



BMJ Open Oncological outcome of single-port insufflation endoscopic nipple-sparing mastectomy versus open mastectomy in early breast cancer patients: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction Breast cancer is the most prevalent cancer and the leading cause of cancer-related death in women. Conventional open mastectomy (C-OM) is one of the most common procedures for breast cancer, which involves the removal of the nipple-areola complex and a large proportion of the breast skin, leading to poor cosmetic effect and restriction of upper extremity function. Single-port insufflation endoscopic nipple-sparing mastectomy (SIE-NSM) could conceal the incision along the wrinkles in the axilla, preserve all the breast skin and nipple-areola complex and provide a better cosmetic outcome and quality of life. This trial aims to investigate the oncological safety between SIE-NSM and C-OM in early breast cancer patients.

Methods and analysis This is a single centre, non-blinded, randomised controlled trial (RCT) and will be conducted at Beijing Friendship Hospital. Patients will be enrolled in the inpatient ward. Breast surgeons will notify patients who meet the inclusion and exclusion criteria with the instruction of this RCT. Patients will be randomly assigned to C-OM or SIE-NSM with a 3:1 allocation as per a computer-generated randomisation schedule. Patients will be followed-up for 12 months for analysing surgical outcomes. The primary outcome is the local recurrence rate at a 12-month follow-up. The secondary outcome is the distant metastasis rate, cosmetic satisfaction score and psychosocial well-being score after a 12-month follow-up. To ensure the accuracy of the cosmetic satisfaction score and psychosocial well-being score, the standard scale, Breast-Q score, will be applied.

Ethics and dissemination This study will be conducted according to the medical ethics committee of the Beijing Friendship Hospital and according to the principles of the Declaration of Helsinki. All patients will receive clear instruction of their disease and treatment plan. Informed consent will be obtained from all patients when they agree to comply with our research plan. The results will be disseminated at academic presentations and publications in peer-reviewed journals. The raw data will

Strengths and limitations of this study

- This trial aims to compare local recurrence and oncological safety of single-port insufflation endoscopic nipple-sparing mastectomy (SIE-NSM) and conventional open mastectomy in early breast cancer patients.
- The major strength of the study will be the number of patients who are expected to be enrolled.
- Blinding of the patients or researchers is not possible in this study due to the visible postoperative scars.
- This study will provide evidence regarding the safety of SIE-NSM.

be confidentially stored in our electronic data capture database. Data will not be shared unless an appropriate data request is submitted after the trial completion and peer-review journal publication.

Trial registration number NCT04461847.

INTRODUCTION

Breast cancer is the most prevalent cancer and the leading cause of cancer-related death in women.^{1,2} Surgery is the cornerstone treatment for breast cancer, where conventional open mastectomy (C-OM) is quite common in routine clinical treatment.^{3,4} In C-OM, a large portion of the breast skin and the nipple-areola complex (NAC) is removed, leaving a linear scar of approximately 20 cm long. The quality of life is also seriously compromised in patients who underwent C-OM.^{5,6} First, the defected skin and scar constrain the free movement of the upper limb.⁷ Second, the extremely large scar makes patients uncomfortable both physically and psychologically.⁸

Given how the oncological efficacy of surgical treatment has reached a relative limitation, organ function preservation is gradually gaining more attention in recent years.⁹ The breast, as the main female characteristic feature, plays an important role in the quality of female life. Several oncologists are considering the preservation of breast function after mastectomy. Nipple-sparing subcutaneous mastectomy (NSM) is becoming an important option for selected patients. NSM partially reduces the length of the scar, preserves NAC and retains the breast skin. However, there is still an obvious scar on the chest wall after NSM, and the incision around the NAC may cause NAC ischaemia or necrosis.^{10 11}

Endoscopic surgeries are minimally invasive and are becoming more popular in breast surgery. Therefore, we designed a single-port insufflation endoscopic nipple-sparing mastectomy (SIE-NSM), which can conceal the small incision along the wrinkles in the axilla, preserving all the breast skin and NAC and avoiding the incision around the NAC.

