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Protocol for a Multicenter, Prospective, Open-label, Randomized Controlled Trial to Compare PROs and Safety Outcomes between Preoperative and Postmastectomy Radiotherapy in Locally Advanced Breast Cancer Patients with Immediate Reconstruction via a Deep Inferior Epigastric Perforator Flap (CAPPELLA)

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Protocol for a Multicenter, Prospective, Open-label, Randomized Controlled Trial to Compare PROs and Safety Outcomes between Preoperative and Postmastectomy Radiotherapy in Locally Advanced Breast Cancer Patients with Immediate Reconstruction via a Deep Inferior Epigastric Perforator Flap (CAPPELLA)

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ABSTRACT

Introduction

Despite its therapeutic advantages, postmastectomy radiotherapy (PMRT) increases the risk of complications and often leads to poor cosmesis in women undergoing breast reconstruction. Preoperative radiotherapy followed by skin-sparing mastectomy and deep inferior epigastric perforator (DIEP) flap reconstruction is technically feasible, with low rates of surgical complications and good short-term oncological outcomes. Further evaluation in a randomized trial comparing preoperative radiotherapy versus conventional PMRT in breast reconstruction is required to assess both oncological and patient-reported outcomes (PROs).

Methods and analysis

The CAPPELLA trial is a prospective, multicenter, open-label, randomized controlled trial across nine centers comparing PROs and safety outcomes between preoperative and postoperative radiotherapy in patients with locally advanced breast cancer requiring immediate DIEP flap reconstruction. Female patients aged >18 years with breast cancer who are treated with neoadjuvant systemic treatment, require both mastectomy and radiotherapy, and are suitable for DIEP flap reconstruction will be included. Patients will be randomly assigned (1:1) to a preoperative radiotherapy group or a postoperative radiotherapy group. Stratification will be performed by cancer center at initial diagnosis. The radiation volumes will include the ipsilateral breast/chest wall, supraclavicular lymph nodes, undissected axilla, and internal mammary nodes. The dose regimen will be 42.56 Gy in 16 fractions. The primary endpoint will be satisfaction with the breast domain of the BREAST-Q at 2 years postoperatively. The secondary endpoints will include PROs at 3, 12, and 24 months postoperatively in both groups, aesthetic assessment, complication rates, rates of total pathologic complete response (tpCR), and tumor safety. All patients will be followed up for 36 months postoperatively. The app software will be used to collect all data prospectively. Data will be analyzed using SPSS and Stata software. The target sample size will be 80 participants.

Ethics and dissemination

This study will be performed according to the Helsinki Declaration. All patients will be

asked to provide informed consent before enrollment. We will present the study results at national and international meetings and publish them in a scientific peer-reviewed journal.

Trial registration number: NCT05512286

INTRODUCTION

With increasing evidence supporting the oncologic safety of immediate reconstruction and advancements in reconstructive techniques, an increasing number of patients have opted for breast reconstruction in recent years [1]. In the United States, the reconstruction rate has increased from 14.8% in 2000 to 31.9% in 2011 [2], and the application of immediate breast reconstruction (IBR) has nearly doubled over the last two decades [3]. Moreover, patients who undergo IBR are more satisfied with their breasts and report several benefits, including in terms of psychosocial and superior aesthetics [4].

In women with locally advanced breast cancer (LABC), breast reconstruction and postmastectomy radiotherapy (PMRT) decrease local-regional recurrence and improve survival in patients with node-positive disease [5–7]. However, PMRT is associated with a high rate of surgical complications and reconstruction failure among patients who undergo IBR [8,9]. Capsular contracture is the most significant long-term risk of implant irradiation. It can result in poor cosmesis, pain, and discomfort for the patient. Similarly, complications of autologous reconstruction with PMRT may include poor wound healing, fibrosis, fat necrosis, and flap shrinkage [10]. Regardless of the reconstructive technique, there is a concern that IBR could affect the technical delivery of radiation therapy, with the largest compromises observed in patients with left-sided cancers [11]. The optimal integration of breast reconstruction and PMRT has long been a challenge in oncoplastic breast surgery.

Although not entirely resolved, in a 2017 study based on the National Cancer Database, the number of patients who underwent IBR significantly increased from 13% in 2004 to 33% in 2013 in the setting of PMRT [12]. Patients who received PMRT had fewer complications (OR =0.47, 95% CI =0.27 to 0.82, p =0.007) with autologous

reconstruction and higher BREAST-Q breast satisfaction scores (63.5 vs. 47.7; p =0.002) compared to implant-based BR.

[13]. Many surgeons in the 2023 Oncoplastic Breast Consortium (OPBC) consensus conference preferred autologous reconstruction over all implant-based reconstruction options in the setting of PMRT [14]. To minimize the risk of complications, plastic surgeons typically suggest postponing reconstruction in cases where autologous reconstruction is desired and when PMRT may be necessary. However, delayed reconstruction is associated with a lower health-related quality of life (QoL) compared to IBR. [4].

To reduce the negative effects of radiation on autologous breast reconstruction, there has been a growing interest in utilizing neoadjuvant radiation therapy (NART). Recent studies have reported that NART is a proven strategy for improving cosmetic outcomes and simplifying the reconstructive process [15–17]. Singh *et al*. conducted a systematic review comprising 10 retrospective and 8 prospective studies analyzing the effects of NART on IBR. The reviews revealed overall complication rates ranging from 3% to 36%, with the rate of excellent-to-good cosmetic outcomes ranging from 66% to 89% [18]. In a recently published multicenter, prospective, nonrandomized study involving 33 patients with breast cancer who underwent immediate abdominal free flap breast reconstruction after NART, not only was the safety and feasibility of NART for DIEP flap reconstruction confirmed, but there was also an even higher breast satisfaction score of 77 at 12 months postoperatively [19]. We aim to conduct a randomized trial comparing QoL and oncological outcomes between preoperative radiotherapy and conventional PMRT in patients undergoing immediate deep inferior epigastric perforator (DIEP) flap breast reconstruction.

Study objectives

The aim of this study is to compare patient-reported outcomes (PROs), aesthetic outcomes, and oncological safety between preoperative radiotherapy and PMRT in patients with LABC undergoing DIEP flap reconstruction.

METHODS AND ANALYSIS

Study type

The CAPPELLA study is a multicenter, prospective, open-label, randomized controlled trial.

Study design

This study is a multicenter, prospective, open-label, randomized controlled trial investigating the time of radiotherapy intervention to compare PROs and safety outcomes in patients with LABC undergoing immediate DIEP flap reconstruction.

Patients with LABC who receive neoadjuvant chemotherapy will be randomized into the following groups: (1) the preoperative radiotherapy group—preoperative radiotherapy followed by skin-sparing or nipple-sparing mastectomy combined with DIEP flap reconstruction; and (2) the postoperative radiotherapy group—skin-sparing or nipple-sparing mastectomy combined with DIEP flap reconstruction, followed by postoperative adjuvant radiotherapy.

Randomization

The study will employ a central randomization scheme for participant allocation to ensure the integrity of random assignment and reduce the potential for allocation bias. The randomization stratification factors will include the cancer center. The study plan and treatment schedule are shown in Figure 1.

Study population

Only adult (>18 years old) female patients with LABC scheduled for both mastectomy and radiotherapy and deemed suitable for DIEP flap reconstruction will be included. Patients diagnosed with LABC who have primary invasive breast cancer without distant metastasis will be offered neoadjuvant therapy.

All patients will be asked to provide informed consent before enrollment and data collection. The key exclusion criteria will be stage IV breast cancer or participation in another clinical trial. Patients who experience disease progression during neoadjuvant chemotherapy will also be excluded. Patients who are pregnant or breastfeeding, who have a previous history of diabetes or who have a history of heavy smoking will also be excluded.

