


BMJ Open Prospective pilot study protocol evaluating the safety and feasibility of robot-assisted nipple-sparing mastectomy (RNSM)

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ABSTRACT

Introduction Nipple-sparing mastectomy (NSM) can be performed for the treatment of breast cancer and risk reduction, but total mammary glandular excision in NSM can be technically challenging. Minimally invasive robot-assisted NSM (RNSM) has the potential to improve the ergonomic challenges of open NSM. Recent studies in RNSM demonstrate the feasibility and safety of the procedure, but this technique is still novel in the USA. **Methods and analysis** This is a single-arm prospective pilot study to determine the safety, efficacy and potential risks of RNSM. Up to 12 RNSM will be performed to assess the safety and feasibility of the procedure. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months and 12 months. The primary outcome is to assess the feasibility of removing the breast gland en bloc using the RNSM technique. To assess safety, postoperative complication information will be collected. Secondary outcomes include defining benefits and challenges of RNSM for both surgeons and patients using surveys, as well as defining the breast and nipple-areolar complex sensation recovery following RNSM. Mainly, descriptive analysis will be used to report the findings. **Ethics and dissemination** The RNSM protocol was reviewed and approved by the US Food and Drug Administration using the Investigational Device Exemption mechanism (reference number G200096). In addition, the protocol was registered with ClinicalTrials.gov (NCT04537312) and approved by The Ohio State University Institutional Review Board, reference number 2020C0094 (18 August 2020). The results of this study will be distributed through peer-reviewed journals and presented at surgical conferences.

Trial registration number NCT04537312.

INTRODUCTION

Breast cancer is the most common solid tumour in women. With advances in breast reconstruction after mastectomy for the treatment of breast diseases including breast cancer, surgical techniques have evolved to preserve the skin flaps and nipple-areolar complex (NAC) to give better aesthetic outcome without compromising

Strengths and limitations of this study

- ⇒ This is the first US investigator-initiated trial assessing the safety and feasibility of robot-assisted nipple-sparing mastectomy (RNSM).
- ⇒ Patient-reported outcome data including nipple sensation after surgery are collected.
- ⇒ If RNSM proves to be safe and feasible, the results will form the basis for a subsequent multicentre trial measuring oncological outcomes.
- ⇒ The small sample size in this pilot study limits the comparison of RNSM outcomes with open NSM.

the oncological outcome.^{1 2} Nipple-sparing mastectomy (NSM) preserves the skin and NAC for improved body image and patient satisfaction.³⁻⁶ However, total mammary glandular excision for oncological purposes in NSM can be technically challenging particularly due to small incision size in relation to the operative field and poor visualisation of the dissection plane due to the curvature of the breast parenchyma and suboptimal illumination.⁷ Surgeons experience greater physical symptoms such as neck and lower back pain, mental strain and fatigue from performing NSM.⁸ A more ergonomically sound technique with greater visualisation is needed to improve surgeon ergonomics and also to improve the ease of the operation.

Open NSM results in a variable rate of sensation in the NAC. In a study by Chirappapha *et al*, evaluation of 55 NSM for sensory recovery demonstrated 11 patients with partial sensation recovery in the first 6 months.⁹ Women undergoing risk-reducing mastectomy with reconstruction report the breast feeling numb and lacking in sensation.¹⁰ These changes in bodily sensations can have long-lasting quality-of-life repercussions and can actually cause harm as the skin acts as a functional protection against thermal injuries.^{11 12} Thus,

understanding the sensation of the breast after RNSM from a patient-centred research perspective is important.

In addition, traditional open NSM is associated with higher rates of mastectomy skin flap and NAC necrosis if performed in larger breasted women.¹³ While bra cup size is not a reliable marker for increased risk of complication, breast volume measured using the area visualised on mammogram can predict large volume associated with higher necrosis rate. For instance, 45% of patients with breast volume on mammogram of 675 cm³ or larger had mastectomy flap or NAC necrosis.¹³ The increased risk of skin flap necrosis complication in larger breast size may be related to increased traction and trauma on the skin flap for dissection of larger surface area. Currently, there is a need to develop innovative approach to NSM in women with larger breast size.

