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PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

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

Authors

Hao, Shuang; hou, jianjing; Zhang, Li; Zhou, Changming; Hou, Yifeng; Yu, Keda; Hu, Zhen; Liu, Guangyu; Di, Genhong; Shao, Zhi Min; Yu, Xiaoli; Wu, Jiong

VERSION 1 - REVIEW

I appreciate the authors for the opportunity to review their work and the study they propose. I believe it is a very interesting project that will provide extremely valuable information for PMRT. The study is coherent and very well designed, with a solid and well-justified foundation. The objectives are achievable and sensible, the expected number of patients is appropriate, and the analysis and evaluation tools are very suitable. As for the manuscript's writing, I would only recommend that the authors remove the word 'total' from the expression 'total complete pathological response' to avoid redundancy.

Reviewer	2
Name	Magno, Stefano
Affiliation IRCCS	Fondazione Policlinico Universitario Agostino Gemelli
Date	31-Jul-2024
COI	none

The study is well designed and described.

I can imagine the reason why you chose to address the patients' satisfaction rates as the primary endpoint, instead of the oncological outcomes of NART, despite the fact that, as you correctly state, we have not prospective controlled studies with sufficient follow-up to assess the oncological outcomes of this new therapeutic sequence. In the PRADA study cited by you, "in the subgroup analyses, NART followed by implant-based reconstruction was associated with similar BCSS (HR 1.039, Log Rank P = 0.921) and OS (HR 1.153, Log Rank P = 0.697) as PORT (Fig. 2C,D), while for cases undergoing autologous-tissue reconstruction, those treated with NART had significantly lower BCSS (HR 2.050, Log Rank P = 0.044) and OS (HR 2.183, Log Rank P = 0.024) compared with PORT"

How would you reply to the concern that you are proposing to one of the two arms a suboptimal treatment, while your trial has a follow-up period "relatively short for assessing prognosis".

In the "follow up" section, you wrote "commodity" among the patients' features to be recorded, but I presume you meant something else.

I would suggest to include in the references the following:

10.1016/j.critrevonc.2019.06.003

10.1016/S1470-2045(22)00145-0

VERSION 1 - AUTHOR RESPONSE

Reviewer:1

Dr.	Angel	Montero,	HM	Hospitales
Comments		to	the	Author:

I appreciate the authors for the opportunity to review their work and the study they propose. I believe it is a very interesting project that will provide extremely valuable information for PMRT. The study is coherent and very well designed, with a solid and well-justified foundation. The objectives are achievable and sensible, the expected number of patients is appropriate, and the analysis and evaluation tools are very suitable. As for the manuscript's writing, I would only recommend that the authors remove the word 'total' from the expression 'total complete pathological response' to avoid redundancy.

Thank you for the suggestion. We have added the information here to explained the definition of tpCR (total pathologic complete response).

Patients underwent surgery at the end of the neoadjuvant course. The response to neoadjuvant treatment was assessed according to RECIST version 1.1. Total pathological complete response

(tpCR) was defined as the absence of any pathological evidence of residual invasive carcinoma in both the breast and axillary lymph nodes (ypT0/isN0 status). A breast pathological complete response (bpCR) was defined as the absence of any pathological evidence of residual invasive carcinoma in the breast (ypT0/is status)[1].

Reviewer:2

Dr. Stefano Magno, Fondazione Policlinico Universitario Agostino Gemelli IRCCS Comments to the Author: The study well designed described. is and I can imagine the reason why you chose to address the patients' satisfaction rates as the primary endpoint, instead of the oncological outcomes of NART, despite the fact that, as you correctly state, we have not prospective controlled studies with sufficient follow-up to assess the oncological outcomes of this new therapeutic sequence. In the PRADA study cited by you, "in the subgroup analyses, NART followed by implant-based reconstruction was associated with similar BCSS (HR 1.039, Log Rank P = 0.921) and OS (HR 1.153, Log Rank P = 0.697) as PORT (Fig. 2C,D), while for cases undergoing autologous-tissue reconstruction, those treated with NART had significantly lower BCSS (HR 2.050, Log Rank P = 0.044) and OS (HR 2.183, Rank P = 0.024) compared with PORT" Log How would you reply to the concern that you are proposing to one of the two arms a suboptimal treatment, while your trial has a follow-up period "relatively short for assessing prognosis".

In the "follow up" section, you wrote "commodity" among the patients' features to be recorded, but I presume you meant something else. Ι include would suggest in the references the following: to 10.1016/j.critrevonc.2019.06.003 10.1016/S1470-2045(22)00145-0

1) We are grateful for the suggestion. Those patients treated with NART had lower BCSS and OS compared with PORT may due to poor response to neoadjuvant systemic therapy[2]. NART may be considered for patients with T4 disease when they do not respond well to neoadjuvant systemic therapy. This may include conditions such as skin nodules, ulcers, edema or rupture.

A retrospective study found that neoadjuvant radiochemotherapy achieved a total pCR rate of 29.2% and a significantly better 10-year survival rate than adjuvant radiochemotherapy in patients with cT2 tumours [3]. The PRADA study recently demonstrated that preoperative radiotherapy followed by skin-sparing mastectomy and DIEP flap reconstruction is technically feasible[4]. The study reported low rates of surgical complications and good short-term oncological outcomes. Hense, we aimed to compare the oncological and quality-of-life outcomes in a randomized trial of preoperative radiotherapy versus conventional post-mastectomy radiotherapy in breast reconstruction.

2) In the "follow up" section, We have corrected the "commodity" into "satisfaction with breast appearance" (Line 23, Page 10).

- Cortazar P, Zhang L, Untch M, *et al.* Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384:164–72. doi: 10.1016/S0140-6736(13)62422-8
- 2 Yuan J, Zhang M, Wang M, *et al.* Neoadjuvant radiochemotherapy is safe and feasible for breast conserving surgery or immediate reconstruction. *Sci Rep.* 2024;14:9208. doi: 10.1038/s41598-024-59961-0
- 3 Roth SL, Audretsch W, Bojar H, *et al.* Retrospective study of neoadjuvant versus adjuvant radiochemotherapy in locally advanced noninflammatory breast cancer : survival advantage in cT2 category by neoadjuvant radiochemotherapy. *Strahlenther Onkol.* 2010;186:299–306. doi: 10.1007/s00066-010-2143-0
- 4 Thiruchelvam PTR, Leff DR, Godden AR, *et al.* Primary radiotherapy and deep inferior epigastric perforator flap reconstruction for patients with breast cancer (PRADA): a multicentre, prospective, non-randomised, feasibility study. *Lancet Oncol.* 2022;23:682–90. doi: 10.1016/S1470-2045(22)00145-0