Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial

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Summary

Background To our knowledge, no randomised study has compared postmastectomy hypofractionated radiotherapy with conventional fractionated radiotherapy in patients with breast cancer. This study aimed to determine whether a 3-week schedule of postmastectomy hypofractionated radiotherapy is as efficacious and safe as a 5-week schedule of conventional fractionated radiotherapy.

Methods This randomised, non-inferiority, open-label, phase 3 study was done in a single academic hospital in China. Patients aged 18–75 years who had undergone mastectomy and had at least four positive axillary lymph nodes or primary tumour stage T3–4 disease were eligible to participate. Patients were randomly assigned (1:1) according to a computer-generated central randomisation schedule, without stratification, to receive chest wall and nodal irradiation at a dose of 50 Gy in 25 fractions over 5 weeks (conventional fractionated radiotherapy) or 43·5 Gy in 15 fractions over 3 weeks (hypofractionated radiotherapy). The modified intention-to-treat population (including all eligible patients who underwent randomisation but excluding those who were considered ineligible or withdrew consent after randomisation) was used in primary and safety analyses. The primary endpoint was 5-year locoregional recurrence, and a 5% margin was used to establish non-inferiority (equivalent to a hazard ratio <1·883). This trial is registered at ClinicalTrials.gov, number NCT00793962.

Findings Between June 12, 2008, and June 16, 2016, 820 patients were enrolled and randomly assigned to the conventional fractionated radiotherapy group (n=414) or hypofractionated radiotherapy group (n=406). 409 participants in the conventional fractionated radiotherapy group and 401 participants in the hypofractionated radiotherapy group were included in the modified intention-to-treat analyses. At a median follow-up of 58·5 months (IQR 39·2–81·8), 60 (7%) patients had developed locoregional recurrence (31 patients in the hypofractionated radiotherapy group and 29 in the conventional fractionated radiotherapy group); the 5-year cumulative incidence of locoregional recurrence was 8·3% (90% CI 5·8–10·7) in the hypofractionated radiotherapy group and 8·1% (90% CI 5·4–10·6) in the conventional fractionated radiotherapy group (absolute difference 0·2%, 90% CI −3·0 to 2·6; hazard ratio 1·10, 90% CI 0·72 to 1·69; p<0·0001 for non-inferiority). There were no significant differences between the groups in acute and late toxicities, except that fewer patients in the hypofractionated radiotherapy group had grade 3 acute skin toxicity than in the conventional fractionated radiotherapy group (14 [3%] of 401 patients *vs* 32 [8%] of 409 patients; p<0·0001).

Interpretation Postmastectomy hypofractionated radiotherapy was non-inferior to and had similar toxicities to conventional fractionated radiotherapy in patients with high-risk breast cancer. Hypofractionated radiotherapy could provide more convenient treatment and allow providers to treat more patients.

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Introduction

Breast cancer is the most common cancer in women globally. In China, the incidence of breast cancer was 37·86 per 100 000 women in 2015, accounting for 15% of all new cancers in women.[1] Randomised trials have shown similar survival between mastectomy and breast-conserving treatment in patients with early-stage breast cancer.[2] Data from the Surveillance, Epidemiology, and End Results database between 2000 and 2008 showed that 37·5% of patients with breast cancer underwent mastectomy, whereas 61·4% underwent breast-conserving surgery in the USA.[3] However, in China, most patients with breast cancer (about 80%) underwent mastectomy around the same period (1999–2008).[4]

Research in context

Evidence before this study

In 2008, we searched PubMed for research articles related to hypofractionated radiotherapy in patients with breast cancer published in English between Jan 1, 1988, and May 31, 2008. We limited this search to the terms "breast cancer", "radiotherapy", "hypofractionation", "fractionation", "randomized", and "phase III". Randomised studies have shown that hypofractionated radiotherapy after breast-conserving surgery, delivered at approximately 3 Gy per fraction, for 13–16 fractions, has equivalent long-term efficacy and similar toxicity profile to conventional fractionated radiotherapy. However, no randomised study has compared hypofractionated radiotherapy with conventional fractionated radiotherapy after mastectomy in patients with breast cancer. The evidence for clinical application of postmastectomy hypofractionated radiotherapy schedule has until now only been available from case series, retrospective studies, or subgroup analyses from the START randomised trials. A randomised trial to assess the efficacy and safety of postmastectomy hypofractionated radiotherapy was urgently needed, especially because regional nodal irradiation is required for almost all patients with high-risk breast cancer.

Added value of this study

To our knowledge, this is the first large-scale randomised trial directly comparing postmastectomy hypofractionated radiotherapy and conventional fractionated radiotherapy in patients with high-risk breast cancer. We found that hypofractionated radiotherapy was non-inferior to, and had similar toxicity to, conventional fractionated radiotherapy. The findings from this study provide high-level evidence for the clinical use of postmastectomy hypofractionated radiotherapy for such patients.

Implications of all the available evidence

Following publication of the long-term results from the Canadian and START trials, there is American Society for Radiation Oncology consensus on the choice of hypofractionated whole-breast radiotherapy in breast cancer after breast-conserving surgery. The results of this trial suggest that hypofractionated radiotherapy can be a treatment option in patients with breast cancer treated with mastectomy. These findings are of high clinical relevance and value for current practice in countries where medical resources might be scarce.