There will be nine centers participating in this study, and 40 consecutive patients will be recruited for each group.

Primary endpoint

The primary endpoint will be satisfaction with the breast domain of the BREAST-Q at 2 years postoperatively. The BREAST-Q is a commonly used PRO instrument for measuring QoL and patient satisfaction in breast surgery [20]. The BREAST-Q questionnaire assesses patient satisfaction with their breasts, surgical outcomes, physical well-being, and surgeon. It offers multiple versions of procedure-specific modules [21,22]. A recent systematic review showed that the BREAST-Q can effectively be used to assess patients' satisfaction and QoL in relation to different types of oncoplastic breast surgeries [23]. This trial will use a 1:1 superiority design, assuming that the preoperative radiotherapy group will be superior to the postoperative radiotherapy group in terms of breast satisfaction.

Secondary endpoints

The secondary endpoints will include PROs at 3, 12, and 24 months postoperatively in both groups, aesthetic assessments, complication rates, rates of total pathologic complete response (tpCR), and tumor safety. Prognosis will be assessed using overall survival (OS), disease-free survival (DFS), and locoregional recurrence-free survival (LRFS). DFS will be calculated as the time from breast cancer diagnosis until tumor recurrence, metastasis, contralateral second primary breast cancer or death from any cause [24,25]. OS will be defined as the time from breast cancer diagnosis to the time of death from any cause or the date of last contact if death is not recorded before the cutoff date. LRFS will be defined as the time from the date of diagnosis to recurrence of ipsilateral chest wall, axillary, supraclavicular, or internal mammary lymph node metastasis or death from any cause. A tpCR will be defined as the absence of invasive cancer in the breast and axillary lymph nodes.

Surgical complications will include hematoma, seroma, poor healing or necrotic splitting of the breast incision, nipple or areola necrosis, infection, loss of volume, unplanned reoperation, DIEP flap failure (defined as complete necrosis or partial necrosis of the flap, requiring debridement), and fat necrosis (defined as a palpable hard

knot of $\geqslant$2 cm maximum diameter within the flap, with or without evidence from pathology or ultrasound).

Radiation-related complications will include radiation dermatitis, breast fibrosis, flap contracture, telangiectasia, radiation pneumonitis/pulmonary fibrosis, and radiation cardiac injury.

Pictures of patients (anterior, lateral, three-fourth angled view from both sides) will be taken at baseline (before surgery) and at 3, 12, and 24 months postoperatively to assess breast aesthetics. For those who will undergo NART, photographs will be taken before NART. Changes in the photographic breast appearance will be assessed at 3, 12, and 24 months postoperatively and compared with the baseline photographs. Breast size and surgical deficit will be scored from the baseline photographs on a 3-point scale (small, medium, large). A panel of at least three independent observers blinded to patient identity, treatment allocation, and radiotherapy center will score the photographs [26,27].

Radiotherapy

Timing

Preoperative radiotherapy group: Preoperative radiotherapy will be initiated 3–4 weeks following the last dose of neoadjuvant chemotherapy. Surgery will be completed within 2–6 weeks after completing radiation therapy.

Postoperative radiotherapy group: Surgery will be completed within 3–4 weeks after the last dose of neoadjuvant chemotherapy. Adjuvant radiotherapy will be initiated within 12 weeks postoperatively.

Localization, simulation, and immobilization

Patients will undergo computed tomography (CT) simulation in the standard supine position using breast boards or other immobilization devices according to the treating physician's discretion. A CT scan image thickness of $\leq$0.5 cm will be employed. Methods to minimize cardiac exposure, such as deep inspiration breath holding (DIBH), will be recommended for left-sided patients if available.

Target and normal tissue volume definitions

Clinical target volumes (CTVs)

The CTVs will include the ipsilateral breast/chest wall, supraclavicular lymph nodes, undissected axilla, and internal mammary nodes (IMNs), as defined according to the European Society for Radiotherapy and Oncology (ESTRO) and Radiation Therapy Oncology Group (RTOG) breast cancer consensus guidelines [28]. Regarding controversial issues, several modifications have been made to establish an in-house consensus by the Fudan University Shanghai Cancer Center. The suggested CTV delineation for breast and lymph node regions is as follows showed in Table1:

Breast CTV (CTV_B): CTV_B is contoured following the definitions of the ESTRO guidelines for the preoperative radiotherapy group, except for the ventral border. The ventral border of the breast CTV can be the skin or 3–5 mm under the skin surface, as determined by a multidisciplinary research team. Generally, for patients with clinical stage T4 disease and extensive skin invasion, the ventral border of the breast CTV should be the skin.

Chest wall CTV (CTV_CW): CTV_CW is also contoured following the definitions of the ESTRO guidelines for the postoperative radiotherapy group, except for the ventral border. The definition of the ventral border of CTV_CW is the same as that of CTV_B.

Undissected axilla CTV (CTV_udALN): CTV_udALN consists of the undissected portions of the axilla extending from the upper extent of axillary surgery for patients with axillary dissection (or planned axillary dissection for the preoperative radiotherapy group). CTV_udALN typically includes level 3, some of undissected axillary level 2, and interpectoral nodes. The lateral and caudal borders of CTV_udALN are defined by the most medial and cranial extent of the axillary dissection, respectively, with the other borders following the definitions of the ESTRO guidelines.

Internal mammary node CTV (CTV_IMN): CTV_IMN includes the internal mammary vessels in the first three intercostal spaces and is contoured as per the definitions of the ESTRO guidelines.

Supraclavicular lymph node CTV (CTV_SCN): CTV_SCN is contoured following the definitions of the ESTRO or RTOG guidelines. The cranial border is caudal to the cricoid cartilage; the caudal border includes the subclavian vein with a 5-mm margin and connects to the cranial border of CTVn_IMN; the medial border includes the internal jugular vein and excludes the common carotid artery and thyroid gland; the lateral border is the sternocleidomastoid muscle (cranial), clavicle, and junction of the first rib (caudal); the ventral border is the sternocleidomastoid muscle and clavicle; and the dorsal border is the anterior aspect of the scalene muscle.

Planning target volumes (PTVs)

PTVs will be generated by adding 5-mm margins in all directions to the above CTVs. The supraclavicular PTV will exclude the ipsilateral thyroid, trachea, esophagus, and ipsilateral lung, and the ventral border will be 3 mm beneath the skin surface. Additionally, PTV_B_evaluation and PTV_CW_evaluation will be generated by limiting the ventral border of PTV_B and PTV_CW at the skin or 3~5 mm beneath the skin surface for dose-volume histogram evaluation.

Organs at risk (OARs)

Normal structures will include the heart, ipsilateral lung, contralateral lung, contralateral breast, thyroid, humeral head, spinal cord, and esophagus.

Technique and treatment planning

Intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), or tomotherapy techniques will be recommended. For patients with a ventral border of the breast CTV at the skin, the application of a 3-mm bolus to the breast skin will be recommended; a 33D-printed bolus will be recommended if available. The suggested PTV dose-volume histogram criteria are as follows: at least 95% of each PTV receives ≥95% of the prescribed dose (≥90% of the prescribed dose is acceptable; for PTV_IMN, it is acceptable if ≥90% of the PTV_IMN receives ≥90% of the prescribed dose). The maximum point dose of each PTV is recommended to be ≤115% of the prescribed dose (≤120% acceptable).

Dose specifications

Patients will be treated with hypofractionated radiotherapy, and the dose regimen will be 42.56 Gy in 16 fractions. For patients with clinical stage N3c disease at initial diagnosis, a s*upraclavicular* nodal boost may be delivered at the discretion of the treating physician. Boost doses will be 10–16 Gy in 5–8 fractions if indicated.

