


BMJ Open Bilateral prophylactic mastectomy: should we preserve the pectoral fascia? Protocol of a Dutch double blinded, prospective, randomised controlled pilot study with a within-subject design (PROFAS)

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ABSTRACT

Introduction Bilateral prophylactic mastectomy (BPM) in women with a high risk of developing breast cancer has shown to provide the greatest risk reduction. Many surgical guidelines recommend the removal of the pectoral fascia (PF) in mastectomies; however, there is no evidence to support this statement. Reported wound-related complications following mastectomy include seroma, flap necrosis, infection and haematoma. Seroma causes discomfort and may delay the reconstructive procedures. Whether removal or preservation of the PF influences drain volume, seroma formation and other postoperative complications following BPM remains unclear. The aim of this study is to assess the impact of removal versus preservation of the PF on drain policy and seroma after BPM.

Methods and analysis This is a double blinded, prospective, randomised controlled pilot study with a within-subject design. The inclusion criteria are women >18 years, presenting in the Academic Breast Cancer Centre Rotterdam, who are opting for BPM. Patients with a history or diagnosis of breast cancer are excluded. According to the sample size calculation based on the difference in total drain volume, a number of 21 eligible patients will be included. Randomisation will occur within the patient, which means PF preservation in one breast and PF removal in the contralateral breast. The primary study endpoint is total drainage volume. Secondary study outcomes include time to drain removal, number of needle aspirations, postoperative complications and length of hospital stay.

Ethics and dissemination The study is approved by the Erasmus Medical Center Review Board (REC 2020–0431). Results will be presented during international conferences and published in a peer-reviewed academic journal.

Trial registration number NCT05391763; clinicaltrials.gov

INTRODUCTION

Bilateral prophylactic mastectomy (BPM) involves removal of healthy breasts for breast cancer prevention. Indications include a BRCA 1 or 2 mutation or other genetic susceptibility,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first surgical study that uses the within-patient randomisation design to evaluate drain volume and seroma after pectoral fascia preservation versus removal, and results will provide clear evidence for causality.
- ⇒ According to the unique within-patient design, possible confounders are eliminated and this will strengthen the outcomes of our study.
- ⇒ The primary limitation of this study is uncertainty of sample size calculation, as mean drain volume (primary outcome) after bilateral prophylactic mastectomy in our institute is unknown. This may challenge the statistical analyses.

a strong family history with no demonstrable mutation, histological risk factors and/or difficult surveillance.¹ The risk of developing breast cancer by the age of 70 years is 57%–65% in woman with a BRCA 1 mutation and 45%–47% in woman with a BRCA 2 mutation.^{1,2} Importantly, BPM has been shown to reduce the risk of breast cancer by up to 95% in woman with BRCA 1 or 2 mutations.^{3–6}

Halsted's radical mastectomy for invasive breast cancer included resection of the breast, overlying skin, pectoral major muscle and an extensive lymph node dissection.⁷ The radical mastectomy was abandoned in 1960 when more limited oncological breast surgery was introduced. Changes towards refined surgery are guided by similar oncologic outcomes and improved cosmetic results or quality of life. The simple and subsequently skin and nipple-sparing mastectomy was introduced in which the pectoral muscle was spared along with removal of the pectoral fascia (PF).⁸ Ever since,

many surgical guidelines recommend the removal of the PF to ensure tumour-free margins.^{9 10} However, there is no evidence to support this statement in early operable breast cancer, except for the minority of patients with tumour invasion in the PF.¹¹ The necessity of PF removal in prophylactic mastectomies is even more questionable.