Minimally invasive robot-assisted NSM (RNSM) has the potential to improve the safety and efficacy of NSM. Studies in RNSM demonstrate the feasibility and safety of performing a minimally invasive NSM using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, California, USA). Preliminary data from a randomised clinical study comparing 40 open with 40 robotic NSM cases indicate the safety of RNSM with regard to low perioperative complication rate, and none of the patients had any mastectomy flap necrosis or loss of nipple due to complication.¹⁴ In addition, in a recent study comparing surgical outcomes between conventional open NSM and RNSM, the latter was associated with significantly lower rates of high-grade postoperative complications and nipple necrosis.¹⁵ In a recent publication of the updated series by Toesca *et al*, between June 2014 and January 2019, 73 women underwent 94 RNSM with immediate implant-based breast reconstruction.¹⁴ There were 39 patients with invasive breast cancer, 17 with ductal carcinoma in situ and 17 without cancer diagnosis but with BRCA mutation. The mean surgery time was 3 hours and 32 min. The most common complication after surgery was seroma (n=5), followed by eschar (n=4). The rates of infection and haematoma were low (n=2 each). Only one patient had necrosis after surgery. There was one patient in the series who had stage IV disease at the time of surgery and died 4 months after surgery. Excluding this patient with metastatic disease, the disease-free survival rate was 100% with a median follow-up of 19 months (range 3.1–44.8 months). Long-term oncological safety of RNSM will take time for data to mature.

To study the technical feasibility and safety of RNSM, we performed a series of cadaveric RNSM and assessed the mastectomy flap for the presence of residual breast tissue.¹⁶ We were able to demonstrate that RNSM is technically feasible. Residual breast tissue was only detectable in the NAC, and none was detectable in the mastectomy flap outside the NAC.

The technique of RNSM is still novel for US surgeons, and to date there are no published studies from US institutions because the use of the da Vinci Surgical System is not US Food and Drug Administration (FDA) approved

for use in breast surgery. This is partly due to the safety concerns expressed by the FDA, which stems from the inferior outcomes of minimally invasive surgery compared with open hysterectomy for cervical cancer.¹⁷ In response to the safety concerns, our institution has received FDA approval of an Investigational Device Exemption (IDE) to initiate the RNSM clinical trial described here. This study aims to define the anatomical challenges and technical feasibility of RNSM and demonstrate its initial safety and efficacy profile. These data will inform a future, larger study of the procedure and help surgeons determine whether to consider the procedure for their practice.

METHODS AND ANALYSIS

Study design

This is a single-arm prospective pilot study to determine the safety, efficacy and potential risks of RNSM, funded by an Ohio State Intramural Research Program IDEA award and National Center for Advancing Translational Sciences award. The study start date is 17 November 2020. The estimated primary completion date is 31 December 2022 and the estimated study completion date is 31 December 2023. All operations will occur at The Ohio State University James Comprehensive Cancer Center. Up to 20 subjects will be enrolled to perform 12 procedures of RNSM. This study will be performed in a single centre, at The Ohio State University Wexner Medical Center James Comprehensive Cancer Center. All eligible interested patients must sign consent for enrollment into the RNSM clinical study. For patients undergoing sentinel lymph node biopsy or axillary lymph node dissection in the same operation, a separate small axillary incision will be made. This is similar to the approach taken in open NSM in our current practice. All axillary surgery will be performed in the traditional open manner.

Eligible patients will undergo RNSM as previously described.¹⁶ Briefly, the anterior axillary incision will be used for dissection. The breast incision, measuring approximately 3 cm, will be placed just lateral to the anterior axillary line. A subcutaneous dissection will be performed to create a working space. The single port system (GelPOINT Mini; Applied Medical, Rancho Santa Margarita, California, USA) combined with a small wound protector (Alexis Wound Protector; Applied Medical) will be inserted into the incision. By intussuscepting the wound protector with the single port system, we are able to move the fulcrum point of the robotic ports approximately 10 cm from the incision and thus create a larger working space for the robotic arms. The three 8 mm diameter robot ports will be inserted and secured into the GelSeal Cap connected to an insufflator to keep the pressure at 8 mm Hg. Once the robot is docked, subcutaneous dissection will be performed using the monopolar-curved scissors and bipolar grasping forceps for traction and exposure. Using similar technique, the gland will be separated from the pectoralis major muscle. The specimen will be removed from the anterior axillary incision. All

breast specimens will be evaluated by pathology through the institutional usual specimen processing protocol. To reconstruct the mound of the breast, an immediate direct to implant or tissue expander (TE) will be placed using the axillary line incision following the standard technique by plastic surgery.

Patients will recover in the postoperative phase following the usual standard of care. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months and 12 months, as well as standard of care follow-up for surveillance for a minimum of 5 years after surgery.