Treatment verification

Portal films or 3D images will be obtained and approved by a physician prior to the initiation of radiotherapy and after every 5 fractions.

Follow-up

Before surgery, patient information, clinical and pathological characteristics, commodity, and breast size measurements will be recorded. During the hospital stay, only complications and pain will be assessed. Postoperatively, at 3, 12, 24, and 36 months, the BREAST-Q score, cosmetic PROs, photographs, prognosis, and long-term complications will be evaluated.

Data collection and management

Data will be recorded on the CAPPELLA case report forms (CRFs). The items collected will include patients' demographic data (including age, sex, BMI, marital status and parental history), clinical and pathological data, surgical information, BREAST-Q score, cosmetic PROs, surgery- and radiotherapy-related complications, photographs, neoadjuvant and adjuvant treatments, and prognosis. Surgery-related complications will include hematoma, seroma, poor healing, nipple or areola necrosis, infection, loss of volume, unplanned reoperation, DIEP flap failure (defined as complete or partial necrosis of the flap requiring debridement surgery), and fat necrosis. Radiotherapy-related complications will include radiation dermatitis, breast fibrosis, flap contracture, capillaritis, radiation pneumonitis/pulmonary fibrosis, and radiation heart injury.

Statistical analysis and sample size calculation

Descriptive statistics will be used to summarize baseline characteristics. Proportional differences between groups will be tested using Pearson's $\chi 2$ test. T-test will be used to compare continuous outcomes between two groups, and one-way analysis of variance

will be used to compare outcomes across groups. Univariate and multivariate logistic regression analyses will be carried out to examine associations between independent variables and outcomes. All available independent variables will be considered in the univariate regression model, and only significant variables ($p < 0.1$) will be included for further multivariate logistic regression analyses. All tests will be two-sided, and a p value of less than or equal to 0.05 will be considered significant.

Sample size calculation

The study has been designed as a randomized, controlled superiority trial with participants allocated at a 1:1 ratio between the preoperative radiotherapy and PMRT groups. According to previous studies, the mean score of the breast domain of the BREAST-Q at 2 years postoperatively was 64 ±16.9 in the PMRT group [29]. The average score in the breast domain of the BREAST-Q at 2 years in the preoperative radiotherapy group is estimated to reach 77 on average. We assume that the breast satisfaction score will be better in the preoperative radiotherapy group than in the PMRT group. A one-sided alpha level of 0.025 will be used for statistical significance. Thus, a sample size of 40 patients per group (80 patients in total) can provide a statistical power of 0.93 to detect significant differences between the groups, assuming equal variance in both groups. PASS 15 Power Analysis and Sample Size Software (2017) (NCSS, LLC, Kaysville, Utah, USA) was used to calculate the sample size

DISCUSSION

IBR is associated with improved QoL, body image, self-esteem, and confidence and has become an increasingly popular choice among patients. Radiotherapy plays an important role in the multidisciplinary treatment of breast cancer. Breast reconstruction and PMRT have become more common in the past decade. However, there is controversy surrounding the typical approach to integrating radiotherapy with IBR in breast cancer management.

Autologous reconstruction followed by radiotherapy may cause several complications, including hematoma, seroma, infection, embolism, fibrosis, fat necrosis, total or partial loss of skin flap volume, and donor site problems, thereby reducing patient satisfaction and the cosmetic outcomes of breast reconstruction. Many surgeons in the UK

recommend delaying reconstruction if PMRT is required [30].

However, an increasing number of studies have provided favorable evidence for immediate autologous reconstruction. In 2017, a Mastectomy Reconstruction Outcomes Consortium (MROC) study provided compelling data for immediate autologous breast reconstruction. This prospective, multicenter study included 175 patients who underwent immediate or delayed autologous reconstruction with PMRT, and the results showed no significant difference in the incidence of complications between the two groups after 1 year (25.9% vs. 26.9%; P = 0.54) [31]. IBR can protect women from psychosocial distress, negative body image, and diminished sexual well-being when compared to delayed reconstruction [4]. This evidence suggests that immediate autologous reconstruction is better tolerated with radiotherapy than does evidence from previous experience, with lower complication rates.

Over the past decade, advances in technologies have reduced the challenges in irradiated patients who have undergone immediate reconstruction. In patients who undergo breast reconstruction, the most commonly used radiotherapy techniques are IMRT and VMAT. Both techniques improve the homogeneity of the dose within the target area while reducing the radiation dose delivered to the lungs and heart. The disadvantage of IMRT and VMAT is the wide range of low-dose zones, resulting in unknown long-term adverse events [32–34].

Radiotherapy techniques play a crucial role in determining the cosmetic outcome of breast reconstruction, including the use of a bolus or boost, fractionation, and nodal target volumes. Orecchia *et al*. reported dosimetric results and toxicity evaluation results of 120 patients who received hypofractionated PMRT with IMRT. Among them, 70.8% of the plans had high scores for optimal chest wall (CW) and nodal region (RN) coverage, and grade 2 acute toxicity was observed in 36.2% of patients [35]. Dumane and colleagues reported the dosimetric results of 10 consecutive patients who underwent tissue expander/permanent implant (TE/PI) reconstruction and who were treated with a combination of VMAT and DIBH. Significant dosimetric gains were demonstrated for low doses to the heart, lungs, and contralateral breast/implants [36].

Although PMRT has therapeutic benefits, it can increase the risk of complications and

often results in poor cosmesis for women undergoing breast reconstruction. Radiation exposure can cause early changes in normal tissues, such as skin erythema, desquamation, and pruritus. These changes are caused directly by DNA damage or indirectly through the release of free radicals or inflammation. Late changes in the affected area may include damage to small blood vessels, cell loss, and fibrosis. These factors can contribute to poor wound healing and potentially worse cosmetic outcomes. Due to the limitations of current methods, there has been growing interest in using preoperative radiotherapy to avoid negative effects on autologous breast reconstruction caused by radiation. Recently, some researchers have published findings supporting preoperative radiotherapy as a proven strategy to improve cosmetic results and simplify the reconstructive process [15–17]. Singh *et al*. performed a systematic review that included 10 retrospective and 8 prospective studies analyzing the effects of NART on IBR; the overall complication rates ranged from 3% to 36%, and the rates of excellent-to-good cosmetic outcomes ranged from 66–89% [18]. However, there is limited data on the effect of preoperative radiotherapy prior to mastectomy and microvascular autologous reconstruction [37]. The PRADA study recently demonstrated that preoperative radiotherapy followed by skin-sparing mastectomy and DIEP flap reconstruction is technically feasible. The study reported low rates of surgical complications and good short-term oncological outcomes. [19]. These studies lack longer follow-up evaluations, and larger prospective controlled clinical trials are required to objectively measure this new therapeutic sequence. We aim to compare the oncological and QoL outcomes in a randomized trial of preoperative radiotherapy versus conventional PMRT in breast reconstruction.

Strengths and limitations

Breast reconstruction is an optional procedure that does not affect the likelihood of recurrence or death. However, it is associated with improved quality of life for many patients. Ghazal reported that immediate reconstruction was associated with less distress and better psychosocial well-being than delayed reconstruction [38]. Moreover, a 2018 MROC study reported that patients who underwent delayed surgery had significantly lower preoperative scores than women who underwent immediate

reconstruction; patients who underwent delayed surgery scored significantly lower on the Physical Function and Anxiety subscales and reported significantly higher levels of pain before reconstruction than patients in the immediate reconstruction group [39]. The use of PROs in monitoring patient satisfaction and complications could increase patient engagement in cancer treatment, which is in line with the objectives emphasized in certain countries. [40]. This study will also establish standards for the indicators, risk, and prognostic value of IBR and the timing of radiotherapeutic interventions and will provide suggestions for future clinical practice and research. However, there are also several limitations to this study. Heterogeneity in radiotherapy between centers may affect cosmetic outcomes. Meanwhile, the follow-up period of this study will be 36 months, which is sufficient for capturing PROs in patients undergoing breast reconstruction but relatively short for assessing prognosis. While this trial was initially designed to follow patients for approximately 3 years, we plan to extend the monitoring of PROs and prognosis for a longer duration.

