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Hypofractionated versus conventional intensity-modulated radiation irradiation (HARVEST-adjuvant): study protocol for a randomised non-inferior multicentre phase III trial

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ABSTRACT

Introduction Short course regimen has become the major trend in the field of adjuvant radiotherapy for patients with breast cancer. Hypofractionated radiotherapy (HF-RT) regimen of 40–42.5 Gy in 15–16 fractions has been established as a preferred option for whole breast irradiation. However, few evidences of hypofractionated regional nodal irradiation (RNI), especially involving internal mammary nodes (IMNs), could be available during the era of intensity-modulated radiation therapy (IMRT). Against this background, we design this trial to explore the hypothesis that HF-RT regimen involving RNI (including infraclavicular, supraclavicular nodes and IMNs) will be non-inferior to a standard schedule by using IMRT technique.

Methods and analysis This is an open-label randomised, non-inferior, multicentre phase III trial. Patients with breast cancer with an indication for RNI after breast conserving surgery or mastectomy are randomised at a ratio of 1:1 into the following two groups: hypofractionated regimen of 2.67 Gy for 16 fractions or conventional regimen of 2 Gy for 25 fractions. The dose was prescribed to ipsilateral chest wall or whole breast and RNI (including infraclavicular, supraclavicular nodes and IMNs, lower axilla if indicated). The trial plans to enrol a total of 801 patients and all patients will be treated using IMRT technique. The primary endpoint is 5-year locoregional recurrence. The secondary endpoints include 5-year distant metastasis free survival, invasive recurrence-free survival, overall survival, accumulative acute radiation-induced toxicity and accumulative late radiation-induced toxicity, cosmetic outcomes and quality of life.

Ethics and dissemination The study has been approved by the Ethical Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine (version 2018-95-3) and approvals from ethical committee of each participating centre have also been obtained. Research findings will be submitted for publication in peer-reviewed journals.

Trial registration number NCT03829553.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first trial to explore efficacy and safety of hypofractionated radiotherapy regimen of 40 Gy in 15 fractions in patients treated with regional nodal irradiation (including internal mammary nodes) in China.
⇒ The design of the trial as an open-labelled, randomised, non-inferior, multicentre phase III trial will enhance the strength of the trial and reduce bias.
⇒ In this trial, all the comprehensive nodal regions are treated with the ipsilateral breast/chest-wall as an integrated planning target with modern intensity-modulated radiation therapy technique to confirm the safety of internal mammary node irradiation.
⇒ One of the limitations is that this study does not stratify according to clinicopathological, subtype or gene information.

INTRODUCTION

Globally, breast cancer is the most common cancer (11.6% of the total cases) and fifth leading cause of cancer death (627 000 deaths) in women.[1] Adjuvant regional nodal irradiation (RNI) has been proved to significantly reduce any first recurrence and improve breast cancer-specific survival in high-risk patients with breast cancer.[2–7] The standard regimen of RNI is 45–50 Gy in 25–28 fractions and with a sequential tumour bed boost of 10–16 Gy in 5–8 fractions in patients treated with breast conserving surgery (BCS). The overall treatment course is up to 5–7 weeks, which brings great inconvenience to patients such that some patients choose mastectomy even if they are indicated to BCS or declined adjuvant radiotherapy (RT) after

BCS. Long course of RT also aggravates the shortage of RT facilities.

The α/β value is a well-established radiobiological parameter to quantify the sensitivity of normal or malignant tissue to fraction size, with lower than 10 Gy indicating higher sensitivity to fraction size. Yarnold *et al*[8] have demonstrated an α/β value of 3.6 Gy for any change in breast appearance and 3.1 Gy for palpable breast induration after a minimum 5-year follow-up for 1410 patients with invasive breast cancer. Similarly, a meta-analysis of the Standardisation of Breast Radiotherapy (START) pilot trial and the START-A trial provided an adjusted α/β value for local-regional relapse of 3.5 Gy, and α/β estimates for normal tissue endpoints in START-A were around 4 Gy after a 10-year follow-up.[9] Based on radiobiological theory and results of previous studies, breast cancer should be more sensitive to hypofractionation with more than 2 Gy of fraction size. Until now, the efficacy and safety of hypofractionated (HF) whole breast irradiation (WBI) has been confirmed by a series of studies including randomised controlled trials with long-term follow-up and real-world studies as well.[9–14] Moderate HF regimen of 40–42.5 Gy in 15–16 fractions has been established as preferred regimen for WBI in international guidelines and clinical practice.[15–17] Recently, the FAST-FORWARD trial further confirmed that 1-week schedule of 26 Gy in five fractions is non-inferior to standard 3-week regimen of 40 Gy in 15 fractions for 5-year local tumour control and similar in terms of late adverse effects in patients treated with WBI alone.[18]

Compared with the maturity of moderate HF in WBI alone, the evidence supporting hypofractionated RNI (HF-RNI) is limited, while its potential benefit attracts increasing concern.[19–22] The safety and efficacy of hypofractionated radiotherapy (HF-RT) has been preliminarily explored in some previous studies.[23–26] The only published randomised trial has demonstrated that HF-RNI of 43·5 Gy in 15 fractions was non-inferior to standard regimen of 50 Gy in 25 fractions in terms of locoregional control and acute or late adverse effects after a median follow-up of 58.5 months in patients receiving mastectomy.[24] All patients enrolled in the study were treated with single low-energy electron beam, and internal mammary nodes (IMNs) were not included in the field of RNI. Neither patients receiving neo-adjuvant systemic therapy nor those with breast reconstruction were enrolled in the study.

Recent meta-analysis of RNI presented by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that improvement in any recurrence, breast cancer mortality and overall mortality associated with RNI only existed in 'newer trials' which is defined as a better coverage of target volume and lower mean dose of heart (<8 Gy) since 1989 but not in 'older trails'.[27] Our previous studies reported the experience of treating chest wall/whole breast and regional nodes as a whole planning treating volume (PTV) using intensity-modulated radiation therapy (IMRT) technique which brought good PTV coverage with homogeneity and reduce dose of heart and lung.[28 29]

With aforementioned background, there is a lack of evidence in current guidelines to support HF-RNI using modern radiotherapeutic technique, adapting current therapeutic strategy. Our current study is an open-labelled, randomised, non-inferior, multicentre phase III trial (Hypofractionated irradiation At Regional nodal area for breast cancer vs Existed Standard Treatment, short name as HARVEST). Our hypothesis is that HF-RT regimen of 40 Gy in 15 fractions is at least as safe and as effective as standard regimen of 50 Gy in 25 fractions in patients treated with RNI using IMRT technique.

METHODS

Study Design

The HARVEST trial is an open-label, randomised, non-inferior, multicentre phase III trial in China. The main objective of this trial is to investigate the hypothesis that HF-RT regimen of 40 Gy in 15 fractions involving RNI (including infraclavicular, supraclavicular nodes and IMNs) will be non-inferior to a standard schedule of 50 Gy in 25 fractions by using IMRT technique among breast cancer treated with mastectomy or BCS. Eligible patients will be randomly assigned in a 1:1 ratio to receive either HF-RT or conventional fractionated RT. Irradiation is delivered to ipsilateral chest wall or whole breast with regional lymphatic regions (supra/infraclavicular nodes and IMN in each patient, lower axilla if indicated). Eligible patients will be followed for at least 5 years. The primary endpoint is 5-year locoregional recurrence rate (LRR). The secondary endpoints include 5-year distant metastasis free survival (DMFS), invasive recurrence-free survival (IRFS), overall survival (OS), accumulative acute radiation-induced toxicity and accumulative late radiation-induced toxicity, cosmetic outcomes and quality of life. Study design is shown in figure 1.