Several studies have reported endoscopic NSM, but most studies were conducted on a small population. Furthermore, few of these studies were prospective, and the majority were retrospective. Most importantly, none of the studies were randomised. This study aims to conduct a randomised controlled trial (RCT) for examining SIE-NSM in comparison to C-OM in a large homogeneous group of patients with early breast cancer.

Objectives

The objective of this RCT is to compare local recurrence between SIE-NSM and C-OM. The hypothesis is that the oncological safety of SIE-NSM is not inferior to that of C-OM.

This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials guideline.^{12 13}

Study design

This is a single-centre, non-blinded, RCT and will be conducted in Beijing Friendship Hospital. Patients will be enrolled in the inpatient ward. Breast surgeons will notify patients who meet the inclusion and exclusion criteria with the instruction of this RCT. After meeting the inclusion criteria and receiving informed consent, patients will be randomly assigned to undergo C-OM or SIE-NSM with 3:1 allocation based on a computer-generated randomisation schedule. Blindness is not possible because all patients have different surgical scars, indicating surgical intervention. However, the local recurrence rate is the primary outcome, which is examined using paraffin pathology. Therefore, the awareness of the group has no influence on this data.

Patients' enrolment started in November 2020 and will be completed by May 2022. Patients will then be followed-up for 12 months for analysing surgical outcomes.

METHODS AND ANALYSIS

Study population

Patients will be recruited after giving their consent in Beijing Friendship hospital. Patients will be assessed by the breast tumour group to decide whether they are eligible or not. All patients have the right to withdraw at any time. At the end of this trial, the results of this study will be disseminated to the public via public talks, conferences and peer-reviewed journals.

Eligibility criteria

1. Pathologically confirmed stage I/II invasive breast cancer.
2. Tumour size < 3 cm, tumour location > 3 cm from the NAC, without severe axillary lymph node and vascular and nerve invasion.
3. Age ranging from 18 to 70 years.
4. Eastern Cooperative Oncology Group score 0–2.
5. Normal liver, kidney, and bone marrow function.

Exclusion criteria

1. Involvement of the nipple and skin as determined by physical examination and MRI.
2. Other cancer history in the past 5 years.
3. Presence of other severe morbidity such as angina pectoris, myocardial infarction and stroke in the past 6 months.
4. Receiving immune suppression medication after organ transplantation.
5. Receiving steroid medication for a long time.
6. Women who are pregnant or breast feeding.

Patients and public involvement

Patients and members of the public were not involved in the design of this study.

Intervention

Group A: C-OM group

1. A fusiform incision of approximately 20 cm long will be performed, including the NAC (figure 1).
2. The breast tissue will be mobilised by dissecting the copper ligament and pectoris fascia, the boundary of the breast tissue.
3. The sentinel lymph nodes will be identified and removed for intraoperative freezing pathology. If the sentinel lymph nodes are positive for cancer cells, axillary lymph node dissection will be performed. The surgical area between the breast skin and pectoris will be washed using sterile distilled water; two drainage tubes will be placed at the axillary and parasternal nodes.

Group B: SIE-NSM group

- ▶ Liposuction liquid will be injected into the superficial area of the breast tissue and the subcutaneous area of the breast skin. The related fat will be resolved after 15 min, and the resolved adipose tissue will be sucked through a liposuction tube, which will leave enough space for surgical procedures.