ETHICS AND DISSEMINATION

This study will be performed in accordance with the Helsinki Declaration. Patients will be provided with details of the study (purpose, risk, and benefits) and have the right to withdraw from the study at any time. Prior to enrollment, an informed consent form will be sent to each patient to ensure their understanding of the cohort study. This study will be conducted according to the requirements of the Good Clinical Practice (GCP) guidelines. The results of the study will be presented at national and international meetings and published in a scientific peer-reviewed journal.

Cancer centers

Shanghai Cancer Hospital

Huashan Hospital

Hunan Cancer Hospital

Cancer Hospital of Guangxi Medical University

Yunnan Cancer Hospital

Zhejiang Cancer Hospital

Henan Cancer Hospital

Tianjin Medical University Cancer Institute and Hospital

Affiliated Hospital of Zunyi Medical University

Authors' contributions

Study design: Jiong Wu, Xiaoli Yu, Shuang Hao, Li Zhang, and Changming Zhou.

Protocol writing: Shuang Hao, Jianjing Hou, and Li Zhang.

Protocol review: Jiong Wu and Xiaoli Yu.

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Competing interests None declared.

Patient consent for publication Not needed.

Ethics approval: Approval for this study was provided by the independent ethics committee and institutional review board of FUSCC (Fudan University Shanghai Cancer Center).

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Table 1 Suggested CTV delineation for breast and lymph node regions

	Cranial	Caudal	Ventral	Dorsal	Medial	Lateral
Breast CTV (CTV_B) (Preoperative radiotherapy group)	Upper border of palpable/visible breast tissue; maximally up to the caudal edge of the sterno-clavicular joint	Most caudal CT slice with visible breast	3~5 mm under skin surface (Skin in cT4b-4 cases with extensive skin invasion)	Major pectoral muscle or costae and intercostal muscles where no muscle (For T4a/T4c cases, the major pectoral muscle and ribs should be included)	Lateral to the medial perforating mammarian vessels; maximally to the edge of the sternal bone	Lateral breast fold; anterior to the lateral thoracic artery
Chest wall CTV (CTV_CW) (Postoperative radiotherapy group)	Guided by palpable/visible signs; if appropriate guided by the contralateral breast; maximally up to the caudal edge of the sterno-clavicular joint	Guided by palpable/visible signs; if appropriate guided by the contralateral breast	Same as above	Same as above	Guided by palpable/visible signs; if appropriate guided by the contralateral breast	Guided by palpable/visible signs; if appropriate guided by the contralateral breast. Usually anterior to the mid-axillary line
Supraclavicular CTV (CTV_SCN)	Caudal to the cricoid cartilage	Includes the subclavian vein with 5 mm margin, thus connecting to the cranial border of CTVn_IMN	Sternocleidomastoid muscle, dorsal edge of the clavicle	Anterior aspect of the scalene muscle	Including the jugular vein without margin; excluding the thyroid gland and the common carotid artery	Cranial: Sternocleidomastoid muscle Caudal: junction of 1st rib and clavicle
Internal mammary node CTV (CTV_IMN)	Caudal limit of CTV_SCN	Cranial side of the 4th rib (in selected cases 5-6th	Ventral limit of the vascular area	Pleura	5 mm from the internal mammary vein (artery in cranial	5 mm from the internal mammary artery

			rib)			part down to and including first intercostal space)	
Undissected axillary CTV (CTV_udALN)	Undissected Axillary level 2	Includes the cranial extent of the axillary artery (i.e. 5 mm cranial of axillary vein)	The caudal border of the minor pectoral muscle, but should exclude the extent of the dissection	Minor pectoral muscle	Up to 5 mm dorsal of axillary vein or to costae and intercostal muscles	Medial edge of minor pectoral muscle	Lateral edge of minor pectoral muscle, but should exclude the extent of the dissection
	Axillary level 3	Includes the cranial extent of the subclavian artery (i.e. 5 mm cranial of subclavian vein)	5 mm caudal to the subclavian vein	Major pectoral muscle	Same as level 2	Junction of subclavian and internal jugular veins, connects to CTV_SCN	Medial side of the minor pectoral muscle
	Interpectoral nodes	Includes the cranial extent of the axillary artery (i.e. 5 mm cranial of axillary vein)	The caudal border of the minor pectoral muscle	Major pectoral muscle	Minor pectoral muscle	Medial edge of minor pectoral muscle	Lateral edge of minor pectoral muscle

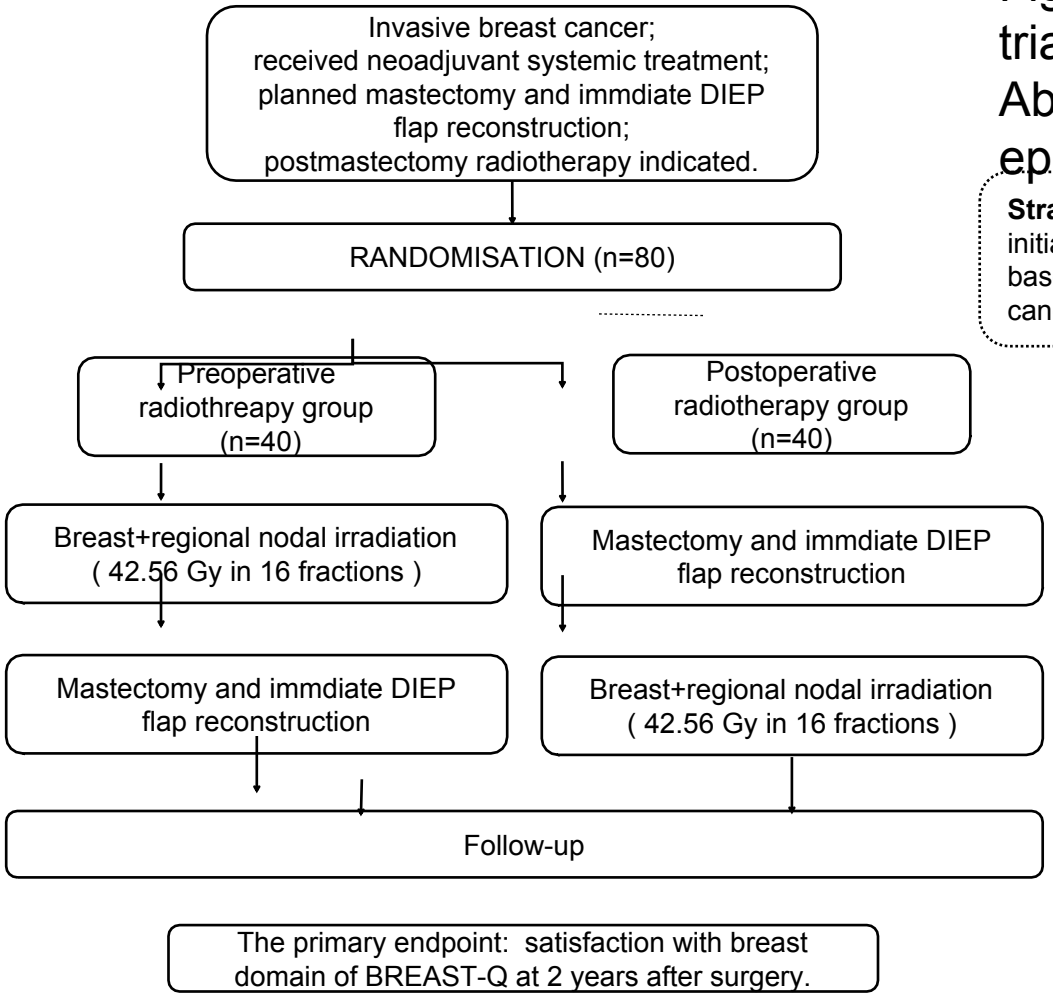

Fig. 1 Flow chart of the CAPPELLA trial.
Abbreviations: DIEP deep inferior epigastric perforator