The survival benefit of postmastectomy radiotherapy in patients with locally advanced or lymph node-positive disease has been demonstrated in randomised trials and meta-analyses.[5–9] Postmastectomy radiotherapy to the chest wall and nodal regions is typically delivered in 25 fractions of 2 Gy over 5 weeks (conventional fractionated radiotherapy). However, there is growing interest in delivering postmastectomy radiotherapy with hypofractionated schedules,[10] because shorter and more convenient hypofractionated dose schedules might help to treat more patients and reduce cost. In 2002, a Canadian trial[11] reported that hypofractionated regimens were as safe and efficacious as the historical standard control schedule of 50 Gy in 25 fractions for breast cancer after breast-conserving surgery. In 2005 and 2006, the UK START pilot study[12,13] reported that an α/β value of around 3 Gy for late normal tissue changes in the breast and an α/β value of 4·0 Gy for breast cancer were derived from the estimated equivalence of hypofractionated radiotherapy and conventional fractionated radiotherapy schedule. In 2008, 5-year results of the START A and B trials[14,15] were published, confirming the equivalent efficacy and safety of hypofractionated radiotherapy with conventional fractionated radiotherapy for patients with breast cancer, in which most patients underwent breast-conserving surgery and received whole-breast radiotherapy only. Hypofractionated radiotherapy cannot be expanded to the postmastectomy setting because of concerns about potential toxicity, particularly those related to nodal irradiation. So far, to our knowledge, no randomised study has compared hypofractionated radiotherapy and conventional fractionated radiotherapy after mastectomy. Therefore, we aimed to determine whether a hypofractionated 3-week schedule of postmastectomy radiotherapy is as efficacious and safe as a standard 5-week schedule of conventional fractionated radiotherapy in patients with high-risk breast cancer.

Methods

Study design and participants

This study is a randomised, non-inferiority, open-label, phase 3 trial, with patients recruited from a single academic hospital (National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College) in Beijing, China. Female patients were eligible if they were aged 18–75 years; had a Karnofksy performance score of 60% or higher; had invasive breast cancer; had undergone mastectomy and axillary dissection with negative margins; had at least four pathological positive axillary lymph nodes or primary tumour stage T3–4 disease if they had undergone primary surgery (or clinical stage III disease or pathological positive axillary lymph nodes if they had received chemotherapy before surgery); were fit for systemic therapy and radiotherapy; and had less than 8 months between radiotherapy and mastectomy, if adjuvant chemotherapy was given first. Patients were excluded if they had bilateral breast cancer; had a supraclavicular node, internal mammary node, or distant metastasis; had breast reconstruction; had previous irradiation; had previous or concurrent malignancies except

non-melonomatous skin cancer; were pregnant; or had active collagen vascular disease or other serious diseases, such as alcohol and drug misuse or mental illness. The clinical stage work-up included physical examination and at least one image (ultrasonography, mammography, or MRI) assessment for the primary tumour; routine nodal ultrasonography and biopsy for suspicious disease; CT scans of the chest, abdomen, and pelvis; and a whole-body bone scan. All patients provided written informed consent. The study protocol (appendix) was approved by the local ethics committee from the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College.

See Online for appendix

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either hypofractionated radiotherapy or conventional fractionated radiotherapy without stratification by simple randomisation (odd number for hypofractionated radiotherapy and even number for conventional fractionated radiotherapy), according to a prescribed computer-generated central randomisation schedule. Radiation oncologists in the study team enrolled participants, and research staff members who were involved in follow-up data collection assigned participants to interventions. Treatment allocation could not be masked because of the different daily schedules of the two radiotherapy procedures.

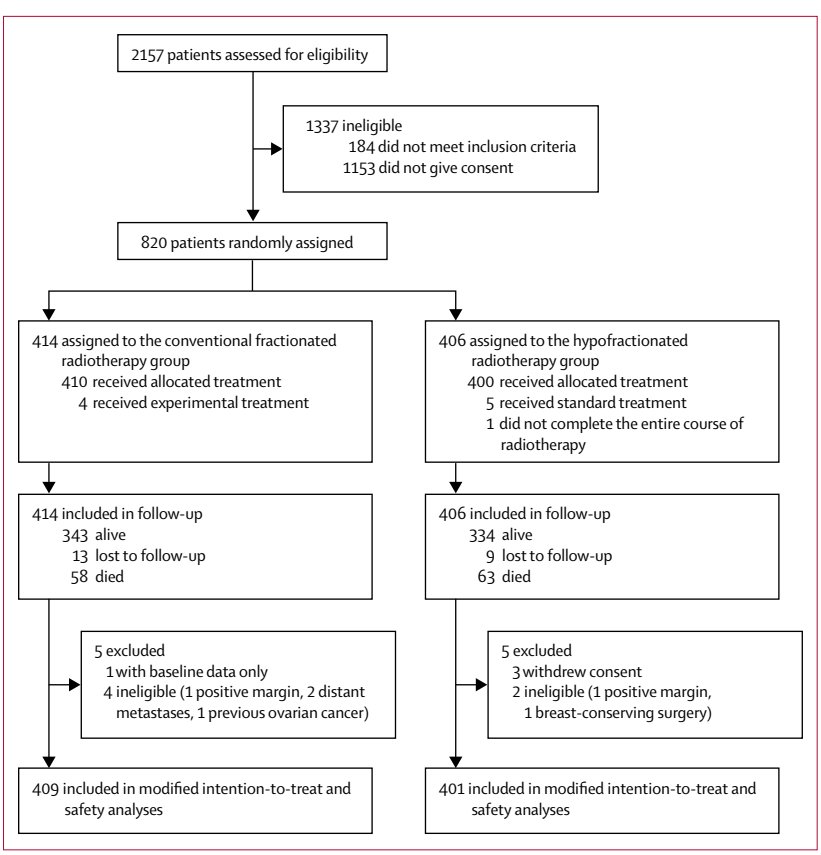

Figure 1: **Trial profile**

Procedures

Conventional fractionated radiotherapy consisted of postmastectomy radiotherapy at 50 Gy in 25 fractions over 5 weeks, and hypofractionated radiotherapy consisted of postmastectomy radiotherapy at 43·5 Gy in 15 fractions over 3 weeks. The total dose of 43·5 Gy in 15 fractions is biologically equivalent to 50 Gy in 25 fractions according to the α/β ratio of 4·0 Gy for breast cancer. Since these radiotherapy regimens are well tolerated according to our experience, no rule on permitted dose reductions or interruptions was predefined.