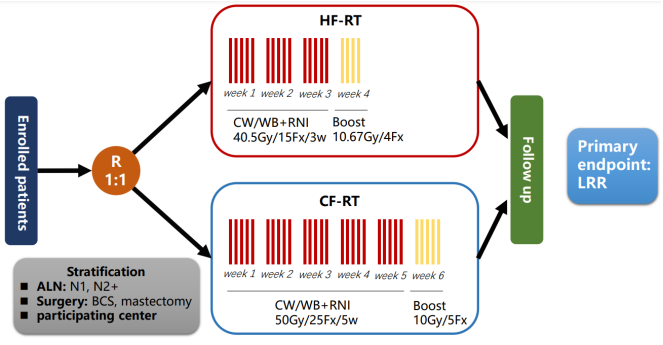

Figure 1 Study design of HARVEST. ALN, axillary lymph nodes; BCS, breast conserving surgery; CF-RT, conventional radiotherapy; CW, chest wall; HF-RT, hypofractionated radiotherapy; LRR, local regional recurrence; R, randomisation; RNI, regional nodes irradiation; w, weeks; WB, whole breast.

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Randomisation

Prior to randomisation, the eligibility electronic edition of case report form (eCRF) must be completed and informed consent must be obtained from patients. Randomisation will be generated via a computer-generated random numbers sequence using SPSS software V.21.0 (IBM Corporation, Armonk, New York, USA), stratified by participating centre, type of primary surgery (BCS or mastectomy) and numbers of positive axillary lymph nodes (1–3 or ≥4). The specific trained staff in Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine is responsible for the randomisation process and provide patient's unique randomisation number (Trial ID) to investigators. Allocation concealment should be ensured, as the service will not release the randomisation group until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. Given the nature of intervention used in the study, no blinding is planned in this study.

Participants and recruitment

Patients will be recruited by radiation oncologists in each study centre. For each potential participant, the background of this trial will be introduced by the clinicians or research nurses at their first visit.

The specific designed manual of this trial will be given to every enrolled patient before they signed the informed consent. Research nurses are responsible for keeping the enrolled patients informed of their treatment and follow-up schedule so as to improve their compliance to the protocol.

The first patient was enrolled on the 21 February 2019 and accrual is expected to last for 3 years (tentatively till December 2022). As the primary endpoint is a 5-year rate of LRR, the final data of collection for the primary outcome measure is expected to be December 2027.

Inclusion and exclusion criteria for the trial

Patients who meet the following criteria will be enrolled in the trial:

- Age 18–75 years old.
- Unilateral histologically confirmed invasive breast carcinoma of pT1–3.
- Breast conserving surgery or mastectomy.
- Breast reconstruction is allowed.
- Histologically confirmed positive axillary lymph nodes (positive sentinel lymph nodes without axillary dissection is allowed).
- Life expectancy of >5 years.
- A minimum negative surgical margin width of >2 mm.
- Karnofsky Performance Status ≥80.
- Estrogen-receptor, progesterone-receptor, human epidermal growth factor receptor-2 (HER-2) and Ki-67 index can be performed on the primary breast tumour or axillary nodes.
- Written informed consent.

Patients who meet the following criteria will be excluded from the trial:

- Supraclavicular lymph nodes, positive ipsilateral internal mammary lymph nodes or residual axillary nodes that may be eligible for a boost dose.
- Pregnant or lactating.
- Severe non-neoplastic medical comorbidities.
- Diagnosis of non-breast malignancy within 5 years preceding enrollment (except for basal cell carcinoma of the skin or carcinoma in situ of the cervix).
- Simultaneous contralateral breast cancer.
- Previous RT to thoracic and/or axillary, cervical region.
- Active collagen vascular disease.
- Evidence of distant metastatic disease and/or T4 disease.

Notes:

1. Patients with severe non-neoplastic medical comorbidities (eg, severe ischaemic heart disease, severe arrhythmia or severe chronic obstructive pulmonary disease) that would preclude radiation treatment will be excluded.
2. Simultaneous contralateral breast cancer includes histologically confirmed pure ductal carcinoma in situ .

Radiotherapy

General consideration

RT should be started within 12 weeks of the last date of surgery or within 8 weeks of last dose of planned adjuvant chemotherapy. The irradiation fields of RNI include supra/infraclavicular nodes and IMN and axilla if indicated. Planned adjuvant endocrine therapy and anti-HER-2 therapy are allowed to continue during the course of RT.

Patient positioning and immobilisation

Patients are positioned supine with both arms abducted (90° or greater) and elevated by a breast board. CT-based treatment planning with scan thickness of 3–5 mm should start at the level of the cranial base to at least 4 cm below the ipsilateral or contralateral inframammary fold. At simulation, the surgical scar should be routinely wired with radiopaque marker.

Volumes of interest

The clinical target volume (CTV) and organs at risk (OAR) must be contoured on all CT slices when these structures are visible based on Radiation Therapy Oncology Group (RTOG) contouring guidelines.[30] In this trial, comprehensive RNI commonly includes supra/infraclavicular nodes and IMNs. Delineation of medial supraclavicular nodes is necessary for all enrolled patients while contouring of lateral supraclavicular nodes is only indicated for patients with the pN2–3 stage. Infraclavicular lymph nodes include axilla level III, rotter's nodes and part of axilla level II without dissection in surgery. For patients with pathological positive sentinel lymph nodes and without subsequent axillary dissection, delineation of axillary levels I and II are indicated when the risk of non-sentinel axillary node involvement is high.

The detailed delineation for CTV and OARs is shown in online supplemental file 1.

The margins between PTV and CTV depend on institutional standards of each study centre with 5 mm in minimum recommended excepted for regional nodes. For planning reasons, the PTV should be cropped 5 mm beneath the skin in case of BCS and 2 mm beneath the skin in case of mastectomy. In case of skin involvement, the ventral border expands to the skin surface.

OARs including ipsilateral and contralateral lung, heart, humeral head and spinal cord were contoured based on RTOG guidelines.

External beam equipment and techniques

The external beam RT are delivered with a linear accelerator with 6 MV of photon in most cases. Integrated multibeam IMRT will be generated and optimised using our predefined protocol for OARs constrains and target coverage.

Dose prescription, fractionation and bolus

Based on an α/β value of 3·5 Gy for breast cancer,[9] 40 Gy in 15 fractions is applied to a hypofractionation group, which has been validated equivalent efficacy and safety to 50 Gy in 25 and recommended as the preferred regimen for WBI in international guidelines and clinical practice.[9–12] Thus, for all enrolled patients, the HF prescribed dose to ipsilateral chest wall or whole breast and regional lymph region is 4005 cGy in 15 fractions over 3 weeks. A sequential tumour bed boost is delivered at 1068 cGy in four fractions to patients treated with BCS. In the control group, the prescribed dose is 50 Gy in 25 fractions and sequential tumour bed boost of 10 Gy in five fractions is delivered with BCS.