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Protocol for a Multicenter, Prospective, Open-label, Randomized Controlled Trial to Compare PROs and Safety Outcomes between Preoperative and Postmastectomy Radiotherapy in Locally Advanced Breast Cancer Patients with Immediate Reconstruction via a Deep Inferior Epigastric Perforator Flap (CAPPELLA) in China

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ABSTRACT

Introduction

Despite its therapeutic advantages, postmastectomy radiotherapy (PMRT) increases the risk of complications and often leads to poor cosmesis in women undergoing breast reconstruction. Preoperative radiotherapy followed by skin-sparing mastectomy and deep inferior epigastric perforator (DIEP) flap reconstruction is technically feasible, with low rates of surgical complications and good short-term oncological outcomes. Further evaluation in a randomized trial comparing preoperative radiotherapy versus conventional PMRT in breast reconstruction is required to assess both oncological and patient-reported outcomes (PROs).

Methods and analysis

The CAPPELLA trial is a prospective, multicenter, open-label, randomized controlled trial across nine centers comparing PROs and safety outcomes between preoperative and postoperative radiotherapy in patients with locally advanced breast cancer requiring immediate DIEP flap reconstruction. Female patients aged >18 years with breast cancer who are treated with neoadjuvant systemic treatment, require both mastectomy and radiotherapy, and are suitable for DIEP flap reconstruction will be included. Patients will be randomly assigned (1:1) to a preoperative radiotherapy group or a postoperative radiotherapy group. Stratification will be performed by cancer center at initial diagnosis. The radiation volumes will include the ipsilateral breast/chest wall, supraclavicular lymph nodes, undissected axilla, and internal mammary nodes. The dose regimen will be 42.56 Gy in 16 fractions. The primary endpoint will be satisfaction with the breast domain of the BREAST-Q at 2 years postoperatively. The secondary endpoints will include PROs at 3, 12, and 24 months postoperatively in both groups, aesthetic assessment, complication rates, rates of total pathologic complete response (tpCR), and tumor safety. All patients will be followed up for 36 months postoperatively. The app software will be used to collect all data prospectively. Data will be analyzed using SPSS and Stata software. The target sample size will be 80 participants.

Ethics and dissemination

This study will be performed according to the Helsinki Declaration. All patients will be

asked to provide informed consent before enrollment. Approval for this study was provided by the independent ethics committee and institutional review board of FUSCC (Fudan University Shanghai Cancer Center). We will present the study results at national and international meetings and publish them in a scientific peer-reviewed journal.

Trial registration number: NCT05512286

Strengths and limitations

- The use of PROs in monitoring patient satisfaction and complications could increase patient engagement in cancer treatment, which is in line with the objectives emphasized in certain countries.
- This study will also establish standards for the indicators, risk, and prognostic value of IBR and the timing of radiotherapeutic interventions and will provide suggestions for future clinical practice and research.
- Heterogeneity in radiotherapy between centers may affect cosmetic outcomes.
- The follow-up period of this study will be 36 months, which is sufficient for capturing PROs in patients undergoing breast reconstruction but relatively short for assessing prognosis.

INTRODUCTION

With increasing evidence supporting the oncologic safety of immediate reconstruction and advancements in reconstructive techniques, an increasing number of patients have opted for breast reconstruction in recent years [1]. In the United States, the reconstruction rate has increased from 14.8% in 2000 to 31.9% in 2011 [2], and the application of immediate breast reconstruction (IBR) has nearly doubled over the last two decades [3]. Moreover, patients who undergo IBR are more satisfied with their breasts and report several benefits, including in terms of psychosocial and superior aesthetics [4].

In women with locally advanced breast cancer (LABC), breast reconstruction and postmastectomy radiotherapy (PMRT) decrease local-regional recurrence and improve

survival in patients with node-positive disease [5–7]. However, PMRT is associated with a high rate of surgical complications and reconstruction failure among patients who undergo IBR [8,9]. Capsular contracture is the most significant long-term risk of implant irradiation. It can result in poor cosmesis, pain, and discomfort for the patient. Similarly, complications of autologous reconstruction with PMRT may include poor wound healing, fibrosis, fat necrosis, and flap shrinkage [10]. Regardless of the reconstructive technique, there is a concern that IBR could affect the technical delivery of radiation therapy, with the largest compromises observed in patients with left-sided cancers [11]. The optimal integration of breast reconstruction and PMRT has long been a challenge in oncoplastic breast surgery.

Although not entirely resolved, in a 2017 study based on the National Cancer Database, the number of patients who underwent IBR significantly increased from 13% in 2004 to 33% in 2013 in the setting of PMRT [12]. Patients who received PMRT had fewer complications (OR =0.47, 95% CI =0.27 to 0.82, p =0.007) with autologous reconstruction and higher BREAST-Q breast satisfaction scores (63.5 vs. 47.7; p =0.002) compared to implant-based BR.[13]. Many surgeons in the 2023 Oncoplastic Breast Consortium (OPBC) consensus conference preferred autologous reconstruction over all implant-based reconstruction options in the setting of PMRT [14]. To minimize the risk of complications, plastic surgeons typically suggest postponing reconstruction in cases where autologous reconstruction is desired and when PMRT may be necessary. However, delayed reconstruction is associated with a lower health-related quality of life (QoL) compared to IBR. [4].

To reduce the negative effects of radiation on autologous breast reconstruction, there has been a growing interest in utilizing neoadjuvant radiation therapy (NART). Recent studies have reported that NART is a proven strategy for improving cosmetic outcomes and simplifying the reconstructive process [15–17]. Singh *et al*. conducted a systematic review comprising 10 retrospective and 8 prospective studies analyzing the effects of NART on IBR. The reviews revealed overall complication rates ranging from 3% to 36%, with the rate of excellent-to-good cosmetic outcomes ranging from 66% to 89% [18]. In a recently published multicenter, prospective, nonrandomized study involving

33 patients with breast cancer who underwent immediate abdominal free flap breast reconstruction after NART, not only was the safety and feasibility of NART for DIEP flap reconstruction confirmed, but there was also an even higher breast satisfaction score of 77 at 12 months postoperatively [19]. We aim to conduct a randomized trial comparing QoL and oncological outcomes between preoperative radiotherapy and conventional PMRT in patients undergoing immediate deep inferior epigastric perforator (DIEP) flap breast reconstruction.

Study objectives

The aim of this study is to compare patient-reported outcomes (PROs), aesthetic outcomes, and oncological safety between preoperative radiotherapy and PMRT in patients with LABC undergoing DIEP flap reconstruction.

METHODS AND ANALYSIS

Study design

This study is a multicenter, prospective, open-label, randomized controlled trial investigating the time of radiotherapy intervention to compare PROs and safety outcomes in patients with LABC undergoing immediate DIEP flap reconstruction.