It is known that the PF plays a role in lymph drainage, however, whether the removal or preservation of the PF influences seroma formation following mastectomy remains unclear.^{12–14} The use of postoperative (suction) drains in breast cancer surgery has been shown to reduce the incidence and degree of seroma.^{15 16} Nevertheless, the incidence of seroma is still 13%–85%, and its sequelae forms the mainstay of complications in breast cancer surgery, varying from delayed wound healing, infection, skin flap necrosis and patient discomfort. These complications will eventually delay the reconstructive procedures.^{17–21} Preserving the PF may also have some advantages when a mastectomy is directly followed by submuscular implant reconstruction. The PF is a thin fibroelastic layer, firmly attached to the pectoral muscle without a separating epimysium as found in other muscle fasciae, which prevents the disruption or detachment of the pectoral muscle during dissection and consequently exposure of the submuscular implant.^{11 22} It is hypothesised that PF preservation may contribute to easier executable and more feasible reconstructive procedures, with superior cosmetic outcomes. Furthermore, as the PF is strongly adherent to the pectoral muscle, PF removal can result in muscle disruption. Most haematomas or postoperative bleedings originate in the pectoral muscle, and PF preservation may lead to less surgical muscle damage and hence reduced bleeding complications.²³

To the best of our knowledge, there are no studies reporting on postoperative complications after PF preservation in women undergoing BPM. This current preclinical study investigates the impact of removal versus preservation of the PF on drain volume and complications after BPM followed by an immediate breast reconstruction using an within-subject randomisation. We hypothesise that PF preservation decreases the total drain volume with subsequently seroma reduction and postoperative complications when compared with PF removal.

Main study objectives

The primary objectives are the impact of removal versus preservation of the PF on (1) the total drainage volume and (2) time to drain removal, and secondary objectives are the impact of removal versus preservation of the PF (1) seroma and number of needle aspirations and (2) on postoperative pain, bleeding, wound-related issues such as haematoma and infection and hospitalisation duration.

METHODS AND ANALYSIS

Study design

This is a Dutch prospective single-centre pilot-study, double blinded and randomised controlled with a within-subject design. The study includes high-risk women

above the age of 18 years presenting in the Erasmus MC Academic Breast Cancer Centre in Rotterdam, who are opting for BPM. Patients will be randomised after informed consent is given. Since the within-subject randomisation design of the trial, preservation of the PF will be performed in one breast (intervention), while removal of the PF will be performed in the contralateral breast of the same patient (control). Consequently, the operation involves a total BPM followed by an immediate reconstruction, with unilateral preservation of the PF. Surgery will be performed by three different experienced breast surgeons. The surgeon will operate both the right and left breast of an individual patient.

Patient and public involvement

There were no patients involved in the design of this study.

Intervention

A total mastectomy will be performed in the control breast: a procedure which includes removal of the breast glandular tissue including the PF and subcutaneously excision of the nipple–areolar complex, while the pectoralis muscle will be spared. As much of the healthy skin envelope will be preserved to enable the performance of an effective breast reconstruction afterwards. When a nipple-sparing mastectomy is performed, the skin envelope together with the nipple–areolar complex will be spared. The investigational part of the operation is preservation of the PF. Dissection of cutaneous flaps and the breast with or without the PF will be performed with electrocautery. In the breast that is randomised to PF removal, the PF will be removed by electrocautery according to standard procedure. The procedure will be followed by an immediate reconstruction, either an autologous or implant-based reconstruction. In case of an implant-based reconstruction, the implants will be placed below the pectoral chest muscle (retropectoral). A closed suction drain will be placed bilaterally in the surgical wound bed at the end of the surgical procedure. The type of drain tube will be selected according to the attending surgeon's preference. For wound closure, one or two layers of (absorbable) sutures will be placed. No compression bandage will be used. The institution's guideline for drain removal will be followed postsurgery (see the section Outcome measurements).

Eligibility criteria

Women are eligible for this study if they are ≥ 18 years old, and scheduled for a BPM in the Erasmus MC Academic Breast Cancer Centre in Rotterdam. The ability to give written consent and adequate understanding of the Dutch language are prerequisite. A subject will be excluded from participation in the study if they have a history or diagnosis of invasive breast cancer or ductal carcinoma in situ or other malignancies.