Postmastectomy radiotherapy was administered daily, from Monday to Friday, to the chest wall and supraclavicular and level III axillary nodal region. None of the patients received irradiation to the levels I and II axilla or internal mammary chain. Radiotherapy techniques have been described in detail previously.[16] Briefly, the chest wall was irradiated using a 6–9 MeV electron beam, depending on chest wall thickness, and the dose was prescribed at the point on the central axis with maximum depth dose. A 5 mm tissue equivalent bolus was applied up to a median of 40% of the total prescribed dose. The supraclavicular nodal region was subjected to two-dimensional radiotherapy, three-dimensional conformal radiotherapy, or intensity-modulated radiotherapy. The prescribed dose to the supraclavicular area was defined as the dose to the isopoint at 3 cm beneath the skin with two-dimensional radiotherapy technique, or the dose covering 95% of the planning target volume with three-dimensional conformal or intensity-modulated radiotherapy.

On the basis of National Comprehensive Cancer Network guidelines, chemotherapy was administered to all patients, hormonal therapy was administered to patients with oestrogen receptor-positive or progesterone receptor-positive tumours, and anti-HER2-targeted therapy (eg, trastuzumab) was recommended for those with HER2-positive disease.

Patients were assessed for medical history, underwent a physical examination, and had a blood test before radiotherapy, once per week during radiotherapy, and 2 weeks after radiotherapy. Patients were followed up every 3 months for 2 years after radiotherapy, then every 6 months from 3 to 5 years, and yearly thereafter. Acute radiation toxicity was assessed and scaled according to the Common Terminology Criteria for Adverse Events, version 3.0. Late radiation toxicity was assessed with the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer late radiation morbidity scale.

Outcomes

The primary endpoint was locoregional recurrence, defined as disease recurrence in the ipsilateral chest wall or regional lymph nodes from the time of randomisation

until the end of follow-up. The primary endpoint was centrally reviewed. The secondary endpoints were overall survival, disease-free survival, and acute and late radiation toxicities. Overall survival events were defined as death from any cause from the time of randomisation until the end of follow-up. Disease-free survival events were defined as locoregional recurrence, distant metastasis, or death from any cause from the time of randomisation until the end of follow-up.

Statistical analysis

The primary hypothesis of the study was that 5-year locoregional recurrence with hypofractionated radiotherapy is non-inferior to that with conventional fractionated radiotherapy. 5-year locoregional recurrence in the conventional fractionated radiotherapy group was assumed to be 6% on the basis of previous results in similar patient groups.[8,16] We accepted a maximum loss of efficacy of 5% in the hypofractionated radiotherapy group; that is, hypofractionated radiotherapy would be considered non-inferior to conventional fractionated radiotherapy if 5-year locoregional recurrence in the hypofractionated radiotherapy group did not exceed 11%, with a non-inferiority margin of 5% (equivalent to a hazard ratio [HR] of <1·883). The non-inferiority margin was chosen on the basis of expert consensus, historical data from institutional experiences and published literature, and the risk–benefit profile of locoregional recurrence and overall survival.[8] Under assumed failure rates and guarding against 5% ineligibility or loss to follow-up, we expected a final target accrual of 820 and at least 62 locoregional recurrence events to provide at least 80% power, with a one-sided significance level of 0·05. The choices of the significance level and power were made to provide an appropriate compromise between feasibility and statistical rigour. We evaluated the non-inferiority of hypofractionated radiotherapy relative to conventional fractionated radiotherapy by comparing whether the upper bound of the two-sided 90% CI for the HR was equal to or below the prespecified non-inferiority margin (HR 1·883).

For the primary efficacy endpoint, we used the cumulative incidence method to estimate the actual incidence of locoregional recurrence at different timepoints, with death without locoregional recurrence as a competing risk. We used the log-rank test and Cox regression model for statistical inference based on cause-specific hazards.[17] We calculated overall survival and disease-free survival using the Kaplan-Meier method, and we analysed these endpoints using the log-rank test and Cox regression model. Acute and late toxicities were summarised as frequency and severity on the basis of their association with protocol treatment; the χ^2 test was used to compare the differences. The primary endpoint and all efficacy endpoints were analysed in the modified intention-to-treat population (ie, including all eligible patients who underwent randomisation but excluding those who were considered ineligible or withdrew consent after randomisation). On the basis of the study design, the primary endpoint locoregional recurrence was analysed at a one-sided significance level of 0·05 and reported with a two-sided 90% CI. All other statistical tests were two sided, and p<0·05 was deemed to indicate significance. The analyses were based on data received up to July 31, 2017. All analyses were done with SAS, version 9.4, and R, version 3.4.1.

This study is registered at ClinicalTrials.gov, number NCT00793962.