Patients with LABC who receive neoadjuvant chemotherapy will be randomized into the following groups: (1) the preoperative radiotherapy group—preoperative radiotherapy followed by skin-sparing or nipple-sparing mastectomy combined with DIEP flap reconstruction; and (2) the postoperative radiotherapy group—skin-sparing or nipple-sparing mastectomy combined with DIEP flap reconstruction, followed by postoperative adjuvant radiotherapy.

Randomization

The study will employ a central randomization scheme for participant allocation to ensure the integrity of random assignment and reduce the potential for allocation bias. The randomization stratification factors will include the cancer center. The study plan and treatment schedule are shown in Figure 1.

Study population

Only adult (>18 years old) female patients with LABC scheduled for both mastectomy and radiotherapy and deemed suitable for DIEP flap reconstruction will be included. Patients diagnosed with LABC who have primary invasive breast cancer without distant metastasis will be offered neoadjuvant therapy.

All patients will be asked to provide informed consent before enrollment and data collection. The key exclusion criteria will be stage IV breast cancer or participation in another clinical trial. Patients who experience disease progression during neoadjuvant chemotherapy will also be excluded. Patients who are pregnant or breastfeeding, who have a previous history of diabetes or who have a history of heavy smoking will also be excluded.

There will be nine centers participating in this study, and 40 consecutive patients will be recruited for each group. The study started in June 2022, expected to complete enrollment in June 2024. Data collection and statistical analyses will complete in July 2026.

Primary endpoint

The primary endpoint will be satisfaction with the breast domain of the BREAST-Q at 2 years postoperatively. The BREAST-Q is a commonly used PRO instrument for measuring QoL and patient satisfaction in breast surgery [20]. The BREAST-Q questionnaire assesses patient satisfaction with their breasts, surgical outcomes, physical well-being, and surgeon. It offers multiple versions of procedure-specific modules [21,22]. A recent systematic review showed that the BREAST-Q can effectively be used to assess patients' satisfaction and QoL in relation to different types of oncoplastic breast surgeries [23]. This trial will use a 1:1 superiority design, assuming that the preoperative radiotherapy group will be superior to the postoperative radiotherapy group in terms of breast satisfaction.

Secondary endpoints

The secondary endpoints will include PROs at 3, 12, and 24 months postoperatively in both groups, aesthetic assessments, complication rates, rates of total pathologic complete response (tpCR), and tumor safety. Prognosis will be assessed using overall survival (OS), disease-free survival (DFS), and locoregional recurrence-free survival

(LRFS). DFS will be calculated as the time from breast cancer diagnosis until tumor recurrence, metastasis, contralateral second primary breast cancer or death from any cause [24,25]. OS will be defined as the time from breast cancer diagnosis to the time of death from any cause or the date of last contact if death is not recorded before the cutoff date. LRFS will be defined as the time from the date of diagnosis to recurrence of ipsilateral chest wall, axillary, supraclavicular, or internal mammary lymph node metastasis or death from any cause. A tpCR will be defined as the absence of invasive cancer in the breast and axillary lymph nodes.

Surgical complications will include hematoma, seroma, poor healing or necrotic splitting of the breast incision, nipple or areola necrosis, infection, loss of volume, unplanned reoperation, DIEP flap failure (defined as complete necrosis or partial necrosis of the flap, requiring debridement), and fat necrosis (defined as a palpable hard knot of $\geqslant$2 cm maximum diameter within the flap, with or without evidence from pathology or ultrasound).

Radiation-related complications will include radiation dermatitis, breast fibrosis, flap contracture, telangiectasia, radiation pneumonitis/pulmonary fibrosis, and radiation cardiac injury.

Pictures of patients (anterior, lateral, three-fourth angled view from both sides) will be taken at baseline (before surgery) and at 3, 12, and 24 months postoperatively to assess breast aesthetics. For those who will undergo NART, photographs will be taken before NART. Changes in the photographic breast appearance will be assessed at 3, 12, and 24 months postoperatively and compared with the baseline photographs. Breast size and surgical deficit will be scored from the baseline photographs on a 3-point scale (small, medium, large). A panel of at least three independent observers blinded to patient identity, treatment allocation, and radiotherapy center will score the photographs [26,27].

Radiotherapy

Timing

Preoperative radiotherapy group: Preoperative radiotherapy will be initiated 3–4 weeks following the last dose of neoadjuvant chemotherapy. Surgery will be completed within 2–6 weeks after completing radiation therapy.

Postoperative radiotherapy group: Surgery will be completed within 3–4 weeks after the last dose of neoadjuvant chemotherapy. Adjuvant radiotherapy will be initiated within 12 weeks postoperatively.

Localization, simulation, and immobilization

Patients will undergo computed tomography (CT) simulation in the standard supine position using breast boards or other immobilization devices according to the treating physician's discretion. A CT scan image thickness of $\leq$0.5 cm will be employed. Methods to minimize cardiac exposure, such as deep inspiration breath holding (DIBH), will be recommended for left-sided patients if available.

Target and normal tissue volume definitions

Clinical target volumes (CTVs)

The CTVs will include the ipsilateral breast/chest wall, supraclavicular lymph nodes, undissected axilla, and internal mammary nodes (IMNs), as defined according to the European Society for Radiotherapy and Oncology (ESTRO) and Radiation Therapy Oncology Group (RTOG) breast cancer consensus guidelines [28]. Regarding controversial issues, several modifications have been made to establish an in-house consensus by the Fudan University Shanghai Cancer Center. The suggested CTV delineation for breast and lymph node regions is as follows showed in Supplementary Table1:

Breast CTV (CTV_B): CTV_B is contoured following the definitions of the ESTRO guidelines for the preoperative radiotherapy group, except for the ventral border. The ventral border of the breast CTV can be the skin or 3–5 mm under the skin surface, as determined by a multidisciplinary research team. Generally, for patients with clinical stage T4 disease and extensive skin invasion, the ventral border of the breast CTV should be the skin.

Chest wall CTV (CTV_CW): CTV_CW is also contoured following the definitions of the ESTRO guidelines for the postoperative radiotherapy group, except for the ventral border. The definition of the ventral border of CTV_CW is the same as that of CTV_B.

Undissected axilla CTV (CTV_udALN): CTV_udALN consists of the undissected portions of the axilla extending from the upper extent of axillary surgery for patients with axillary dissection (or planned axillary dissection for the preoperative radiotherapy group). CTV_udALN typically includes level 3, some of undissected axillary level 2, and interpectoral nodes. The lateral and caudal borders of CTV_udALN are defined by the most medial and cranial extent of the axillary dissection, respectively, with the other borders following the definitions of the ESTRO guidelines.

Internal mammary node CTV (CTV_IMN): CTV_IMN includes the internal mammary vessels in the first three intercostal spaces and is contoured as per the definitions of the ESTRO guidelines.

Supraclavicular lymph node CTV (CTV_SCN): CTV_SCN is contoured following the definitions of the ESTRO or RTOG guidelines. The cranial border is caudal to the cricoid cartilage; the caudal border includes the subclavian vein with a 5-mm margin and connects to the cranial border of CTVn_IMN; the medial border includes the internal jugular vein and excludes the common carotid artery and thyroid gland; the lateral border is the sternocleidomastoid muscle (cranial), clavicle, and junction of the first rib (caudal); the ventral border is the sternocleidomastoid muscle and clavicle; and the dorsal border is the anterior aspect of the scalene muscle.

Planning target volumes (PTVs)

PTVs will be generated by adding 5-mm margins in all directions to the above CTVs. The supraclavicular PTV will exclude the ipsilateral thyroid, trachea, esophagus, and ipsilateral lung, and the ventral border will be 3 mm beneath the skin surface. Additionally, PTV_B_evaluation and PTV_CW_evaluation will be generated by limiting the ventral border of PTV_B and PTV_CW at the skin or 3~5 mm beneath the skin surface for dose-volume histogram evaluation.