Skin bolus of 3 mm on the whole chest wall is recommended to use in case of mastectomy and be documented as well as evaluated within the quality assurance-programmer of the study. If bolus is used, the skin dose must accord with the dose-volume histogram (DVH) constraints of CTV and the volume of CTV should include the bolus.

DVH constraints

DVH constraints predefined for dose specification and dose reporting in PTV and OARs are detailed in tables 1 and 2. The goal of treatment planning is to provide best possible coverage of PTV and at the same time minimise the radiation dose-volume to OARs. The heart was contoured according to heart atlas published by Feng *et al*,[31] which include the whole heart and major cardiac substructures (right atrium, left atrium, right ventricle, left ventricle, left main coronary artery and left anterior descending artery, left circumflex artery and right coronary artery). The DVH constraints was set for the whole heart, while the DVH data of cardiac substructures were collected for further exploratory analyses.

Treatment verification schedule and quality assurance

Daily patient set-up should be performed using laser alignment to skin markers. Online cone-beam CT verification with action level of correction being 5 mm, which must be taken during the first three treatment session and weekly thereafter. The delineations and the DVH constraints for CTV, PTV and OARs of the first 20 patients will be checked by a senior radiation oncologist in each participated centre. Acceptable deviations have been defined in the protocol and should be recorded.

Criteria for discontinuing interventions

Criteria for discontinuing intervention (exiting the trial) for a given trial participant are contemplated in the informed consent from (at patient's legal representative request). Enrolled patients can withdraw their informed consent and exit the trial at any time. If patients withdraw from the trial before RT, institutional standard fractionated RT will be applied. Adverse events should be

Table 1 DVH constraints for PTV

Structures	Constraints	Hypofractionated regimen	Conventional regimen
PTV of chest wall/breast+RNI	Per protocol	D95% >40 Gy	D95% >50 Gy
	Acceptable variation	D90% >40 Gy	D90% >50 Gy
	Per protocol	V43Gy <5%	V55Gy <5%
	Acceptable variation	V45Gy <5%	V56Gy <5%
	Per protocol	V38Gy >99%	V48Gy >99%
	Acceptable variation	V36Gy >99%	V45Gy >99%
PTV of breast+tumour bed boost+RNI	Per protocol	D95% >50 Gy	D95% >60 Gy
	Acceptable variation	D90% >50 Gy	D90% >60 Gy
	Per protocol	V55Gy <5%	V66Gy <5%
	Acceptable variation	V58Gy <5%	V69Gy <5%
	Per protocol	V48Gy >99%	V57Gy >99%
	Acceptable variation	V45Gy >99%	V54Gy >99%

DVH, dose-volume histogram; PTV, planning target volume; RNI, regional nodal irradiation.

Table 2 DVH constraints for OARs

OARs	Hypofractionated regimen			Conventional regimen		
	Dosimetric parameter	Per protocol	Acceptable variation	Dosimetric parameter	Per protocol	Acceptable variation
Heart for left-sided breast cancer	Mean	<5.5 Gy	<6.5 Gy	Mean	<7 Gy	<8 Gy
	V25Gy	<10%	<15%	V30Gy	<10%	<15%
	V8Gy	<20%	<25%	V10Gy	<20%	<25%
Heart for right-sided breast cancer	Mean	<2 Gy	<3 Gy	Mean	<2 Gy	<3 Gy
	V4Gy	<15%	<20%	V4Gy	<15%	<20%
Ipsilateral lung	Mean	<13 Gy	<14 Gy	Mean	<15 Gy	<16 Gy
	V8Gy	<45%	<55%	V10Gy	<45%	<55%
	V16Gy	<30%	<35%	V20Gy	<30%	<35%
	V25Gy	<23%	<25%	V30Gy	<23%	<25%
Contralateral lung	Mean	<2 Gy	<3 Gy	Mean	<2 Gy	<3 Gy
	V4Gy	<10%	<15%	V4Gy	<10%	<15%
Spinal cord	Max	<40 Gy	N/A	Max	<45 Gy	N/A
Ipsilateral humeral head	Mean	<20 Gy	<25 Gy	Mean	<20 Gy	<25 Gy

DVH, dose-volume histogram; OAR, organs at risk.

recorded in eCRF and reported to principal investigator (PI). Whether RT should be discontinued is at the discretion of individual investigator.

Endpoints

The primary endpoint of the trial is LRR, which is defined as any first recurrence confirmed by histology or cytology in the ipsilateral chest wall or breast or regional nodes areas (including axillary, supraclavicular, infraclavicular lymph nodes or IMNs).

Secondary endpoints are as following:

- DMFS: the time from the date of randomisation to any recurrence of tumour at distant sites or death from any cause.
- IRFS: the time from the date of randomisation to any invasive recurrence of tumour, distant metastases or death from any cause and second invasive primaries, including invasive neoplasms of the breast.
- OS: the time from the date of randomisation to the date of death from any cause or end of the follow-up.
- Cosmetic outcomes: patients receiving BCS are graded according to the BCS-Harvard/National Surgical Adjuvant Breast and Bowel Project /RTOG scoring scale grades: excellent, when compared with the untreated breast, there is a minimal or no difference in the size or shape of the treated breast; good, slight difference in the size or shape of the treated breast; fair, obvious difference in the size or shape of the treated breast; and poor, marked change in the size or shape of the treated breast.
- Acute toxicities: number of participants with ≥Grade 1 acute radiation-induced toxicities within time from beginning of RT to 6 months after completion of RT assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) V.3.0.
- Late toxicities: number of participants with ≥Grade 1 late radiation-induced toxicities within time from 6 months after completion of RT to 5 years after completion of RT assessed according to the RTOG/European Organization for Research on Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema and CTCAE V.3.0
- Reconstruction complications: number of participants with any reconstruction complications (flap necrosis, capsular contracture, infection, loss of implant/expander or flaps and so on) and the interval between the RT and reconstruction complications will be recorded. Patient reported outcome with reconstruction will be evaluated by Breast-Q questionnaires before RT and 12 months after RT.

Exploratory endpoints of the trial are quality of life using self-administered questionnaire EORTC QLQ-C30 and QLQ-BR23.

Outcome measures and follow-up

Schedule of enrollment, interventions and assessments are shown in table 3. Any tumour recurrence, metastasis, death and radiation-related toxicity should also be recorded in the eCRF at each time of follow-up. Survival events will be assessed by physical examination, serum test, ultrasound of the breast, regional nodes and abdomen every 6 months, breast mammography and chest CT scan annually after completion of RT. Any additional examinations are at the discretion of clinicians. An increase in arm circumference of at least 10% in the lower arm or the upper arm, or both, compared with the contralateral

Table 3 Schedule of enrollment, interventions and assessments

	Study period														
	Pre-radiotherapy	Interventions: radiotherapy						Post-radiotherapy							
Timepoint	0	1w	2w	3w	4w	5w	6w	4w	6m	12m	18m	2y	3y	4y	5y
Enrollment															
Eligibility screening	X														
Informed consent	X														
Randomisation	X														
Interventions															
Hypofractioned regimen		X	X	X	X										
Conventional regimen		X	X	X	X	X	X								
Assessments															
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest CT scan	Simulation CT is acceptable									X		X	X	X	X
Mammography										X		X	X	X	X
Ultrasound for breast and regional nodes	X								X	X	X	X	X	X	X
ECG	X								X	X	X	X	X	X	X
Echocardiography	X								X	X	X	X	X	X	X
Cosmetic outcomes for BCS	X							X	X	X	X	X	X	X	X
Quality of life	X							X	X	X	X	X	X	X	X

BCS, breast conserving surgery.

arm at the same timepoint is recorded as clinically significant lymphoedema. Shoulder mobility, skin changes and overall change in breast appearance should be recorded using photos or videos. Quality of life data will be obtained using self-administered questionnaire EORTC QLQ-C30 and QLQ-BR23.