Study population and eligibility criteria

Patients who present to the breast surgical oncology clinic will be screened for eligibility for RNSM. These patients typically have small breasts (bra cup size B or smaller, less than 500 g of breast tissue) and no extensive ptosis of the breast. The cohort for this pilot study is limited to smaller breasted women (traditional open NSM candidates) but will expand in future studies to larger breasted patients (greater than C cup). Prior to consenting, patients will be informed that cancer treatment outcomes using RNSM have not been evaluated by the FDA, and this is an 'off label' use of the device. Eligible patients will be informed of the purpose, procedures and potential risks of the study. Patients will be eligible for inclusion in the study if they meet all the following inclusion criteria and excluded from participation in the study if they meet any of the following exclusion criteria (table 1). Interested eligible patients will be screened and consented by the clinical research coordinator.

Sample size

The number of cases to enrol in the pilot study has been set to 12 based on a previous study investigating the learning curve of RNSM.¹⁸ The previous study of 39 cases found that docking time, robot console time and overall operative time decreased on the 13th case, thus concluding that 12 cases were needed to decrease the operative time.

Subject withdrawal

Patients will be free to withdraw from the study at any point without consequence. In addition, subjects may be withdrawn if during surgery the principal investigator determines that the patient requires surgery in the conventional manner and a pivot to this standard care surgery is immediately undertaken. For this initial trial, no patients will be replaced after their surgery for non-compliance to follow-up in The Ohio State University Wexner Medical Center breast oncological clinic.

TRIAL PROCEDURES

Surgery and biospecimen collection

Standard of care preoperative work-up will be followed prior to surgery. RNSM will be performed using the da Vinci Xi Robotic Surgical System, a software-controlled, electromechanical system designed for surgeons to perform minimally invasive surgery. The breast specimen will be removed via gentle manual extraction through the anterior axillary incision using the 'waving flag technique' (move the gland back and forth and up and down gently until it is removed). For specimen extraction, no devices such as the morcellator will be used. To assure en bloc removal of the specimen, if it is not feasible to remove the entire gland as a single piece, the incision will be extended to assure removal of the intact specimen. The specimen will be labelled, as per standard of practice, with sutures and right/left orientation by the surgeon. All relevant data pertaining to the surgical procedure will be collected, and breast specimens will be oriented for pathological evaluation through the institution's usual specimen processing protocol. The entire robotic portion of the surgery will be recorded. Representative portions of the predocking and postdocking procedure will be videotaped as well.

Postoperative phase

Per the usual standard of care, the patient will follow up in the breast surgical oncology clinic around postoperative

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Adults: age ≥18 years ▶ Surgical candidates, per standard of care for open nipple-sparing resection and reconstruction for following indications: <ul style="list-style-type: none"> – For risk reduction mastectomy – Treatment of ductal carcinoma in situ or clinically node-negative cT1-T3 breast cancer ▶ Surgical candidates for open NSM, per standard of care, with regard to patient anatomical factors and tumour location ▶ Patient has an Eastern Cooperative Oncology Group performance status of 0 or 1 	<ul style="list-style-type: none"> ▶ Pregnant ▶ Patients with: <ul style="list-style-type: none"> – Inflammatory breast cancer skin involvement with tumour preoperative diagnosis (clinical, radiological or pathological) of nipple-areolar complex involvement with tumour – Grade 3 ptosis of nipple – Bra cup size greater than C cup ▶ Smokers with heavy current use of nicotine (defined as >20 cigarettes/day) ▶ Patients who are at high risk for anaesthesia, defined by the American Society of Anesthesiologists Scale, grade 4 or higher ▶ Patients who do not have the ability to give informed consent ▶ Prisoner status at surgical clinic visit ▶ Previous thoracic radiation history

NSM, nipple-sparing mastectomy.

day 14, day 30, 6 months and 1 year. Preoperative and postoperative photographs and study-related assessments will be obtained and completed at each of the previously stated time points. All images will be taken in a fashion that minimises subject identification, such as exclusion of the head and neck region, and any identifiers removed including tattoos and birthmarks. At 6 weeks, a review of the patient's records will also occur to capture any reoperations/readmissions from a safety perspective. An implant exchange surgery will be performed around 3–6 months after expansion is complete or later if chemotherapy is required or the patient desires to wait.

Stopping criteria

The study will be stopped if (a) en bloc removal of the breast specimen is not achieved during the RNSM surgery, or (b) the specimen is incorrectly labelled or oriented for pathological evaluation. Specimen labelling with sutures is a part of standard practice and is performed by the investigator-surgeon. Any occurrence of the aforementioned events will trigger a temporary suspension of further enrollment into the study until additional evaluation using the Corrective And Preventive Action process has been completed. Should the study be stopped, all regulating bodies (eg, FDA, data safety monitoring committee) will be notified.