Organs at risk (OARs)

Normal structures will include the heart, ipsilateral lung, contralateral lung, contralateral breast, thyroid, humeral head, spinal cord, and esophagus.

Technique and treatment planning

Intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), or tomotherapy techniques will be recommended. For patients with a ventral border of the breast CTV at the skin, the application of a 3-mm bolus to the breast skin will be recommended; a 33D-printed bolus will be recommended if available. The suggested PTV dose-volume histogram criteria are as follows: at least 95% of each PTV receives ≥95% of the prescribed dose (≥90% of the prescribed dose is acceptable; for PTV_IMN, it is acceptable if ≥90% of the PTV_IMN receives ≥90% of the prescribed dose). The maximum point dose of each PTV is recommended to be ≤115% of the prescribed dose (≤120% acceptable).

Dose specifications

Patients will be treated with hypofractionated radiotherapy, and the dose regimen will be 42.56 Gy in 16 fractions. For patients with clinical stage N3c disease at initial diagnosis, a s*upraclavicular* nodal boost may be delivered at the discretion of the treating physician. Boost doses will be 10–16 Gy in 5–8 fractions if indicated.

Treatment verification

Portal films or 3D images will be obtained and approved by a physician prior to the initiation of radiotherapy and after every 5 fractions.

Follow-up

Before surgery, patient information, clinical and pathological characteristics, Satisfaction with breast appearance, and breast size measurements will be recorded. During the hospital stay, only complications and pain will be assessed. Postoperatively, at 3, 12, 24, and 36 months, the BREAST-Q score, cosmetic PROs, photographs, prognosis, and long-term complications will be evaluated.

Data collection and management

Data will be recorded on the CAPPELLA case report forms (CRFs). The items collected will include patients' demographic data (including age, sex, BMI, marital status and parental history), clinical and pathological data, surgical information, BREAST-Q score, cosmetic PROs, surgery- and radiotherapy-related complications, photographs, neoadjuvant and adjuvant treatments, and prognosis. Surgery-related complications will include hematoma, seroma, poor healing, nipple or areola necrosis, infection, loss of volume, unplanned reoperation, DIEP flap failure (defined as complete or partial necrosis of the flap requiring debridement surgery), and fat necrosis. Radiotherapy-related complications will include radiation dermatitis, breast fibrosis, flap contracture, capillaritis, radiation pneumonitis/pulmonary fibrosis, and radiation heart injury.

Statistical analysis and sample size calculation

Descriptive statistics will be used to summarize baseline characteristics. Proportional differences between groups will be tested using Pearson's $\chi 2$ test. T-test will be used to compare continuous outcomes between two groups, and one-way analysis of variance will be used to compare outcomes across groups. Univariate and multivariate logistic regression analyses will be carried out to examine associations between independent variables and outcomes. All available independent variables will be considered in the univariate regression model, and only significant variables ($p < 0.1$) will be included for further multivariate logistic regression analyses. All tests will be two-sided, and a p value of less than or equal to 0.05 will be considered significant.

Sample size calculation

The study has been designed as a randomized, controlled superiority trial with participants allocated at a 1:1 ratio between the preoperative radiotherapy and PMRT groups. According to previous studies, the mean score of the breast domain of the BREAST-Q at 2 years postoperatively was 64 ±16.9 in the PMRT group [29]. The average score in the breast domain of the BREAST-Q at 2 years in the preoperative radiotherapy group is estimated to reach 77 on average. We assume that the breast satisfaction score will be better in the preoperative radiotherapy group than in the PMRT group. A one-sided alpha level of 0.025 will be used for statistical significance. Thus, a sample size of 40 patients per group (80 patients in total) can provide a

statistical power of 0.93 to detect significant differences between the groups, assuming equal variance in both groups. PASS 15 Power Analysis and Sample Size Software (2017) (NCSS, LLC, Kaysville, Utah, USA) was used to calculate the sample size

Patient and public involvement

Patients and the public were not involved in the design, recruitment to and conduct of study. The research question and outcome measures were not informed by patients' priorities and preferences. The aim of this study was to evaluate patients' experiences, including quality of life, symptoms, physical and social functional abilities, and psychosocial concerns. Healthcare providers and hospital staff will support this work. No patient advisers were involved in this study.

DISCUSSION

IBR is associated with improved QoL, body image, self-esteem, and confidence and has become an increasingly popular choice among patients. Radiotherapy plays an important role in the multidisciplinary treatment of breast cancer. Breast reconstruction and PMRT have become more common in the past decade. However, there is controversy surrounding the typical approach to integrating radiotherapy with IBR in breast cancer management.

Autologous reconstruction followed by radiotherapy may cause several complications, including hematoma, seroma, infection, embolism, fibrosis, fat necrosis, total or partial loss of skin flap volume, and donor site problems, thereby reducing patient satisfaction and the cosmetic outcomes of breast reconstruction. Many surgeons in the UK recommend delaying reconstruction if PMRT is required [30].

However, an increasing number of studies have provided favorable evidence for immediate autologous reconstruction. In 2017, a Mastectomy Reconstruction Outcomes Consortium (MROC) study provided compelling data for immediate autologous breast reconstruction. This prospective, multicenter study included 175 patients who underwent immediate or delayed autologous reconstruction with PMRT, and the results showed no significant difference in the incidence of complications between the two groups after 1 year (25.9% vs. 26.9%; P = 0.54) [31]. IBR can protect women from psychosocial distress, negative body image, and diminished sexual well-

being when compared to delayed reconstruction [4]. This evidence suggests that immediate autologous reconstruction is better tolerated with radiotherapy than does evidence from previous experience, with lower complication rates.

Over the past decade, advances in technologies have reduced the challenges in irradiated patients who have undergone immediate reconstruction. In patients who undergo breast reconstruction, the most commonly used radiotherapy techniques are IMRT and VMAT. Both techniques improve the homogeneity of the dose within the target area while reducing the radiation dose delivered to the lungs and heart. The disadvantage of IMRT and VMAT is the wide range of low-dose zones, resulting in unknown long-term adverse events [32–34].

Radiotherapy techniques play a crucial role in determining the cosmetic outcome of breast reconstruction, including the use of a bolus or boost, fractionation, and nodal target volumes. Orecchia *et al*. reported dosimetric results and toxicity evaluation results of 120 patients who received hypofractionated PMRT with IMRT. Among them, 70.8% of the plans had high scores for optimal chest wall (CW) and nodal region (RN) coverage, and grade 2 acute toxicity was observed in 36.2% of patients [35]. Dumane and colleagues reported the dosimetric results of 10 consecutive patients who underwent tissue expander/permanent implant (TE/PI) reconstruction and who were treated with a combination of VMAT and DIBH. Significant dosimetric gains were demonstrated for low doses to the heart, lungs, and contralateral breast/implants [36].

Although PMRT has therapeutic benefits, it can increase the risk of complications and often results in poor cosmesis for women undergoing breast reconstruction. Radiation exposure can cause early changes in normal tissues, such as skin erythema, desquamation, and pruritus. These changes are caused directly by DNA damage or indirectly through the release of free radicals or inflammation. Late changes in the affected area may include damage to small blood vessels, cell loss, and fibrosis. These factors can contribute to poor wound healing and potentially worse cosmetic outcomes. Due to the limitations of current methods, there has been growing interest in using preoperative radiotherapy to avoid negative effects on autologous breast reconstruction caused by radiation. Recently, some researchers have published findings supporting

preoperative radiotherapy as a proven strategy to improve cosmetic results and simplify the reconstructive process [15–17]. Singh *et al*. performed a systematic review that included 10 retrospective and 8 prospective studies analyzing the effects of NART on IBR; the overall complication rates ranged from 3% to 36%, and the rates of excellent-to-good cosmetic outcomes ranged from 66–89% [18]. However, there is limited data on the effect of preoperative radiotherapy prior to mastectomy and microvascular autologous reconstruction [37]. The PRADA study recently demonstrated that preoperative radiotherapy followed by skin-sparing mastectomy and DIEP flap reconstruction is technically feasible. The study reported low rates of surgical complications and good short-term oncological outcomes. [19]. These studies lack longer follow-up evaluations, and larger prospective controlled clinical trials are required to objectively measure this new therapeutic sequence. We aim to compare the oncological and QoL outcomes in a randomized trial of preoperative radiotherapy versus conventional PMRT in breast reconstruction.