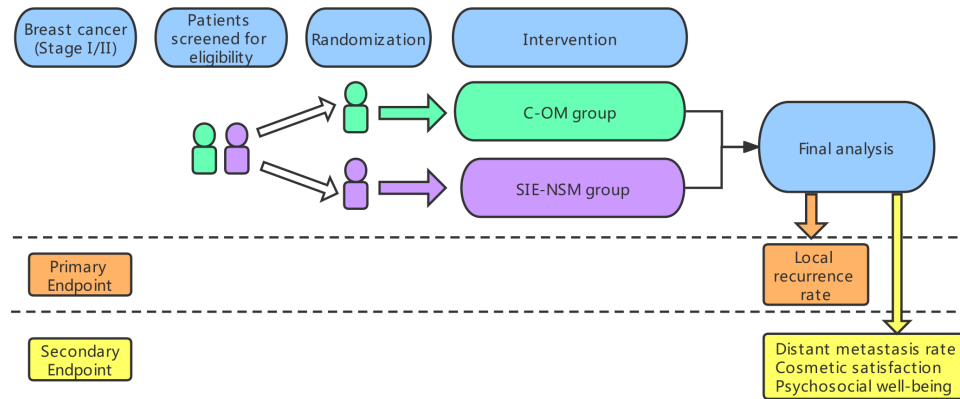


Figure 1 Flow chart of the trial design with endpoint and proposed experimental analyses. C-OM, conventional open mastectomy; SIE-NSM, single-port insufflation endoscopic nipple-sparing mastectomy.

- ▶ To conceal the incision, a 2.5 cm long single-port incision will be made along the wrinkles in the axilla. The single-port insufflation kit (HTKD-Hang T Port, China) will be placed into the incision through which an adequate working space will be created by insufflating to an 8 mm Hg of pressure using 8 L of carbon dioxide per minute.
- ▶ Using endoscopy, the breast tissue will be mobilised from the skin and pectoris by severing the copper ligament and fascia. The surgical field will be washed, and two drainages will be placed.

Follow-ups

Chest X-ray, abdomen and breast ultrasound and tests for tumour biomarkers (CA153, CEA and CA125) will be performed every 4–6 months. Mammography and bone scintigraphy will be performed every 12 months. Tumour evaluation will be performed at any time when there is a recurrence or clinical sign of metastasis.

Outcome measurements

Primary outcome

The primary outcome is the local recurrence rate at a 12-month follow-up (figure 2). When a lump is found on the breast tissue, chest wall, skin or scar of the same surgical side either by physical examination or ultrasound, a biopsy will be performed to confirm the pathology. A recurrence is defined when the lump has the same pathological type as the primary tumour tissue.

Secondary outcome

The secondary outcome was the distant metastasis rate at a 12-month follow-up. Distant metastasis is defined as distant metastasised lump in distant organs such as the lung, bone, liver, and brain, with pathological confirmation.

Cosmetic satisfaction will be scored at a 12-month follow-up. We will use BREAST-Q scoring questionnaire to ask patients to score the satisfaction of cosmetic effects, including breast location, shape, consistency and naturalness.^{14 15}

Psychosocial well-being will be scored at a 12-month follow-up. BREAST-Q questionnaire will be used for

evaluating the psychosocial well-being. Patients can score such questions, the confidence in social settings, the enthusiasm they focus on daily work, the acceptance of their identity and physical body.^{14 16}

Sample size

As reported, the local recurrence rate is 2.1% in the C-OM group.^{17–19} A non-inferiority margin of 5% is considered as clinically significant between the C-OM and SIE-NSM groups. The sample size is calculated with a 3:1 ratio between the C-OM group and SIE-NSM group since more patients will choose to receive C-OM surgery.²⁰ A sample size of 68 patients in the SIE-NSM group and 204 patients in the C-OM group is required, with 80% power allowing for one-sided $\alpha=0.025$. Considering a drop-out rate of