Randomisation, blinding and allocation to intervention

Patients will be enrolled by the treating surgeon at the outpatient clinic. Randomisation will be performed by

computer-generated simple block randomisation, with blocks of 4 and 6, which will be conducted by Castor Electronic Data Capture System. Per patient, each breast is allocated to the intervention or control arm (ie, preservation or removal of de PF, respectively). Allocation sequence is concealed until participants are enrolled. Randomisation is revealed to the surgeon in the operating room shortly before start of the surgery. The patient and the outcome assessors (observer for drain volume) are both blinded for the assigned breast randomisation. The surgeon(s) and coordinating researcher will not be blinded and are, therefore, not allowed to measure the drain production. For this reason, the study is considered to be a double blind randomised controlled trial. The risk of exceptional circumstances that require unblinding is considered low, however, unblinding is permissible when necessary.

Outcome measurements

Each patient has the first scheduled clinical visit within postoperative week 1 or 2 and ad hoc thereafter, if needed. The drain production is observed by a nurse or ward doctor and is reported in the patients' medical file. When patients are discharged from the hospital with drains in situ, they will receive information from the ward nurse about drain care and drain amount measurements. The volume of 30 mL in 24 hours is established as a guideline for timing of drain removal. When drain discharge is reduced to less than 30 mL per 24 hours, the drain will be removed by a nurse in the hospital. The follow-up time of each patient will be 6 weeks postsurgery.

The main endpoints are the impact of removal or preservation of the PF on the total drainage volume and the time to drain removal. Secondary endpoints are seroma and number of needle aspirations. The indication to perform a needle aspiration is the occurrence of seroma, which is defined as any clinically detected collection of fluid in the axilla or anywhere along the skin incisions requiring aspiration. Differences in drain policy will be measured according to the number of days the drain will be left in situ and the total drain volume. A volume of 30 mL in 24 hours is established as a guideline for timing of drain removal.

The definitions for the other secondary study endpoints are postoperative pain, measured with the Visual Analogue Scale; infection, defined as any wound appearance that is treated with antibiotics; haematoma, defined as collection of blood under the flaps that require evacuation. Hospitalisation is determined as duration of days in the hospital and/or readmissions.

Data collection

The patient's electronic health record will be viewed after removal of the drain for additional recorded variables, for example, hospital stay, the duration of drain use, the total drain volume of each breast, wound-related issues such as haematoma and infection, the total volume of aspirated fluid and the number of needle aspirations (see figure 1).