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)
Age ≥50 years	202 (49%)	194 (48%)
Tumour size, cm	2·5 (2·0–3·5)	2·5 (2·0–3·5)
Lymphovascular invasion	132 (32%)	136 (34%)
Grade 3	111 (27%)	121 (30%)
ER positive	311 (76%)	300 (75%)
PR positive	304 (74%)	294 (73%)
HER2 positive	111 (27%)	135 (34%)
Stage III*	384 (94%)	377 (94%)
Number of axillary nodes removed	23 (19–30)	23 (18–29)
Number of positive axillary nodes	6 (4–11)	7 (4–12)
Chemotherapy	409 (100%)	401 (100%)
Neoadjuvant chemotherapy	113 (28%)	86 (21%)
Adjuvant chemotherapy	296 (72%)	315 (79%)
Hormonal therapy	315 (77%)	305 (76%)
Trastuzumab	60 (15%)	76 (19%)
Two-dimensional radiotherapy	401 (98%)	385 (96%)
Three-dimensional conformal radiotherapy	7 (2%)	10 (3%)
Intensity-modulated radiotherapy	1 (<1%)	6 (2%)
Ipsilateral lung V20	19·6 (15·4–23·9)	17·8 (13·1–24·6)
Ipsilateral mean lung dose, Gy	9·6 (7·7–11·8)	9·3 (6·5–10·6)
Mean heart dose, Gy	0·8 (0·5–1·6)	0·3 (0·5–1·5)

Data are n (%) or median (IQR). ER=oestrogen receptor. PR=progesterone receptor. V20=relative volume receiving more than 20 Gy. *For patients who did not receive neoadjuvant chemotherapy, we used pathological stage because it is more accurate than clinical stage. For patients who received neoadjuvant chemotherapy, we used whichever stage was higher (clinical or pathological) to reflect the actual tumour burden.

Table 1: **Baseline characteristics of the modified intention-to-treat population**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

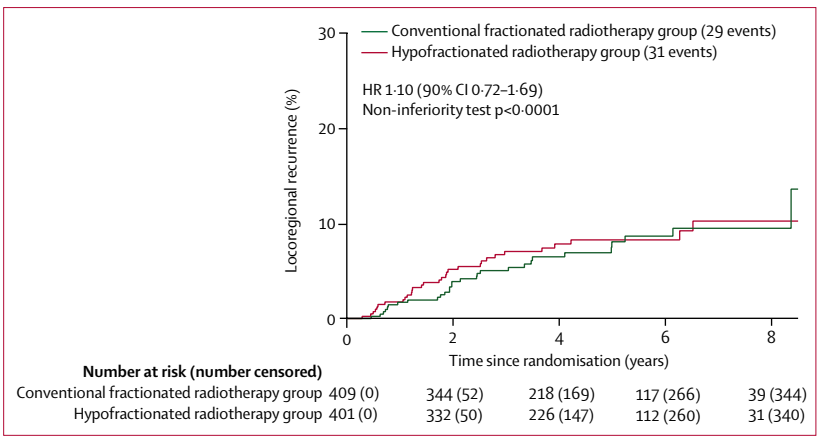

Figure 2: **Kaplan-Meier plot of cumulative locoregional recurrence**
HR=hazard ratio.

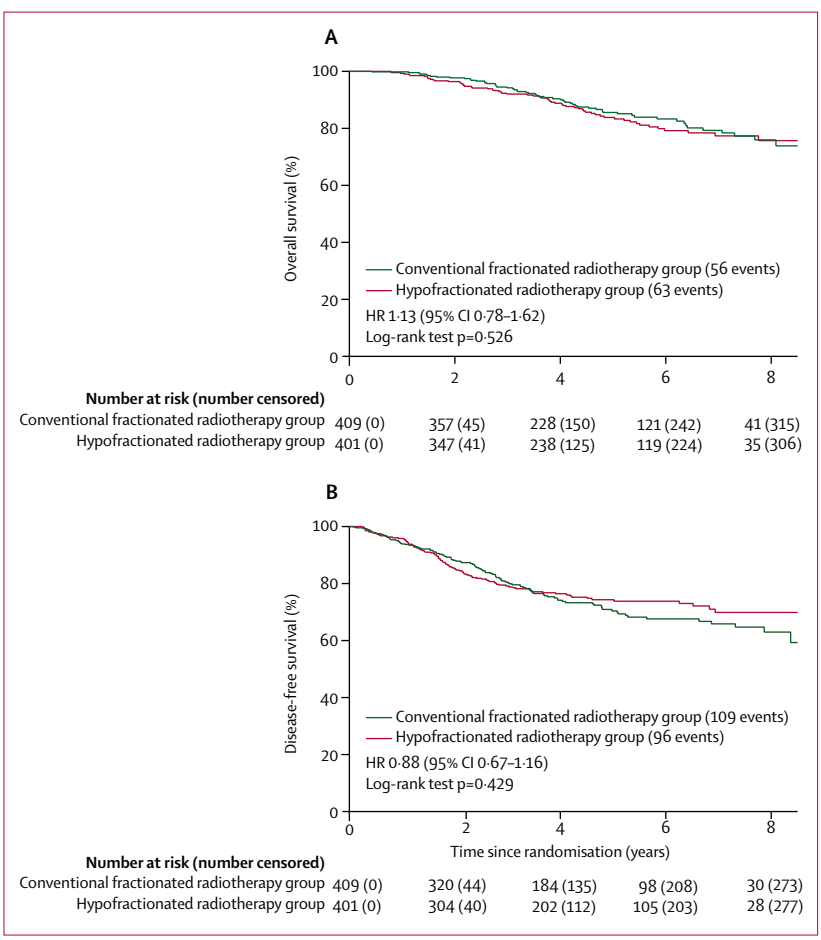

Figure 3: **Kaplan-Meier plots of overall survival (A) and disease-free survival (B)**
HR=hazard ratio.