Data collection and management

Data of the trial will be collected and recorded in the eCRF established on the online clinical system build by Shanghai Jiao Tong University School of Medicine affiliated Ruijin Hospital. Participating centres have access to the online clinical system. The following forms have been created in the online system for the data collection: baseline information before randomisation, pretreatment assessment and RT plan details for HF or conventional group, acute toxicities reporting form during RT, follow-up review forms for different timepoints, quality of life questionnaire forms and serious adverse events (SAEs) reporting form. For patients who withdraws from the study, the effective date of notification is defined as the date when their withdrawal is received by the study team and information about these patients will not be collected afterwards.

The PIs, ethical committees, sponsors are allowed to access database for analysing and data monitoring at any time. Participating centres could have access to the data of their own centre. The leading investigators in each centre are responsible for monitoring the quality of data. Once the trial is completed, the data quality and integrity will be checked by specific trained staffs and then closed for analysis.

All data generated in this study will remain confidential. Any public reports of this study will not disclose the personal identity of the patients. The research centre will keep all relevant data of this study for at least 5 years after the completion of study and permission of the ethical committee is need for destruction of data.

Calculation of samples

The sample size is calculated with Power Analysis and Sample Size Software (2017) (NCSS, Kaysville, Utah, USA, www.ncss.com/software/pass) with sample allocation ratio of 1:1 between HF-RT regimen and conventional regimen. The primary objective is to compare the cumulative incidence of patients experiencing an LRR by 5 years between HF-RT and conventional course of RT. Based on the outcomes of patients treated at our institute, the cumulative proportion of the LRR in the control arm is expected to be 8% at 5 years. We accepted a maximum loss of efficacy of 6% points in the HF radiation group (corresponding to an HR of 1.81). This non-inferiority margin was determined through consultation with radiation oncologists. The sample size for the trial, a total of 801 patients, was based on these assumptions and a power of 80% with a one-sided type I error of 2.5%, and the anticipated drop-out rate of 10%. Patients will be recruited over a period of 3 years and followed up for a further 5 years thereafter.

Statistical analysis

For the primary endpoint, Kaplan-Meier curves of 5-year LRR incidence rates will be reported. Cumulative incidence of LRR will also be estimated using the competing risk model, with death as a competing event, and compared by Gray's test. The HR and the 95% CIs for LRR will be computed using the Cox proportional hazards regression. Primary assessment of non-inferiority is based on whether the upper limit of the two-sided 95% CI (corresponding to one-sided 97·5% CI) for the absolute difference in 5-year LRR was less than 6%. Non-inferiority of HF versus conventional group will also be tested using the a priori critical HR of 1·81 (ln0.86/ln0.92, from protocol-specified incidence) with estimated accrual of 3 years. Cumulative proportions of time to survival endpoints like DMFS, IRFS, OS will be computed using Kaplan-Meier method, and compared between groups by the log-rank test. Acute and late toxicities were summarised as frequency and severity on the basis of their association with protocol treatment. Categorical variables including acute or late toxicities and cosmetic outcomes for BCS will be compared using χ^2 test or Wilcoxon test while multivariate logistic regression will be performed to explore influencing factors. Severe radiation-related toxicity events will be listed one by one. The t-test was used for comparison of the continuous variables. Subgroup analysis for LRR according to number of positive lymph nodes and type of breast surgery will be also computed. Last observation carried forward will be performed for missing data. All tests will be two-sided with a significance level of 0.05 except the primary endpoint. All efficacy and safety analyses are based on the intention-to-treat principle, and per-protocol analysis will be performed for the primary endpoint. Statistical analysis will be performed with SPSS software V.21.0 (IBM Corporation, Armonk, New York, USA).

Monitoring

All leading investigators of the participating centres are members of the trial steering committee (TSC). Study coordination, monitoring, data acquisition, management and statistical analysis will be performed by the statisticians in Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine. An independent data safety and monitoring committee is constituted for monitoring the trial progress, safety data, data quality and making recommendations to the TSC about the continuation of the trial based on the available data provided by investigators.

The adverse event is defined as any untoward medical occur to the patient during the trial, which do not necessarily have a causal relationship with RT. All SAEs should be reported to the ethical committee within 24 hours after being received by the PI. Once a patient has an SAE, all anti-tumour treatments should be stopped immediately.

All adverse events should be followed until resolution or until the event is considered stable, including adverse events that induce patient's withdrawal from the study. The time, severity, expectedness, duration, measures taken and outcome of SAEs should be recorded in the eCRF. General adverse events are required to be reported to the ethical committee and the PI regularly, once every 6–12 months.

Ethics and dissemination

The study has been approved by the Ethical Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine (version 2018-95-3) and approvals from ethical committee of each participating centre have also been obtained. Any modifications to the protocol will be documented in the protocol amendments, which should be approved by the ethical committee prior to implementation. This study is conducted in accordance with the Declaration of Helsinki and good clinical practice. Written informed consent is obtained from all participants before enrollment.

Research findings will be submitted for publication in peer-reviewed journals. Authors will be individuals who have made key contributions to study design and conduct. The clinical study reports and summary thereof will be provided to the local ethical committee of the institutes and sponsors participating in the protocol.

Patient and public involvement

Patients or members of the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

This is an open-label, randomised, non-inferior, multicentre phase III trial. Our primary objective is to investigate whether the efficacy and safety of 3-week HF-RT regimen is non-inferior to 5-week conventional regimen in patients receiving comprehensive RNI not limited to supra/infraclavicular nodes and IMNs, but also axillary nodes when indicated such as patients receiving sentinel lymph nodes biopsy (SLNB) with positive pathological nodes without undergoing subsequent axillary dissection while the risk of non-sentinel axillary nodes involvement is high. In this trial, all the comprehensive nodal regions are treated with the ipsilateral breast/chest-wall as an integrated planning target with inverse planning IMRT. These are two key features in the design of this trial compared with other ongoing and published trials of HF-RNI.