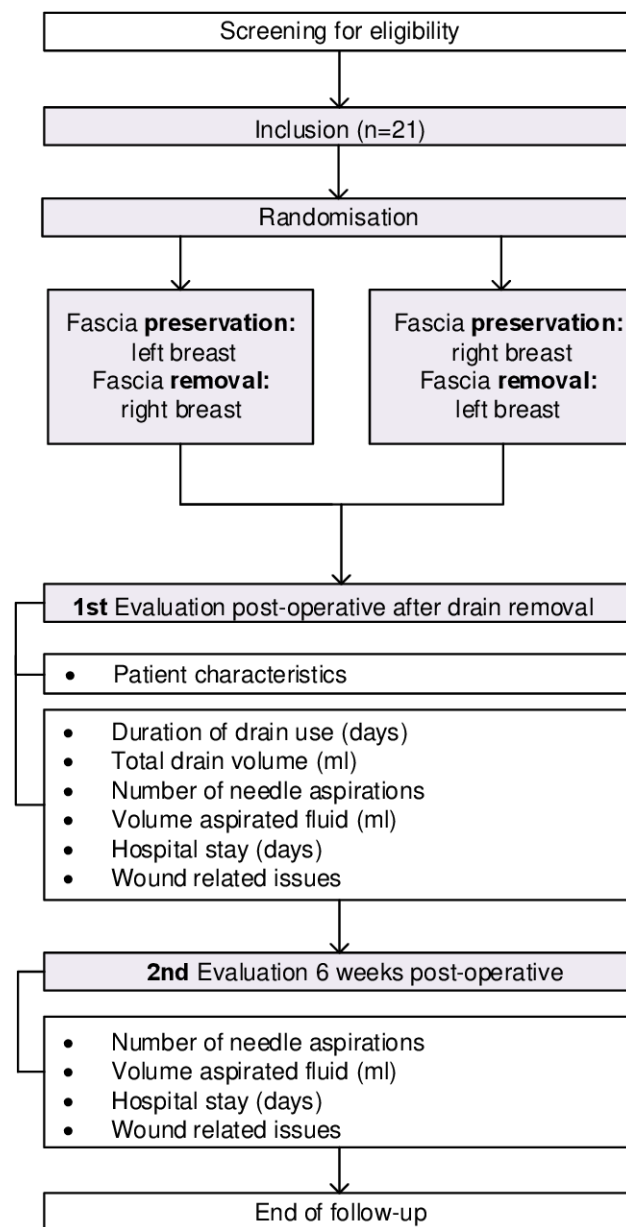


Figure 1 Study design.

Patient characteristics will be collected from the patient's electronic health record. These characteristics include (1) familial history of breast cancer, (2) BRCA1/2 mutation or other genetic susceptibility, (3) patient age at time of operation, (4) right/left dominance, (5) smoking status, (6) time since start of surveillance if applicable (in case of gene mutation), (7) body mass index and (8) comorbidities.

Research data will be stored in a Castor database. Data are handled confidentially and will be coded (PROFAS 00 to 21). This record is filed at the investigational site and can only be accessed by the investigator and the supporting site staff. Data will be stored at the Erasmus Digital Research Archive. Study data will be stored for a maximum of 15 years after completion of the study.

ETHICS AND DISSEMINATION

The study was approved by the local ethics committee of the Erasmus Medical Center (REC 2020–0431). The study is registered at trialregister.nl (NTR7620) and Clinicaltrials.gov. Written informed consent will be obtained from all participants prior to enrolment in the study. Results will be presented during international conferences and published in a peer-reviewed academic journal.

STATISTICS

Sample size

This is a pilot study assessing the effect of removal versus preservation of the PF on seroma formation, and, thus, postoperative drain policy. There is no previous data of fascia preservation on drain volume in prophylactic bilateral mastectomies. According to the literature, a mean total drainage volume of approximately 545 mL is reported following mastectomy. In our institute, the total drainage volume in prophylactic mastectomies is lower because no axillary dissection is performed. It is expected that fascia preservation will lower the drainage fluid with 100–150 mL of the total volume to be clinically relevant. In order to have sufficient statistic power to detect a difference of 100–150 mL in drainage volume between the intervention and control breast, with a power of 80% and a two-tailed alpha (error of 0.025), a number of 12–21 pairs is required. An SD of 165 mL for the control group and 135 mL for the intervention group was used. This means we aim to include 21 patients in this pilot study. This allows for using the results of this preliminary pilot study for an adequate power calculation of a full scale study.

Planned analysis

In the analyses of total drain volume, differences in means between the PF preservation and PF removal breast within one subject will be calculated using the paired t test. The McNemar test will be used to analyse differences in proportions of needle aspirations. Time to drain removal will be analysed with a paired t test or Wilcoxon Signed Rank test if not normally distributed. For the secondary study parameters, differences in proportions will be analysed using the McNemar test and differences in means with the paired t test. All statistical analyses will be stratified for left or right dominance. Differences in means or proportions will be supplemented with corresponding 95% confidence intervals. A two-tailed alpha of 0.05 will be considered statistically significant. All standard statistical analyses will be performed using SPSS (V.25.0, Chicago, Illinois) or R (current version 4.1.0, R Foundation for statistical computing, Vienna, Austria).

DISCUSSION

As an alternative to intensive breast cancer screening, women with a high breast cancer risk (eg, BRCA 1/2 mutation) may choose for a risk-reducing bilateral mastectomy

mostly followed by an immediate breast reconstruction. In a multicentre cohort study with eight Dutch academic centres, 38% of BRCA 2 and 42% of BRCA 1 mutation carriers choose for BPM.²⁴ The rate of prophylactic surgery varies widely and is determined by several factors, such as cultural context, alternative screening options or country-specific established guidelines.^{25 26} In the early 2000s, one of the highest reported incidences of prophylactic mastectomies in mutation carriers was in the Netherlands.²⁷ A trend towards prophylactic mastectomies may be very well supported by breast reconstruction availability. The reconstruction options after BPM are either autologous or implant based or a combination of both. Nowadays, de-escalating surgical procedures are becoming increasingly relevant.^{28 29} From Halsted's radical mastectomy to the modified radical mastectomy, and more recently the introduction of skin-sparing and nipple-sparing mastectomies; more and more breast components have been left intact. To note, some institutes are already preserving the PF as part of standard procedure.^{12 14} In the light of this, we believe that PF preservation should be reconsidered, and results of this preliminary pilot trial will be helpful to gain knowledge about the role of the PF in seroma formation.