Results

Between June 12, 2008, and June 16, 2016, 820 patients were enrolled and randomly assigned to the conventional fractionated radiotherapy group (n=414) or the hypofractionated radiotherapy group (n=406). The last follow-up date was Aug 1, 2017. After five patients were excluded from each group, 409 participants in the conventional fractionated radiotherapy group and 401 in the hypofractionated radiotherapy group were included in the modified intention-to-treat analyses (figure 1). The reasons for exclusion included positive margin, distant metastases, previous cancer, breast-conserving surgery, or withdrawal of consent by patients. One patient in the hypofractionated radiotherapy group did not complete the entire course of radiotherapy (at 37·7 Gy in 13 fractions) because of shortness of breath. Protocol non-compliance was found in nine patients (five in the hypofractionated radiotherapy group received conventional fractionated radiotherapy and four in the conventional fractionated radiotherapy group received hypofractionated radiotherapy).

Patient demographics and disease and treatment characteristics were well balanced between the two groups (table 1). The median age was 49 years (range 24–74). 381 (93%) of 409 patients in the conventional fractionated radiotherapy group and 379 (95%) of 401 patients in the hypofractionated radiotherapy group had invasive ductal carcinoma. 384 (94%) of 409 patients in the conventional fractionated radiotherapy group and 377 (94%) of 401 patients in the hypofractionated radiotherapy group had stage III disease.

All patients received adjuvant (611 [75%] patients) or neoadjuvant (199 [25%]) standard chemotherapy, including anthracycline plus taxane-based (716 [88%]), taxane-based (71 [9%]), and anthracycline-based regimens (23 [3%]), with a median of six cycles (IQR 6–8). Full details of the chemotherapy and hormonal therapy regimens given to patients in the two treatment groups are in appendix p 18. The median duration of hormonal therapy was 41 months (IQR 22–59). Of the 246 patients with HER2-positive disease, 136 (55%) patients received trastuzumab therapy (table 1).

The median time between surgery and the start of radiotherapy in all patients was 5·3 months (IQR 4·2–5·9). 403 (99%) of 409 patients in the conventional fractionated radiotherapy group and 399 (99%) of 401 patients in the hypofractionated radiotherapy group received a 6 MeV electron beam to the chest wall, six (1%) of 409 patients in the conventional fractionated radiotherapy group and one (<1%) of 401 patients in the hypofractionated radiotherapy group received a 9 MeV electron beam to the chest wall, and one (<1%) patient in the hypofractionated radiotherapy group received two tangential fields with 6 MV photons. With the exception of two (<1%) patients (one in each group) who received irradiation to the supraclavicular nodal region with 12 MeV electrons, all other patients received irradiation to the supraclavicular nodal region with 6 MV photons (208 [51%] of 409 patients in the conventional fractionated radiotherapy group and 221 [55%] of 401 patients in the hypofractionated radiotherapy group) or mixed 6 MV photons and 12–15 MeV

electrons (200 [49%] of 409 patients in the conventional fractionated radiotherapy group and 179 [45%] of 401 patients in the hypofractionated radiotherapy group). Most patients received two-dimensional radiotherapy (786 [97%]), and the minority of patients received three-dimensional conformal radiotherapy (17 [2%]) or intensity-modulated radiotherapy (seven [1%]; table 1).

The median follow-up was 58·5 months (IQR 39·2–81·8) for all patients. At the time of analysis (Aug 1, 2017), 60 (7%) patients had developed locoregional recurrence (31 patients in the hypofractionated radiotherapy group and 29 in the conventional fractionated radiotherapy group). Of these, 12 patients (six in each group) had developed disease recurrences in the chest wall, 44 (22 in each group) in regional nodes, and four (one in the conventional fractionated radiotherapy group and three in the hypofractionated radiotherapy group) in both the chest wall and regional nodes. The 5-year cumulative incidence of locoregional recurrence was 8·3% (90% CI 5·8–10·7) in the hypofractionated radiotherapy group compared with 8·1% (90% CI 5·4–10·6) in the conventional fractionated radiotherapy group (absolute difference 0·2%, 90% CI –3·0 to 2·6; HR 1·10, 90% CI 0·72 to 1·69; figure 2). Thus, there was a 90% probability that the locoregional recurrence in the hypofractionated radiotherapy group was no worse than that in the conventional fractionated radiotherapy group by 3·0%. The test of the null hypothesis that the locoregional recurrence in the hypofractionated radiotherapy group would be worse than that in the conventional fractionated radiotherapy group (by >5%) was rejected in favour of non-inferiority (p<0·0001).

205 (25%) patients developed disease recurrence (109 in the conventional fractionated radiotherapy group and 96 in the hypofractionated radiotherapy group), and 119 (15%) patients died (56 in the conventional fractionated radiotherapy group and 63 in the hypofractionated radiotherapy group). 114 (96%) of 119 patients died of breast cancer (62 in the hypofractionated radiotherapy group and 52 in the conventional fractionated radiotherapy group), four (3%) died of second malignancy (one in the hypofractionated radiotherapy group and three in the conventional fractionated radiotherapy group), and one (1%) died of an accident (in the hypofractionated radiotherapy group). 5-year overall survival for all patients in either group was 84% (95% CI 82–88) and disease-free survival for all patients was 73% (69–76). There was no significant difference in overall survival or disease-free survival between the groups (figure 3). 5-year overall survival was 86% (95% CI 82–89) for the conventional fractionated radiotherapy group and 84% (80–88) for the hypofractionated radiotherapy group. 5-year disease-free survival was 70% (95% CI 65–76) for the conventional fractionated radiotherapy group and 74% (70–79) for the hypofractionated radiotherapy group.