The role of IMN irradiation has been well established in clinical randomised trials and series of meta-analyses published by EBCTCG.[2–4] In MA20 trial, RNI was found to significantly increase the rate of disease-free survival (DFS) from 77% to 82% (HR, 0.76; 95% CI, 0.61 to 0.94; p value=0.01) at 10 years follow-up in BCS patients with node-positive or high-risk node-negative breast cancer.[3] EORTC 22922/10925 trial also reported that RNI was associated with significant improvements in DFS (72.1% vs 69.1%; HR, 0.89; 95% CI, 0.80 to 1.00; p=0.04) and DMFS (78.0% vs 75.0%; HR, 0.86; 95% CI, 0.76 to 0.98; p=0.02) and reduction in breast-cancer mortality (12.5% vs 14.4%; HR, 0.82; 95% CI, 0.70 to 0.97; p=0.02) with a median follow-up of 10.9 years in patients with positive axillary nodes or a centrally or medially located primary tumour.[2] Both of these two trials included the IMN in the fields of RNI. Danish breast cancer cooperation group IMN study demonstrated that addition of IMN irradiation to RNI significantly improved OS and breast cancer-specific survival in node positive patients after a median follow-up of 8.9 years.[4] In the EBCTCG meta-analysis, post mastectomy RT (PMRT) was found to significantly reduce LRR, any recurrence and breast cancer mortality. In 20 out of 22 trials enrolled in this meta-analysis, RT was given to the IMN.[5] Based on these evidences, the latest version of NCCN Guidelines (V.3.2020) recommends delivery of IMN irradiation in patients with ≥4 positive axillary lymph nodes (ALNs) (category 1) and in those with 1–3 positive ALNs (category 2A).[32]

Nevertheless, the inclusion of RNI does increase the complexity of treatment planning, potentially increase the risk of dose-volume to the heart and lung.[33] Thus, IMN was not mandatory in irradiation fields of RNI in the published randomised trial and in majority of ongoing trials of HF-RNI (shown in table 4). With the maturity of IMRT and increasing awareness of OAR sparing in RNI, it is now possible to minimise the increase of normal tissue irradiated volume associated with IMN irradiation. In the recent EBCTCG meta-analysis of RNI, 12 out of 14 enrolled trials had IMN irradiation.[27] The results showed that RNI in 'newer trials' since 1989 significantly reduced breast cancer mortality (risk ratio=0.82, p value=0.00006) and had no significant impact on non-breast cancer mortality (risk ratio=0.96, p value=0.66), while non-breast cancer mortality was significantly increased in 'older trails'. These data prove that the therapeutic benefit of comprehensive nodal irradiation in high-risk patients is significantly displayed when OAR dose-volume is well controlled.

Another characteristic of this trial is that it enrols patients undergoing SLNB with positive pathological nodes without subsequent axillary dissection, and the RNI field is allowed to include the axilla as long as the treatment planning meets the target and OAR DVH constraints. In Z0011 trial, SLNB had been proved as safe as axillary lymph node dissection (ALND) for patients with 1 to 2 SLNs.[34] The EORTC 10981/22023 trial demonstrated that axillary RT and ALND after a positive sentinel node provide excellent and comparable axillary control for patients with T1–2 primary breast cancer,[35] while axillary RT was associated with significantly less lymphoedema events during the long-term follow-up.[35 36] In a recent prospective screening trial, 1815 patients were enrolled to explore the impact of axillary surgery type and regional lymph node radiation on lymphoedema.[37] The

Table 4 The ongoing trials on HF-RNI in breast cancer

NCT number	Country	Start year	Randomised	Enrolled patients	Reconstruction	IMN	Study group	Control group	No	Endpoint	Status
NCT03319069	Egypt	2017	Yes	T3–4 or ≥N2	No	No	43.5 Gy/15 Fx/3w	50 Gy/25 Fx/3w	60	Locoregional control	Unknown
NCT02958774	America	2017	No	Stage II–III with N+ or T3N0	Not mentioned	Not mentioned	40.05 Gy/15 Fx/3w	N/A	389	Lymphoedema rates	Recruiting
NCT03127995	France	Not yet	Yes	pT1–3N0–3M0	Not mentioned	Not mentioned	40 Gy/15 Fx/5w	50 Gy/25 Fx/5w	1265	Arm lymphoedema	Not yet recruiting
NCT03856372	China	2018	Yes	T1–2N1 with high risk factor* or T3–4, or N2–3	Yes	Not mentioned	42.56 Gy/16 Fx/3w	50 Gy/25 Fx/5w	1494	Locoregional control	Recruiting
NCT02690636	Egypt	2016	Yes	pT1–3, N1–2	Not mentioned	Not mentioned	42.56 Gy/16 Fx/3w	50 Gy/25 Fx/5w	500	Locoregional control	Recruiting
NCT02912312†	America	2017	Yes	T0–T3, N0–N2a or N3a	Not mentioned	Not mentioned	15 Fx in 3w	25 Fx in 5w	290	Lymphoedema rates	Recruiting
NCT02700386	America	Not yet	No	Stage IB–IIIB	Yes	Not mentioned	40.05 Gy/15 Fx/3w	N/A	112	Treatment-related adverse events	Not yet recruiting
NCT02515110	America	2015	No	T1–3, N1–2a	Yes	Not mentioned	42.56 Gy/16 Fx/3w	N/A	137	Lymphoedema rates	Recruiting
NCT04228991	Canada	2021	Yes	T1–3, N1–2	No	Yes	26 Gy/5 Fx/1w	40 Gy/15 Fx/3w	588	Lymphoedema rates	Recruiting
NCT03414970	America	2018	Yes	Stage IIa–IIIa	Yes	Yes	15 Fx in 3w	25 Fx in 5w	880	Reconstruction complication rate	Recruiting
NCT04472845	India	2020	Yes	pT3–4pN2–3 M0	No	Partly‡	26 Gy/5 Fx/1w	40 Gy/15 Fx/3w	1018	Locoregional control	Not yet recruiting
NCT04509648	China	2021	No	pT1–3N1–3	Yes	Yes	26 Gy/5 Fx/1w	N/A	197	Acute radiation-induced toxicity	Recruiting

*At least one of the following risk factors: <40 years, Grade 3, lymphovascular invasion positive, ER/PR negative or HER-2 overexpression.
†The trial included preoperative radiation therapy.
‡In T3–4 central and inner quadrant lesions and patients with N2 disease.
ER, estrogen receptor; Fx, factions; HER-2, human epidermal growth factor receptor-2; HF-RNI, hypofractionated regional nodal irradiation; N/A, not applicable; PR, progesterone receptor; w, weeks.

results showed that ALND-alone group had a significantly higher lymphoedema risk compared with the axillary RT following SLNB (HR=2.66, p=0.02). These prospective trials have provided evidences that omitting the ALND for patients with limited positive sentinel lymph nodes is safe and will result in less lymphoedema. There is lack of literature to support the use of axillary RT with HF. Therefore, our trial enrols patients undergoing SLNB with positive pathological nodes without subsequent axillary dissection.

The negative influence of PMRT on cosmetic outcome in patients receiving immediate breast reconstruction (IBR), especially implant-based IBR has been widely reported.[38–41] Efforts including more sophisticated delineation of CTV based on different T stage, implant-pectoris muscle special relationship and improved dose homogeneity are being made to ameliorate the detrimental effect of ionising irradiation to cosmesis.[42–45] Some retrospective studies and subgroup analysis of a prospective phase II study have indicated that the feasibility of adjuvant HF among breast cancer treated with IBR.[26 46 47] Thus, patients with breast cancer receiving IBR would be enrolled in the present study.