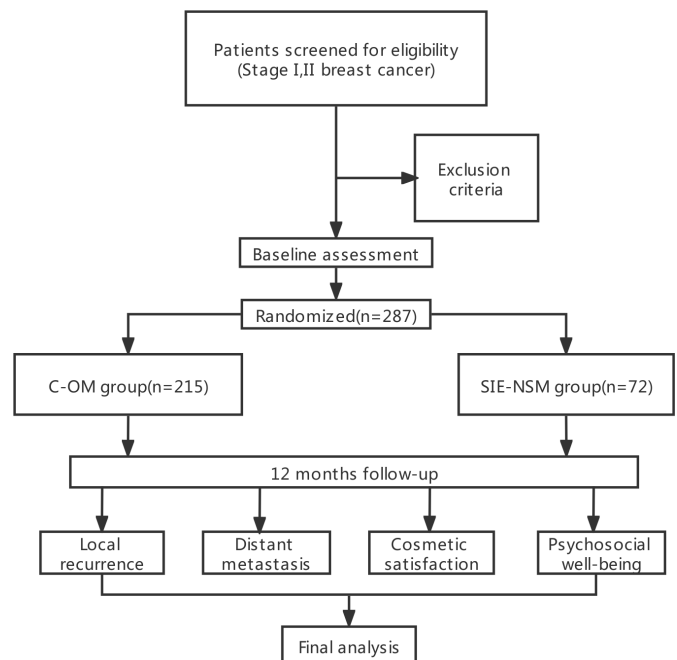


Figure 2 SPIRIT patient flow diagram of the trial. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; C-OM, conventional open mastectomy; SIE-NSM, single-port insufflation endoscopic nipple-sparing mastectomy.



5% during the 2 years, a sample size of 72 patients in the SIE-NSM group and 215 patients in the C-OM group is needed (figure 2).

Data analyses

Descriptive statistics will be summarised for all baseline characteristics with mean±SD for continuous variables with a normal distribution, median (lower quartile, upper quartile) for continuous variables without a normal distribution, and absolute number with percentage for categorical variables. Fisher's exact test or the χ^2 test will be used for comparing the local recurrence, distant metastasis and adverse event rates between the C-OM group and SIE-NSM group. Student's t test will be used for evaluating changes in the questionnaire score, including cosmetic satisfaction score and psychosocial well-being score, between the two groups. All efficacy analysis will be conducted using the full analysis set (FAS), and safety analysis will be performed using the safety set.

The FAS will consist of all the randomised patients treated with C-OM or SIE-NSM with a baseline and at least one postsurgery measurement, equating to an intention to treat analysis. All patients treated with C-OM or SIE-NSM will be included in the analysis of safety.

ETHICS AND DISSEMINATION

Data monitoring and auditing

The data monitoring committee group will consist of clinical research methodology workers from Beijing Friendship Hospital. The committee will be completely independent from the study investigators and will be responsible for data monitoring, storage, audit and statistical analyses. Data of all records, adverse events and questionnaires will be stored in an electronic data capture (EDC) system.

Harm and protocol amendment

Adverse events are defined as any unintended harmful events related to the surgical procedure during the perioperative period. All the adverse events will be reported and recorded directly into the EDC system. Patients who are enrolled into the study are covered by indemnity for negligent harm through the standard National Health Service Indemnity arrangements. We plan to perform an interim analysis when half of the patients are included.

Ethics consideration

This study will be conducted according to the medical ethics committee of Beijing Friendship Hospital (document number: 2019-P2-052-02) and according to the principles of the Declaration of Helsinki. All participants will receive clear instruction regarding their disease and treatment plan. Informed consent will be obtained from all patients when they agree to comply with our research plan.

Dissemination

The results will be disseminated at academic presentations and publications in peer-reviewed journals. The

raw data will be stored confidentially in our EDC database. Data will not be shared unless an appropriate data request is submitted after the trial completion and peer-review journal publication.

Trial status

Because of the COVID-19 pandemic, patient enrolment for the study started in November 2020 at the Beijing Friendship Hospital in Beijing, China. To date, 188 patients have been enrolled. We anticipate that more patients will be enrolled to allow for the futility assessment by May 2022.