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)	p value
Acute toxicity			
Skin toxicity	..	..	<0·0001
Grade 1–2	357 (87%)	351 (89%)	..
Grade 3	32 (8%)	14 (3%)	..
Pneumonitis	..	..	0·278
Grade 1	62 (15%)	61 (15%)	..
Grade 2	7 (2%)	14 (3%)	..
Grade 3	..	..	..
Late toxicity			
Skin toxicity	..	..	0·669
Grade 1–2	90 (22%)	86 (21%)	..
Grade 3	0	1 (<1%)	..
Lymphoedema	..	..	0·961
Grade 1–2	81 (20%)	78 (19%)	..
Grade 3	3 (1%)	3 (1%)	..
Shoulder dysfunction	..	..	0·734
Grade 1–2	13 (3%)	7 (2%)	..
Grade 3	1 (<1%)	1 (<1%)	..
Lung fibrosis	..	..	0·081
Grade 1–2	42 (10%)	62 (15%)	..
Grade 3	0	0	..
Ischaemic heart disease	..	..	0·569
Grade 1–2	1 (<1%)	3 (1%)	..
Grade 3	3 (1%)	4 (1%)	..

Data are n (%). The χ^2 test was used to calculate p values. No grade 4 events or deaths due to adverse effects were reported.

Table 2: **Adverse events**

At baseline, the incidence of grade 1 and grade 2 lymphoedema was 5% (n=20) and none for the conventional fractionated radiotherapy group, and 5% (n=20) and <1% (n=1) for the hypofractionated radiotherapy group (p=0·561). At baseline, the incidence of grade 1 and grade 2 shoulder dysfunction was 2% (n=7) and 1% (n=3) for the conventional fractionated radiotherapy group compared with 2% (n=6) and <1% (n=2) for the hypofractionated radiotherapy group (p=0·679). Table 2 shows the results of acute and late toxicities in the two groups after radiotherapy. No grade 4 toxicities or deaths due to adverse events were observed in either group during or after radiotherapy. The hypofractionated radiotherapy group had less frequent grade 3 acute skin toxicity than the conventional fractionated radiotherapy group (14 [3%] of 401 patients *vs* 32 [8%] of 409 patients; p<0·0001). There were no significant differences between groups in the incidence of other acute or late toxicities, including symptomatic radiation pneumonitis, lymphoedema, ischaemic heart disease, and shoulder dysfunction. None of the patients had brachial plexopathy or rib fractures during follow-up.

Discussion

This large-scale randomised study assessed the non-inferiority of hypofractionated radiotherapy after mastectomy relative to conventional fractionated radiotherapy in patients with high-risk breast cancer. We found that postmastectomy radiotherapy is efficacious and safe when administered in a larger fractionation dose and in a shorter period of time compared with the standard 5-week schedule. Postmastectomy hypofractionated radiotherapy and conventional fractionated radiotherapy were associated with a low risk of 5-year locoregional recurrence, with the difference between the two groups less than our predefined non-inferiority margin of 5%. This finding indicates that hypofractionated radiotherapy is non-inferior to conventional fractionated radiotherapy in patients with breast cancer after mastectomy and, hence, treatment time can be reduced from 5 weeks to 3 weeks while preserving a high degree of locoregional control and tolerability. Overall survival and disease-free survival were similar in the hypofractionated radiotherapy and the conventional fractionated radiotherapy groups.

Because of the scarcity of high-level evidence, only a few patients with breast cancer have received hypofractionated radiotherapy following mastectomy.[10] This randomised trial with more than 800 patients with high-risk breast cancer has shown that hypofractionated radiotherapy to the chest wall and nodal regions is efficacious and safe in a postmastectomy setting. This option makes treatment more convenient and allows providers to treat more patients with fewer resources, particularly in China. By use of this hypofractionated 3-week schedule instead of the conventional 5-week schedule, up to 40% more women can be treated with existing equipment and personnel, and its availability as a treatment option might lead to an increase in the number of women who receive postmastectomy radiotherapy, which could consequently improve survival in low-income and middle-income countries.

Data about the use of postmastectomy hypofractionated radiotherapy and its effects on normal tissues are scarce. Previous studies have either been small or retrospective in nature. In the 1980s, a randomised trial[18] comparing the use of 23 Gy in four fractions over 17 days with 45 Gy in 25 fractions over 33 days found no differences in survival, locoregional recurrence, or toxicities in a heterogeneous population of patients with breast cancer (81 mastectomy, 101 tumourectomy, and 48 radiotherapy alone). In the START A and B trials[14,15] comparing hypofractionated radiotherapy and conventional fractionated radiotherapy after breast-conserving surgery, only a small proportion of patients (8–15%) received mastectomy. Subgroup analysis of 513 patients with mastectomy in these trials showed equivalent 10-year locoregional recurrence between hypofractionated radiotherapy and conventional fractionated radiotherapy.[19] In a recent phase 2 trial,[20] 67 women who received a hypofractionated postmastectomy radiotherapy regimen of 36·6 Gy in 11 fractions over 11 days to the chest wall and lymph nodes with a scar boost of four fractions of 3·33 Gy showed low toxicity and high local control. In two recent small restrospective cohort studies,[21,22] hypofractionated postmastectomy radiotherapy at 2·3–2·8 Gy per fraction was effective and had acceptable toxicity after approximately 5 years of follow-up. On the basis of an α/β value of 4·0 Gy for breast cancer, our hypofractionation dose of 43·5 Gy in 15 fractions (equivalent dose in 2 Gy fractions [EQD2]=50 Gy) is slightly higher than that of the START B trial,[15] with 40 Gy in 15 fractions (EQD2=44·4 Gy), and the Canadian trial,[11] with 42·56 Gy in 16 fractions (EQD2=47·2 Gy). Our study included high-risk patients who received mastectomy, whereas the previous two trials included patients with low-risk, early-stage disease who received breast-conserving surgery. The findings indicate that these hypofractionated dose schemes are efficacious and safe, and can be recommended in clinical practice.