In our previous study, treating chest wall/whole breast and at-risk nodal volume including IMN as a whole PTV using IMRT technique has been proved to achieve good PTV coverage, satisfactory dose coverage and homogeneity of PTV and irradiation dose of OARs.[48 49] Based on the strict DVH constraints and maturation of IMRT technique, we include the IMN in the fields of RNI by using IMRT technique in this trial, in order to investigate the efficacy toxicity of HF-RNI.

We hope that our trial could provide high-level evidence to support 3-week regimen of RNI as standard option in patients with breast cancer with an indication for RNI following BCS or mastectomy. And we also aim to clearly define the safety of IMN irradiation using modern IMRT technique.

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Contributors W-XQ, LC and JC designed the original protocol for the study. FX contributed to study management. JX, FX, W-XQ, LC and XT drafted the manuscript. JX submitted the study. W-XQ and JL performed the sample size calculation and data analysis. JX, FX, YZ, GC, XL, QZ, QL, YY, CX, RC, SW, XT, CC, SZ, MeC, MiC, XQ, CS, JL, HX, FX, YH, ML, DO, KWS, W-XQ, LC, XH, JC participated in enrollment, treatment and follow-up of patients.

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Definitions of chest wall/breast, regional nodes and tumor bed

Page2:

Table S1 Anatomical boundaries of chest wall/whole breast CTV

Page3:

Table S2 Anatomical boundaries of CTV for regional nodes

Page4:

Table S3 Tumor bed contours

Table S1. Anatomical boundaries of chest wall/whole breast CTV

	Chest wall	**Whole breast**
Cranial	Caudal border of clavicle head	Clinical reference+ second rib junction
Caudal	Clinical reference+ loss of CT apparent contralateral breast	Clinical reference+ loss of CT apparent breast
Medial	Sternal-rib junction	Sternal-rib junction
Lateral	Clinical reference/mid-axillary line typically excludes latissimus dorsi muscle	Clinical reference/mid-axillary line typically excludes latissimus dorsi muscle
Anterior	Skin	5 mm below the skin surface
Posterior	Rib-pleural interface	Excludes pectoralis muscles, chest-wall muscles, ribs

Table S2. Anatomical boundaries of CTV for regional node

	Cranial	Caudal	Medial	Lateral	Anterior	Posterior
Medial Supra-clavicular	Caudal to the cricoid cartilage	Junction of Brachioceph. -axillary veins /Caudal edge clavicle head	Medial border of internal carotid vessels	Medial border of clavicle head or 5 mm below the skin surface	Posterior edge of sternocleidomastoid muscle	Posterior surface of internal carotid artery or anterior surface of scalene muscles
Lateral Supra-clavicular *	Caudal to the cricoid cartilage	Junction of Brachioceph. -axillary veins. /Caudal edge clavicle head	At the longus coli	Medial border of clavicle head or 5mm below the skin surface	At the trapezius	Posterior surface of internal carotid artery or anterior surface of scalene muscles
Axilla level III	Pectoralis minor muscle insert on Coracoid	Axillary vessels cross medial edge of pectoralis minor muscle	lateral border of clavicle, ribs, junction of brachioceph- axillary veins.	Medial border of pectoralis minor muscle	Posterior surface of pectoralis major muscle	Anterior border of ribs or posterior border of subclavian or axillary vessels
Axilla level II	Insertion point of pectoralis minor muscle	The caudal border of the pectoralis minor muscle	Medial edge of pectoralis minor muscle	Lateral edge of pectoralis minor muscle	Pectoralis minor muscle	Anterior border of ribs and serratus anterior
Axilla level I	below the humeral head	At the point where the pectoralis major inserts on the ribs (around 4th to 5th rib)	Lateral border of pectoralis minor muscle	Cranially up to an imaginary line between the major pectoral and deltoid muscles, and further caudal up to a line	At posterior pectoralis major & minor muscles	An imaginary line anterior to the surface of latissimus dorsi muscle, subscapularis muscle and teres major

				between the major pectoral and latissimus dorsi muscles		muscle
Rotter's nodes	Insertion point of pectoralis minor	The caudal border of the pectoralis minor muscle	Medial edge of pectoralis minor muscle	Lateral edge of pectoralis minor muscle	Pectoralis major muscle	Pectoralis major muscle
Internal mammary nodes	Junction of Brachioceph-axillary veins.	Cranial side of the 4rd rib (in selected cases 5th rib)	7mm from internal mammary vessels	7mm from internal mammary vessels	Ventral limit of the vascular area	Pleura

Notes:

Comprehensive RNI commonly includes supra/infraclavicular nodes and internal mammary nodes. Delineation of medial supraclavicular nodes is necessary for all enrolled patients while contouring of lateral supraclavicular nodes is only indicated for patients with the pN2-3 stage. Infraclavicular lymph nodes include axilla level III, rotter's nodes, and part of axilla level II without dissection in surgery. For patients with pathological positive sentinel lymph nodes and without subsequent axillary dissection, delineation of axillary levels I and II are indicated when the risk of non-sentinel axillary node involvement is high.

Table S3. Tumor bed contours

GTV	Includes seroma and surgical clips
CTV	GTV with a margin of 1 cm in all directions and without exceeding CTV of whole breast and midline
PTV	GTV with a margin of 0.7 cm in all directions and without exceeding PTV of whole breast

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Page	Section/item	Item No	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
4	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
		2b	All items from the World Health Organization Trial Registration Data Set
20	Protocol version	3	Date and version identifier
20	Funding	4	Sources and types of financial, material, and other support
20	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
1-2		5b	Name and contact information for the trial sponsor
20		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
14		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
	Introduction		

5-6	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
5-6		6b	Explanation for choice of comparators
6	Objectives	7	Specific objectives or hypotheses
6	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
	Methods: Participants, interventions, and outcomes		
6	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
7,8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
6,8-10	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
10		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
7		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
8		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial

10-12	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
11,28	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
12-13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
7	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
7	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Not applicable	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
Not applicable		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
12	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
7,12		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
12	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
13-14	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

13-14		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
13-14		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
14	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
Not applicable		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
14	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
14	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
14,17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
14	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

7,20	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
Not applicable		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
12	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
20	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
12,14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
14	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
14-15	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
14-15		31b	Authorship eligibility guidelines and any intended use of professional writers
Not applicable		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
	Appendices		
20	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates

Not applicable	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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乳腺癌术后区域淋巴结大分割对比常规分割一体化 IMRT 的多中心、随机对照 III 期临床研究

知情同意书·知情告知页

医院：_____ 研究者姓名：_____

病人姓名：_____病人编号：_____

亲爱的患者：

您的医生已经确诊您患有乳腺癌，将会接受包括内乳淋巴结在内的区域淋巴结放疗。

我们将邀请您参加一项“乳腺癌术后区域淋巴结大分割对比常规分割一体化 IMRT 的多中心、随机对照 III 期临床研究”，以评估联合区域淋巴结（包含内乳淋巴结）大分割放疗与常规分割放疗在乳腺癌术后患者中的疗效和不良反应。

在您决定是否参加这项研究之前，请尽可能仔细阅读以下内容，它可以帮助您了解该项研究以及为何要进行这项研究，研究的程序和期限，参加研究后可能给您带来的益处、风险和不适。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请您的医生给予解释，帮助您做出决定。