Balancing the remaining oncological risk versus expected beneficial surgical outcomes (eg, less complications, better cosmetic outcome, etc) remains, however, challenging. BPM has shown excellent survival rates in high-risk women.³⁰ When PF preservation was introduced in mastectomy patients, a main concern was the oncologic safety of the procedure. The PF was thought to act as a tumour barrier and preserving the PF could potentially lead to more chest wall recurrences. As BPM is an important part of cancer risk management, unnecessarily exposing this specific population of high-risk women to oncological risks should be avoided. The oncologic safety of PF preservation in breast cancer patients has been previously studied. These results have been summarised and described in a recently published systematic review.¹⁴ Of the five included articles, three studies investigated oncological outcomes after PF preservation. In conclusion, there were no significant differences in chest wall and (loco)regional recurrences or distant metastasis, along with similar mortality rates.^{13 31 32} PF preservation seems safe, even in patients with breast cancer with an indication or wish for a mastectomy.^{33 34} A general remark is to recognise the importance of the tumor-to-PF distance when PF preservation is considered. A distance of less than 5 mm between the tumour and PF increases the risk of PF involvement and could, therefore, be a contraindication for PF preservation.

The occurrence of seroma was compared between preservation or removal of the PF in two studies.^{12 32} Dalberg *et al* found no differences between those two groups, although lower seroma rates appeared in the PF preservation group compared with the PF removal group (31/100 (31%) vs 39/98 (39.8%), $p=0.2$). A statistically significant higher seroma rate was found in the short-term axillary

drainage group compared with standard axillary drain removal (if drain discharge was less than 40 mL per 24 hours) (48/99 vs 22/99, $p < 0.001$). Because a 2×2 factorial design was used, patients were randomly assigned to four study groups based on short-term or standard axillary drainage and PF preservation or removal.¹² However, the exact number of patients in each group was not presented and results were not analysed according to the four randomisation groups. As both axillary drainage and PF preservation may influence seroma, outcomes were prone to bias. Abdelhamid *et al* found significant lower incidence of seroma in the PF preservation group (5.6% vs 24.3%, $p = 0.025$), however, a clear definition of seroma was not provided.³²

A thorough search in the literature revealed no articles describing the effect of fascia preservation on cosmetic outcomes or quality of life. To evaluate the success of the breast reconstruction, both objective measurements as well as a patient's own evaluation are needed. Patient-reported outcomes (PROs) are direct assessments from patients that reflect a patient's quality of life, psychosocial or functional status and they have become increasingly important in breast cancer research. BPM is associated with cancer-related distress in mutation carriers, however, it appears to be also inherent to lower physical well-being compared with active surveillance.^{35 36} PROs are measured with validated questionnaires, of which nowadays the Breast-Q is the golden standard to evaluate cosmetic and reconstructive breast surgery. As the reconstruction module of the Breast-Q is not designed for a within-subject randomisation, PROs were not included in our protocol.

An advantage of the within-subject design is omitting possible confounding factors (except for left or right dominance, or performing surgeon), resulting in sufficient statistical power with a relative small sample size. With a small sample size, only the necessary number of patients will be given the intervention, and if PF preservation seems to be superior to removal, implementation in routine breast (cancer) care will not be delayed. Moreover, this method is time efficient and will provide important information for a prospective full-scale study. Patient inclusion started at the end of 2021. Due to the COVID-19 pandemic, prophylactic mastectomies were one of the many surgical procedures that were postponed because of other medical priorities. Despite this, six patients are included in the study and the first four procedures were successfully performed.

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