In this study, hypofractionated radiotherapy was found to be safe and had less frequent grade 3 acute skin toxicity than conventional fractionated radiotherapy. Symptomatic (ie, grade 2 or worse) radiation pneumonitis occurred in less than 5% of patients in both groups, and late skin toxicity and symptomatic lung fibrosis were uncommon. This finding is similar to results in previous hypofractionated whole-breast irradiation trials.[11,14,15,19,23] A particularly important finding of this study is the safe use of hypofractionated nodal irradiation. Hypofractionated radiotherapy showed similar incidences of late complications such as lymphoedema, shoulder dysfunction, and ischaemic heart disease as conventional fractionated radiotherapy, and no brachial plexopathy or rib fractures were noted in either group. Consistent with our findings, 864 women who received locoregional radiotherapy in three START trials showed no significant difference in late arm or shoulder toxicity between the hypofractionated radiotherapy and conventional fractionated radiotherapy groups.[24] 45% of patients with nodal irradiation in the START trials received additional axilla irradiation; however, 60% of these patients did not undergo axilla dissection.[24] Patients in this study received radiation to the chest wall and supraclavicular nodal region, and none of the patients received radiation to the axilla or internal mammary chains because the most common pattern of locoregional recurrence is still the chest wall, followed by supraclavicular nodes after mastectomy and axillary dissection,[25] and there is no level I evidence that inclusion of internal mammary chains in the radiation field will improve overall survival. The randomised EORTC 22922 and MA.20 trials[26,27] have shown that regional radiotherapy (including supraclavicular, axillary, and internal mammary nodes) significantly improved distant disease-free survival or disease-free survival, but not overall survival, in patients who received

breast-conserving surgery or mastectomy. Care should be taken when extrapolating our results to women for whom axillary or internal mammary nodal irradiation has been planned.

A median follow-up of 5 years in this study is insufficient to allow for the assessment of all potential late toxicities. All patients in this study had an axillary nodal dissection, and the potential effect of regional node hypofractionated radiotherapy on the risk of late effects such as lymphoedema is a major concern. However, longer follow-up is unlikely to lead to the detection of further differences in late toxic effects between the two groups. In previous studies on whole-breast irradiation after breast-conserving surgery, most radiation-induced toxicities would be expected within 5 years,[12,19] although the incidence of late toxicities did slightly increase over time.[23,24] In a Canadian trial,[23] the incidence of grade 3 late skin toxicity only increased from 0·7–0·9% at 5 years to 2·5–3·6% at 10 years. In the START trials, there was a slight increase in lymphoedema and shoulder stiffness from 5 to 10 years.[24] The absolute increases in late toxicities are small, but we assume adverse events might continue to develop for the lifetime of the patient. In this respect, it is relevant that the relative increase is no different at 10 years than 5 years after hypofractionated radiotherapy compared with conventional fractionated radiotherapy for patients receiving nodal irradiation in the START and Canadian trials.[23,24] In this study, the dose to the heart was very low because an electron beam was directed to the chest wall; hence, we do not expect further differences in heart toxicity between groups. Moreover, brachial plexopathy is a major concern with hypofractionated nodal irradiation, since toxicity can significantly impair arm or shoulder function and quality of life when the dose to the brachial plexus is more than 66 Gy (EQD2).[28,29] In view of the hypofractionated schedule (EQD2=51 Gy for the brachial nerve, when $\alpha/\beta=3$) used in this study, we speculate that the risk of brachial plexopathy is very low. With a similar hypofractionated dose schedule in the START A and B trials, only one of 479 patients who received regional nodal irradiation developed brachial plexopathy after a median follow-up of 10 years.[19]

This study had some limitations. First, the trial was restricted to women who had undergone mastectomy without breast reconstruction. Since the use of breast reconstruction and postmastectomy radiotherapy has increased in the 21st century,[30,31] the application of hypofractionated postmastectomy radiotherapy should minimise the frequency of complications, without compromising the cosmetic outcomes of the reconstructed breast. However, because hypofractionated radiotherapy in the START trials was not associated with excess fibrosis, but was associated with slightly reduced fibrosis and improved cosmesis, there is no reason to assume hypofractionated postmastectomy radiotherapy will compromise breast reconstruction any more than conventional fractionated radiotherapy.[14,15] Two randomised trials comparing hypofractionated radiotherapy with conventional fractionated postmastectomy radiotherapy in women with immediate breast reconstruction have just been initiated by the Alliance for Clinical Trials in Oncology cooperative group (A221505) and Dana-Farber Cancer Institute (NCT03422003). The Dana-Farber study permits inclusion of axillary and internal mammary nodes in the radiation field. Thus far, postmastectomy hypofractionated radiotherapy remains a reasonable, alternative schedule for patients who might have difficulty receiving the full 25 fractions and who are not undergoing breast reconstruction. Second, our study did not include patients with supraclavicular or internal mammary nodal metastases at diagnosis and, therefore, our results are not applicable to patients who require high doses with an additional nodal bed boost. Patients in this study received radiation to the chest wall and supraclavicular and level III axillary nodal region without inclusion of the internal mammary nodes. Given the potential increased dose to the heart and lung, the effects of hypofractionated radiotherapy to the internal mammary node remain uncertain. Because trastuzumab treatment was not covered by the national health insurance plan during the period of this study, only half of the patients with HER2-positive breast cancer received anti-HER2 therapy. However, since the two groups had similar proportions of patients with anti-HER2 therapy, this limitation should not affect the results of this study. Finally, our study was done in a single centre, and the patients received relatively homogeneous guideline-based treatments. A multicentre study is warranted to support our findings. However, because the national cancer centre is well known in China, the majority of our patients were from throughout the country. Although all patients received radiotherapy in our institution, some patients received mastectomy or chemotherapy at other hospitals. The inclusion of patients from throughout China suggests generalisability in terms of population and treatment. We acknowledge that the study's external validity could be further enhanced had this been a multicentre study. Meanwhile, a series of factors that contribute to the strong internal validity of our study should not be overlooked, including potentially more uniform disease diagnosis, a higher degree of control in protocol implementation, and precise quality assurance, data collection, and follow-up, among others.