一、研究背景和研究目的：

全国肿瘤登记中心发布的年报显示，乳腺癌已经位列我国女性恶性肿瘤发病率首位，其死亡率也位居前列，严重威胁我国女性健康。放射治疗是乳腺癌的主要治疗手段，可显著降低术后复发和死亡风险。尽管乳腺癌术后放疗的疗效确切，但是传统放疗(50Gy/25 次，2Gy/次/天，每周 5 次；保乳瘤床加量 10-16Gy/5-8 次)的疗程长达 5-7 周，需要患者每天往返医院或者进行长时间的住院治疗。这给患者带来了巨大的时间成本和包括治疗费用、护理费用、交通费用等在内的沉重经济压力，严重影响患者及其家庭的正常生活。另外，在全球范围内放射治疗设备短缺均是影响患者从放射治疗手段中获益的重要障碍，中国作为发展中国家的放射治疗设备短缺情况更为突出。而长达 5-7 周的治疗疗程使单个乳腺癌术后放疗患者对放射治疗设备的累积占用时间过长，进一步加剧了放射治疗设备短缺的现状。

大分割放疗是一种在与常规分割模式下的放疗总剂量生物等效的前提下，通过增加单次照射剂量（>2Gy/次），减少实际放疗总剂量，从而缩短治疗疗程的放疗新模式。既往研究已经证实大分割全乳放疗可以在不影响疗效和不增加不良反应的前提下，将放疗疗程缩短至 3-4 周，极大的减轻了患者的时间成本和经济压力，提高放射治疗的性价比。同时，大分割放疗治疗计划的实施显著减少单个乳腺癌放疗患者对放射治疗设备的占用时间，使有限的设备可以服务于更多的乳腺癌患者，从而使更多的患者有条件从术后放射治疗中获益。

尽管目前指南已将大分割放疗作为全乳放疗的优选推荐，但是对于大分割放疗在联合区域淋巴结照射的乳腺癌术后放疗患者中的疗效和不良反应，目前仍缺乏成熟的大样本前瞻性随机对照临床研究数据。近年来，有关区域淋巴结预防性照射和内乳淋巴结放疗的获

益和不良反应受到越来越多的关注。随着 2015 年有关乳腺癌术后区域淋巴结放疗（包括内乳淋巴结）的三项大型 III 期临床研究试验结果的公布，包含内乳淋巴结的区域淋巴结放疗在乳腺癌术后放疗中的地位得到了进一步确立。但是，目前已报道和已注册在研的联合区域淋巴结大分割放疗研究的研究设计中，区域淋巴结放疗范围都仅包含同侧锁骨上淋巴结引流区，而将内乳淋巴结引流区排除在外。这主要是因为将内乳淋巴结引流区包括在靶区范围内，可能增加肺组织和心脏组织的辐射剂量，继而带来放射性肺损伤和心脏损伤增加风险。本课题申请人陈佳艺教授所指导博士研究生的研究证实，瑞金医院放疗科通过多年临床实践，应用一体化 IMRT 技术，已经可以实现在照射内乳淋巴引流区的同时，不明显增加心肺正常组织剂量。因此，本中心可以在一体化 IMRT 技术应用下，在保证安全的前提下，对包含内乳淋巴结的联合区域淋巴结照射大分割放疗进行探索，以期给患者带来更大潜在获益。

希望通过开展此项前瞻性 III 期随机对照临床研究，探讨应用一体化 IMRT 技术模式下联合区域淋巴结（包含内乳淋巴结）大分割放疗与常规分割放疗在乳腺癌术后患者中的疗效和毒副反应，为大分割放疗治疗有区域淋巴结（包含内乳淋巴结）放疗指征的乳腺癌术后患者中的应用提供高级别的循证医学证据，从而填补目前乳腺癌放射治疗相关指南的空白。

本研究将在国内多个研究中心（三级甲等医院）进行，预计共有 801 名受试者参加。

二、哪些人不宜参加研究

您若有下列情况则不适合参加本研究:

1) 经病理证实的同侧锁骨上淋巴结阳性患者
2) 经病理或者影像学证实的同侧内乳淋巴结转移患者
3) 妊娠期或哺乳期女性
4) 有严重的非肿瘤性内科合并症，影响放疗实施
5) 既往 5 年内有恶性肿瘤病史（不包括既往小叶原位癌，皮肤基底细胞癌、皮肤原位癌及宫颈原位癌）
6) 同时性对侧乳腺癌
7) 既往颈部、胸部或者同侧腋窝放疗史
8) 有活动性胶原血管病
9) 病理或者影像学证实的远隔部位转移
10) 原发肿块分期为 T4 的患者
11) 不能在乳腺癌根治手术后（乳房保留手术或者乳房切除手术）12 周内（或距辅助化疗结束 8 周内）开始放疗
12) 其他审查员从登记研究中认为有充分理由是不合格的情况：如有潜在的与临床方案不符的情况等；不能或不愿意签署知情同意书；经医疗机构出具的精神疾病患者或者不能配合治疗患者。

三、如果参加研究将需要做以下工作：

在您入选研究前，您将接受以下检查以确定您是否可以参加研究：

1) 医生将询问、记录您的病史，对您进行体格检查。

2） 您需要做胸部 CT、乳腺钼靶、乳腺腋窝锁骨区淋巴结超声、腹部超声、心电图、心脏超声等检查。

您是合格的纳入者,您可自愿参加研究,签署知情同意书；如您不愿参加研究,我们将按您的意愿施治。

若您自愿参加研究，将进行随机分组，并根据分组结果接受相应方案的术后放疗，具体如下：

Arm A，大分割组放射治疗，具体如下：

1. 所有患者的乳腺癌术后辅助放疗均通过一体化 IMRT 技术实施。
2. 分割剂量实现方式：
   1） 乳房切除术后患者：靶区范围包括同侧胸壁+锁骨上下区+内乳区，处方剂量：40Gy/15 次，2.67Gy/次/天，每周 5 次，3 周完成
   2） 乳房保留术后患者：靶区范围包括同侧全乳+锁骨上下区+内乳区，处方剂量：40Gy/15 次，2.67Gy/次/天，每周 5 次，3 周完成；序贯局部瘤床加量，10.68Gy/4 次，2.67Gy/次/天，每周 5 次，1 周完成

Arm B：常规分割组放射治疗，具体如下：

1. 所有患者的乳腺癌术后辅助放疗均通过一体化 IMRT 技术实施。
2. 分割剂量实现方式：
   1） 乳房切除术后患者：靶区范围包括同侧胸壁+锁骨上下区+内乳区，处方剂量：50Gy/25 次，2Gy/次/天，每周 5 次，5 周完成
   2） 乳房保留术后患者：靶区范围包括同侧全乳+锁骨上下区+内乳区，处方剂量：50Gy/25 次，2Gy/次/天，每周 5 次，5 周完成；序贯局部瘤床加量，10Gy/5 次，2Gy/次/天，每周 5 次，1 周完成

两组患者在放疗前、放疗期间及放疗结束后都将接受放疗医师安排的疗效及不良反应评估，随访项目及间隔如下：

1） 随访项目：体格检查、胸部 CT、乳腺钼靶、乳腺和区域淋巴结超声、腹部超声、心电图、心脏超声、乳房美容效果评估、生活质量量表问卷
2） 随访间隔：放疗开始前进行基线检查；放疗结束后 4 周；放疗结束后 2 年内，每 6 个月一次；放疗结束 2 年后，每 12 个月一次。随访医师将根据指南及本研究方案要求安排患者进行相关随访项目。