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Contributors Z-hW and G-qD are responsible for manuscript writing and will be cofirst authors. Corresponding authors, Z-tZ and XQ, are responsible for the concept and protocol development. S-sW is responsible for sample size calculation and statistical analyses. J-nS, Z-cG, H-mZ, ZY, Y-gG and T-rG are responsible for recruitment of patients. All authors are responsible for the final approval of the manuscript and are accountable for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Ferlay J, Colombet M, Soerjomataram I, *et al*. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018;103:356–87.
- 2 Anastasiadi Z, Lianos GD, Ignatiadou E, *et al*. Breast cancer in young women: an overview. *Updates Surg* 2017;69:313–7.
- 3 Ou H-T, Chung W-P, Su P-F, *et al*. Health-related quality of life associated with different cancer treatments in Chinese breast cancer survivors in Taiwan. *Eur J Cancer Care* 2019;28:e13069.
- 4 Schmidt ME, Scherer S, Wiskemann J, *et al*. Return to work after breast cancer: the role of treatment-related side effects and potential impact on quality of life. *Eur J Cancer Care* 2019;28:e13051.
- 5 Akça M, Ata A, Nayir E, *et al*. Impact of surgery type on quality of life in breast cancer patients. *J Breast Health* 2014;10:222–8.
- 6 Enien MA, Ibrahim N, Makar W, *et al*. Health-related quality of life: impact of surgery and treatment modality in breast cancer. *J Cancer Res Ther* 2018;14:957–63.
- 7 Shi HY, Uen YH, Yen LC, *et al*. Two-year quality of life after breast cancer surgery: a comparison of three surgical procedures. *Eur J Surg Oncol* 2011;37:695–702.
- 8 Türk KE, Yılmaz M. The effect on quality of life and body image of mastectomy among breast cancer survivors. *Eur J Breast Health* 2018;14:205–10.

- 9 Reddy D, Bedi N, Dudderidge T. Focal therapy, time to join the multi-disciplinary team discussion? *Transl Androl Urol* 2020;9:1526–34.
- 10 Kaidar-Person O, Poortmans P, Offersen BV, *et al.* Spatial location of local recurrences after mastectomy: a systematic review. *Breast Cancer Res Treat* 2020;183:263–73.
- 11 Rawlani V, Fiuk J, Johnson SA, *et al.* The effect of incision choice on outcomes of nipple-sparing mastectomy reconstruction. *Can J Plast Surg* 2011;19:129–33.
- 12 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- 13 Chan A-W, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
- 14 Cohen WA, Mundy LR, Ballard TNS, *et al.* The BREAST-Q in surgical research: a review of the literature 2009-2015. *J Plast Reconstr Aesthet Surg* 2016;69:149–62.
- 15 Liu LQ, Branford OA, Mehigan S. BREAST-Q measurement of the patient perspective in oncoplastic breast surgery: a systematic review. *Plast Reconstr Surg Glob Open* 2018;6:e1904.
- 16 Mundy LR, Homa K, Klassen AF, *et al.* Breast cancer and reconstruction: normative data for interpreting the BREAST-Q. *Plast Reconstr Surg* 2017;139:1046e–55.
- 17 Lee SB, Lee JW, Kim HJ, *et al.* Long-term outcomes of patients with breast cancer after nipple-sparing mastectomy/skin-sparing mastectomy followed by immediate transverse rectus abdominis musculocutaneous flap reconstruction. *Medicine* 2018;97:e0680.
- 18 Gieni M, Avram R, Dickson L, *et al.* Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: a meta-analysis. *Breast* 2012;21:230–6.
- 19 Brett EA, Aitzetmüller MM, Sauter MA, *et al.* Breast cancer recurrence after reconstruction: know thine enemy. *Oncotarget* 2018;9:27895–906.
- 20 Huang N-S, Liu M-Y, Chen J-J, *et al.* Surgical management of breast cancer in China: a 15-year single-center retrospective study of 18,502 patients. *Medicine* 2016;95:e4201.