the findings of the Whelan study, previously described. Another group compared the 5-year local relapse rates between hypofractionated radiotherapy and conventionally fractionated schedules [19–21]. Results from this study showed that hypofractionated radiotherapy did not increase the local relapse rate. Overall, both treatment regimens showed good efficacy and aesthetic outcomes. Additionally, adverse reactions were acceptable, and the cost of treatment was significantly reduced. Taken together, these studies show that hypofractionated radiotherapy following breast-conserving surgery is a feasible and worthwhile option.

It should be noted that the study by Whelan et al. did not include a concomitant boost to the tumor bed, which may prevent direct comparison to our study. Bartelink et al. assessed the effect of concomitant radiation boost on several outcomes [10]. There was a statistically significant difference (P<.0001) in local recurrence at 10-year follow-up (10.2% versus 6.2%). There was also a significant increase in the amount of fibrosis detected in the boost group. In contrast to these 2 outcomes, there was no difference in overall survival between the 2 groups. Another study reported that patients receiving a concomitant boost of 14Gy to the tumor bed had an increased risk of breast hardening and telangiectasia [22]. However, there were no reported differences in breast appearance, aesthetic outcomes, breast contractures, deformation, edema, or swelling between the 2 groups. Recently, Raza et al. compared accelerated intensity-modulated radiation therapy (IMRT) with

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a concomitant boost to the tumor bed delivered over 3 or 5 weeks against standard 6-week accelerated radiotherapy with a sequential electron boost [23]. Acute complications such as breast pain, fatigue, and dermatitis were significantly less in the 3-week regimen compared to the other treatment schedules (P<0.05). Results from studies such as these have made whole-breast radiotherapy with a concomitant boost the standard of treatment in China.

While our study supports a shorter radiation schedule, it has certain limitations, including the short follow-up time and the limited number of patients enrolled. Different conclusions might be reached over a longer follow-up period. Thus, additional studies with larger sample sizes must be performed to understand the long-term effects of hypofractionated radiation.

Conclusions

In conclusion, our results show that abbreviated hypofractionated radiation is well-tolerated and comparable to longer standard treatment regimens. Thus, shortened whole-breast hypofractionated irradiation schedule with a concomitant boost is as effective as standard radiation and may be a reasonable alternative following breast conservation surgery.

Conflict of interests

All authors declare that they have no conflicts of interests.

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