ETHICS AND DISSEMINATION

This study will be performed in accordance with the Helsinki Declaration. Patients will be provided with details of the study (purpose, risk, and benefits) and have the right to withdraw from the study at any time. Approval for this study was provided by the independent ethics committee and institutional review board of FUSCC (Fudan University Shanghai Cancer Center) and approval ID number was 2208258-5-2402C. Prior to enrollment, an informed consent form will be sent to each patient to ensure their understanding of the cohort study. This study will be conducted according to the requirements of the Good Clinical Practice (GCP) guidelines. The results of the study will be presented at national and international meetings and published in a scientific peer-reviewed journal.

Cancer centers

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Huashan Hospital

Hunan Cancer Hospital

Cancer Hospital of Guangxi Medical University

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Protocol review: Jiong Wu, Xiaoli Yu, Yifeng Hou, Keda Yu, Zhen Hu, Guangyu Liu, Genhong Di, Zhiming Shao

Guarantor is Jiong Wu.

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Competing interests None declared.

Patient consent for publication Not needed.

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Figure legend

Fig. 1 Flow chart of the CAPPELLA trial.

Abbreviations: DIEP = deep inferior epigastric perforator

Table 1 Suggested CTV delineation for breast and lymph node regions.

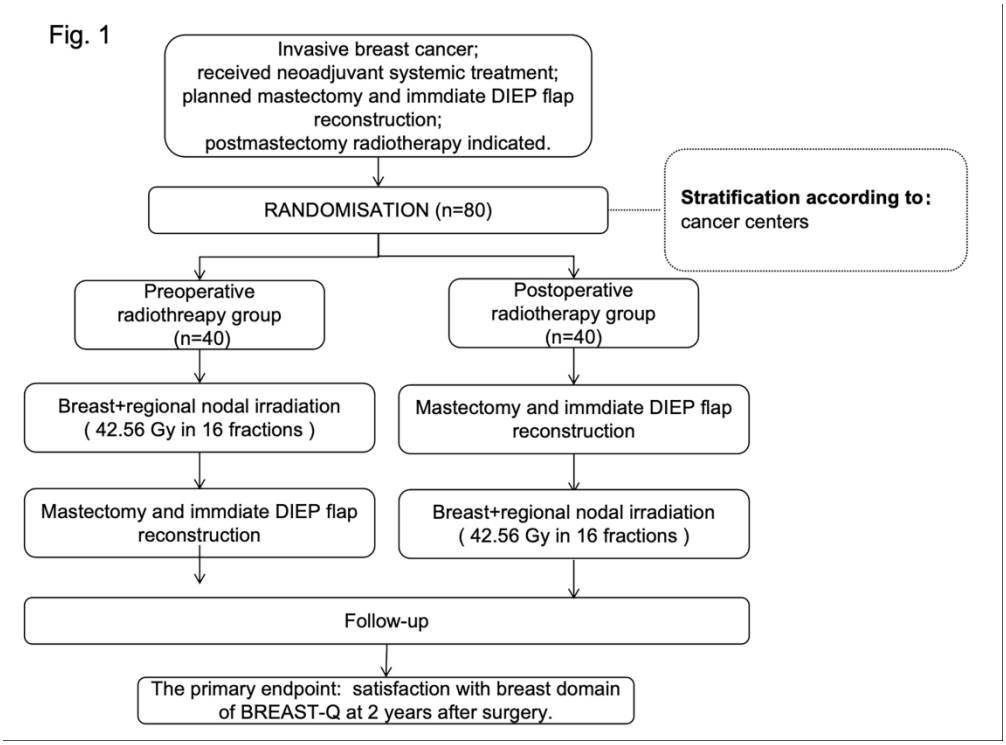

Fig. 1 Flow chart of the CAPPELLA trial. Abbreviations: DIEP = deep inferior epigastric perforator

252x185mm (300 x 300 DPI)

Table 1 Suggested CTV delineation for breast and lymph node regions

	Cranial	Caudal	Ventral	Dorsal	Medial	Lateral
Breast CTV (CTV_B) (Preoperative radiotherapy group)	Upper border of palpable/visible breast tissue; maximally up to the caudal edge of the sterno-clavicular joint	Most caudal CT slice with visible breast	3~5 mm under skin surface (Skin in cT4b-4 cases with extensive skin invasion)	Major pectoral muscle or costae and intercostal muscles where no muscle (For T4a/T4c cases, the major pectoral muscle and ribs should be included)	Lateral to the medial perforating mammarian vessels; maximally to the edge of the sternal bone	Lateral breast fold; anterior to the lateral thoracic artery
Chest wall CTV (CTV_CW) (Postoperative radiotherapy group)	Guided by palpable/visible signs; if appropriate guided by the contralateral breast; maximally up to the caudal edge of the sterno-clavicular joint	Guided by palpable/visible signs; if appropriate guided by the contralateral breast	Same as above	Same as above	Guided by palpable/visible signs; if appropriate guided by the contralateral breast	Guided by palpable/visible signs; if appropriate guided by the contralateral breast. Usually anterior to the mid-axillary line
Supraclavicular CTV (CTV_SCN)	Caudal to the cricoid cartilage	Includes the subclavian vein with 5 mm margin, thus connecting to the cranial border of CTVn_IMN	Sternocleidomastoid muscle, dorsal edge of the clavicle	Anterior aspect of the scalene muscle	Including the jugular vein without margin; excluding the thyroid gland and the common carotid artery	Cranial: Sternocleidomastoid muscle Caudal：junction of 1st rib and clavicle
Internal mammary node CTV (CTV_IMN)	Caudal limit of CTV_SCN	Cranial side of the 4th rib (in selected cases 5-6th	Ventral limit of the vascular area	Pleura	5 mm from the internal mammary vein (artery in cranial	5 mm from the internal mammary artery

			rib)			part down to and including first intercostal space)	
Undissected axillary CTV (CTV_udALN)	Undissected Axillary level 2	Includes the cranial extent of the axillary artery (i.e. 5 mm cranial of axillary vein)	The caudal border of the minor pectoral muscle, but should exclude the extent of the dissection	Minor pectoral muscle	Up to 5 mm dorsal of axillary vein or to costae and intercostal muscles	Medial edge of minor pectoral muscle	Lateral edge of minor pectoral muscle, but should exclude the extent of the dissection
	Axillary level 3	Includes the cranial extent of the subclavian artery (i.e. 5 mm cranial of subclavian vein)	5 mm caudal to the subclavian vein	Major pectoral muscle	Same as level 2	Junction of subclavian and internal jugular veins, connects to CTV_SCN	Medial side of the minor pectoral muscle
	Interpectoral nodes	Includes the cranial extent of the axillary artery (i.e. 5 mm cranial of axillary vein)	The caudal border of the minor pectoral muscle	Major pectoral muscle	Minor pectoral muscle	Medial edge of minor pectoral muscle	Lateral edge of minor pectoral muscle