In conclusion, this study provides high-level evidence for the clinical use of hypofractionated postmastectomy radiotherapy for patients with high-risk breast cancer. It can be recommended in clinical practice to patients who do not plan breast reconstruction and will not receive internal mammary node irradiation. The results of this study have important implications for patients with breast cancer and for health-care systems. Longer follow-up at 10 years is needed to document the long-term toxicities and the effect of no internal mammary

node irradiation on clinical outcomes, especially distant disease-free survival.

Contributors

S-LW and Y-XL designed the study, analysed the data, and wrote the manuscript. S-LW, HF, Y-WS, W-HW, Y-PL, JJ, X-FL, Z-HY, HR, and Y-XL contributed to the study concept. S-LW, HF, Y-WS, YuanT, RP, and SL contributed to study coordination. S-LW, G-YS, RP, and SL contributed to data collection. S-LW, CH, and YY did the statistical analysis. All authors contributed to data interpretation and approved the manuscript.

Declaration of interests

CH has received grants from the US National Cancer Institute and personal fees from Varian Medical Systems. All other authors declare no competing interests.

Data sharing

Individual participant data that underlie the results and the study protocol will be shared with researchers who provide a methodologically sound proposal for individual participant data meta-analysis. Proposals should be directed to yexiong@yahoo.com; to gain access, data requestors will need to sign a data access agreement. Data will be made available beginning 3 months and ending 5 years following article publication.

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References

1 Chen W, Zheng R. Incidence, mortality and survival analysis of breast cancer in China. *Chin J Clin Oncol* 2015; **42:** 668–71.

2 Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347:** 1233–41.

3 Mahmood U, Hanlon AL, Koshy M, et al. Increasing national mastectomy rates for the treatment of early stage breast cancer. *Ann Surg Oncol* 2013; **20:** 1436–43.

4 Wang SL, Li YX, Zhang BN, et al. Epidemiologic study of radiotherapy use in China in patients with breast cancer between 1999 and 2008. *Clin Breast Cancer* 2013; **13:** 47–52.

5 Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b trial. *N Engl J Med* 1997; **337:** 949–55.

6 Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; **337:** 956–62.

7 Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999; **353:** 1641–48.

8 Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366:** 2087–106.

9 McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383:** 2127–35.

10 Venigalla S, Guttmann DM, Jain V, Sharma S, Freedman GM, Shabason JE. Trends and patterns of utilization of hypofractionated postmastectomy radiotherapy: a National Cancer Database analysis. *Clin Breast Cancer* 2018; **18:** e899–908.

11 Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002; **94:** 1143–50.

12 Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005; **75:** 9–17.

13 Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006; **7:** 467–71.

14 Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; **9:** 331–41.

15 Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; **371:** 1098–107.

16 Wang SL, Li YX, Song YW, et al. Postmastectomy chest wall radiotherapy with single low-energy electron beam: an assessment of outcome and prognostic factors. *Pract Radiat Oncol* 2012; **2:** 106–13.

17 Freidlin B, Korn EL. Testing treatment effects in the presence of competing risks. *Stat Med* 2005; **24:** 1703–12.

18 Baillet F, Housset M, Maylin C, et al. The use of a specific hypofractionated radiation therapy regimen versus classical fractionation in the treatment of breast cancer: a randomized study of 230 patients. *Int J Radiat Oncol Biol Phys* 1990; **19:** 1131–33.

19 Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14:** 1086–94.

20 Khan AJ, Poppe MM, Goyal S, et al. Hypofractionated postmastectomy radiation therapy is safe and effective: first results from a prospective phase II trial. *J Clin Oncol* 2017; **35:** 2037–43.

21 Kouloulias V, Mosa E, Zygogianni A, et al. A retrospective analysis of toxicity and efficacy for 2 hypofractionated irradiation schedules versus a conventional one for post-mastectomy adjuvant radiotherapy in breast cancer. *Breast Care* 2016; **11:** 328–32.

22 Bellefqih S, Elmajjaoui S, Aarab J, et al. Hypofractionated regional nodal irradiation for women with node-positive breast cancer. *Int J Radiat Oncol Biol Phys* 2017; **97:** 563–70.

23 Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362:** 513–20.

24 Haviland JS, Mannino M, Griffin C, et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: results from the UK START (Standardisation of Breast Radiotherapy) trials. *Radiother Oncol* 2018; **126:** 155–62.

25 Karlsson P, Cole BF, Chua BH, et al. Patterns and risk factors for locoregional failures after mastectomy for breast cancer: an International Breast Cancer Study Group report. *Ann Oncol* 2012; **23:** 2852–58.

26 Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; **373:** 317–27.

27 Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015; **373:** 307–16.

28 Johansson S, Svensson H, Denekamp J. Timescale of evolution of late radiation injury after postoperative radiotherapy of breast cancer patients. *Int J Radiat Oncol Biol Phys* 2000; **48:** 745–50.

29 Johansson S, Svensson H, Denekamp J. Dose response and latency for radiation-induced fibrosis, edema, and neuropathy in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2002; **52:** 1207–19.

30 Lang JE, Summers DE, Cui H, et al. Trends in post-mastectomy reconstruction: a SEER database analysis. *J Surg Oncol* 2013; **108:** 163–68.

31 Jia-jian C, Nai-si H, Jing-yan X, et al. Current status of breast reconstruction in Southern China: a 15 year, single institutional experience of 20,551 breast cancer patients. *Medicine* 2015; **94:** e1399.