研究对象需要根据随机分组情况接受相应分割方案的放射治疗，并且按照研究方案设计的随访时间点在放疗科医生处接受相应项目的随访，期间需要接受生活质量量表问卷评估。

四、参加研究可能的受益

您若随机至常规分割放疗组将接受标准术后放射治疗，本研究有规范的靶区及正常组织勾画指南图谱以及严格的正常组织剂量限制的保障。因此，可以得到更有安全保障的术后放射治疗。您若随机至大分割组，放疗疗程将缩短至 3-4 周，这将极大降低您整个治疗过程的时间成本、治疗负担和护理费用，减少放射治疗对您本人及家庭的工作和生活影响。本研究所有入组患者的放射治疗将采用一体化 IMRT 技术。IMRT 技术是前沿的精准放疗技术，与传统放疗技术相比较，IMRT 技术具有放射剂量控制的明显优势，所有参加本研究的均可在 IMRT 这种前沿技术保障下，得到更加安全有效的治疗。同时通过本研究得到的有关研究信息将有益于您及其他患者，推动相关研究的发展。

五、参加研究可能的不良反应、风险和不适、不方便

本研究无侵入性操作，入组条件基于现有的国际标准，无额外风险。但抗肿瘤标准治疗可带来相关风险，本研究中所有患者均需按照规范接受放射治疗，已知的潜在风险

为乳腺癌放射治疗相关的急性和晚期放射性损伤，主要包括：皮肤损伤、胸壁或者乳房疼痛、肺损伤、心脏损伤、上肢水肿、上肢活动功能障碍、臂丛损伤、乳房外形改变等。潜在风险为大分割的剂量分割模式的疗效和安全性尚未在乳腺癌术后区域淋巴结放疗中得到大型临床研究证实，因此该剂量分割模式在理论上存在增加放射性损伤和复发风险的可能。如果出现上述急性和晚期放射性损伤，我们将根据最新国际诊疗指南进行相应处理。

如果在研究期间您出现任何不适，或病情发生新的变化，或任何意外情况，不管是否与研究有关，均应及时通知您的医生，他/她将对此作出判断并给予适当的医疗处理。

六、有关费用

本研究应用的IMRT技术已在国内实践多年，相关检查也是临床应用多年的常规检查，相关诊疗和复查费用需要您自行承担。

考虑到目前技术条件下，真实世界的临床实践中乳腺癌放疗相关轻-中度不良反应常见，因此对于轻-中度放疗不良反应及不适不进行经济补偿，但可提供临床诊疗协助。

如在临床研究中出现出现严重不良反应，被证实确实与临床研究干预有关，我们将按照我国相关法律法规的规定，对于研究相关损害的诊断治疗提供协助和一定经济补偿。

七、个人信息的保密

您的医疗记录(研究病历/CRF、化验单等)将完整地保存在您所就诊的医院。医生会将化验和其它检查结果记录在您的病历上。研究者、伦理委员会和药品监督管理部门将被允许查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在法律允许的范围内,尽一切努力保护您个人医疗资料的隐私。

按照医学研究伦理,除了个人隐私信息外,试验数据将可供公众查询和共享,查询和共享将只限于基于网络的电子数据库,保证不会泄漏任何个人隐私信息。

八、怎样获得更多的信息?

您可以在任何时间提出有关本项研究的任何问题,并得到相应的解答。如果在研究过程中有任何重要的新信息,可能影响您继续参加研究的意愿时,您的医生将会及时通知您。

九、可以自愿选择参加研究和中途退出研究

是否参加研究完全取决于您的意愿。您可以拒绝参加此项研究,或在研究过程中的任何时间退出本研究,这都不会影响您和医生间的关系,都不会影响对您的医疗或有其他方面利益的损失。如果您选择不参加本研究，根据NCCN指南（2020 V1版），将给予您同本研究常规分割组相同的放射治疗方案,具体如下：1)乳房切除术后患者：靶区范围包括同侧胸壁+锁骨上下区+内乳区，处方剂量：50Gy/25次，2Gy/次/天，每周5次，5周完成；2）乳房保留术后患者：靶区范围包括同侧全乳+锁骨上下区+内乳区，处方剂量：50Gy/25次，2Gy/次/天，每周5次，5周完成；序贯局部瘤床加量，10Gy/5次，2Gy/次/天，每周5次，1周完成。

出于对您的最大利益考虑,医生或研究者可能会在研究过程中随时中止您继续参加本项研究。

如果您因为任何原因从研究中退出,您可能被询问有关您使用相关治疗的情况。如果医生认为需要,您也可能被要求进行实验室检查和体格检查。

十、现在该做什么?

是否参加本项研究由您自己(和您的家人)决定。在您做出参加研究的决定前,请尽可能向你的医生询问有关问题。

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感谢您阅读以上材料。如果您决定参加本项研究,请告诉您的医生,他/她会为您安排一切有关研究的事务。请您保留这份资料。

知情同意书.同意签字页

临床研究项目名称:乳腺癌术后区域淋巴结大分割对比常规分割一体化 IMRT 的多中心、随机对照 III 期临床研究

课题承担单位:上海交通大学医学院附属瑞金医院

课题协作单位:上海交通大学医学院附属仁济医院；上海市第十人民医院；上海交通大学医学院附属第九人民医院；复旦大学附属中山医院；中山大学孙逸仙纪念医院；无锡市第四人民医院；中国科学院大学附属肿瘤医院（浙江省肿瘤医院）；南通市肿瘤医院。

同意声明

我已经阅读了上述有关本研究的介绍,而且有机会就此项研究与医生讨论并提出问题。我提出的所有问题都得到了满意的答复。

我知道参加本研究可能产生的风险和受益。我知晓参加研究是自愿的,我确认已有充足时间对此进行考虑,而且明白:

1、 我可以随时向医生咨询更多的信息。
2、 我可以随时退出本研究,而不会受到歧视或报复,医疗待遇与权益不会受到影响。
3、 我同样清楚,如果我中途退出研究,特别是由于药物的原因使我退出研究时,我若将我的病情变化告诉医生,完成相应的体格检查和理化检查,这将对整个研究十分有利。
4、 如果因病情变化我需要采取任何其他的药物治疗,我会在事先征求医生的意见,或在事后如实告诉医生。
5、 我同意相关部门伦理委员会或申办者代表查阅我的研究资料。
6、 我将获得一份经过签名并注明日期的知情同意书副本。
7、 最后,我决定同意参加本项研究,并保证尽量遵从医嘱。

患者签名： ＿＿ ＿＿ ＿＿ ＿＿ 年 ＿＿ ＿＿ 月 ＿＿ ＿＿ 日

联系电话：

我确认已向患者解释了本试验的详细情况，包括其权力以及可能的受益和风险，并给其一份签署过的知情同意书副本。

医生签名： ＿＿ ＿＿ ＿＿ ＿＿ 年 ＿＿ ＿＿ 月 ＿＿ ＿＿ 日

医生的工作电话：＿＿＿＿＿＿＿＿＿＿＿＿

（注：如果受试者无行为能力时则需法定代理人签名）