Data collection and management

The Ohio State Comprehensive Cancer Center clinical trial office research informatics services will be used as a central location for data processing and management, following standard operating procedures for the collection, storage and analysis of electronic case report forms. Data obtained from the patient's electronic medical record and surveys will be stored on a secure drive on university password-protected computers and/or entered into a secure username/password-protected database using OnCore as the electronic data capture tool. Data will be accessible only to the research personnel approved for this study. As part of the FDA IDE study, additional data will be provided to the FDA.

STUDY OBJECTIVES AND OUTCOMES

The primary objectives are to generate preliminary data on the safety and complications from RNSM. En bloc resection and removal of the breast specimen will be assessed as a primary end point. We will also investigate the total duration of the operation, the frequency of conversion to open technique, the length of hospitalisation and postoperative complications. Reported complications after RNSM include NAC necrosis, mastectomy flap necrosis, temporary skin blistering, haematoma, seroma, infection, loss of implant from infection, delayed axillary wound healing, transient brachial plexus neurapraxia and transient neurapraxia due to intraoperative patient positioning. Safety will be assessed by monitoring for all adverse events/serious adverse events, reoperations and readmissions. Mastectomy and NAC

necrosis will be assessed using a validated scoring system called the SKIN score.¹⁹ To assess outcome, routine follow-up visits will occur at 14 days, 30 days, 6 weeks, 6 months and 12 months. Patients will complete the study-related assessments within the 12 months of completion of operation. Patients will continue standard of care follow-up for surveillance at a minimum of 5 years after surgery.

Beyond this, we aim to define the benefits and challenges of RNSM from the surgeon's perspective. Additional end points include Non-Motor Symptoms Questionnaire (NMSQ) and Surgery Task Load Index (SURG-TLX) validated surveys to determine surgeon musculoskeletal fatigue. To assess patient satisfaction with the breast after surgery and sensation recovery after surgery, BREAST-Q and NAC modules for patient-reported outcomes and satisfaction, and Semmes-Weinstein monofilament skin testing will be used. An exploratory end point is technical familiarity, which will be measured through operative robot console time.

As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long-term known implant-related adverse events, including, but not limited to, the following: capsular contraction, implant rupture and deflation, breast implant-associated anaplastic large cell lymphoma, asymmetry, chest wall deformity, extrusion, infection, malposition/displacement, seroma, skin rash, wrinkling/rippling of implant and unsatisfactory shape/size.

This study is a pilot study to demonstrate initial feasibility. Ultimately, these data will be used to inform a larger multicentre study in the future. Specific outcomes of interest in future studies include oncological safety and cost-effectiveness of RNSM.

Safety assessments

For this study, an adverse effect/event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs. All observed or subject-described AEs—serious or non-serious—and abnormal test findings, regardless of the suspected causal relationship to the investigational device or other procedures, will be assessed beginning on the day of surgery and at every follow-up visit thereafter. As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long-term known implant-related AEs. AEs or abnormal test findings felt to be associated with the investigational device or, if applicable, other study procedures will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilises at a level acceptable to the investigator. To ensure patient safety, all adverse events will be recorded, evaluated and reported to FDA and institutional review board (IRB) as required for all patient visits, including long-term follow-up.

Statistical analysis plan

This is a single-arm pilot study for feasibility and safety. Mainly, descriptive analysis will be used to report the findings. Patient demographics, pathological data, perioperative data, complication rate, mastectomy skin flap and NAC necrosis,

monofilament testing and patient-reported outcomes will be reported. Patient-reported outcomes will be evaluated by specific domains and compared with previously reported results in the literature.⁵ In addition, mastectomy flap complication rate will be compared with previously reported results in the literature using a one-sample proportion test. One-sample Wilcoxon signed-rank test will be used to assess the duration of surgery and length of hospital stay. For the analyses, statistical significance is set at two-sided α of <0.05 .

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not directly involved in the development of the protocol design. However, our group discussed the study protocol with our local patient advocate prior to developing the trial design. We plan to actively engage with our patient advocates for future dissemination strategies and translation of the study findings to a larger multicentre trial.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance with Good Clinical Practices. The protocol was reviewed and approved by the FDA using the IDE mechanism (reference number G200096). The trial was registered with ClinicalTrials.gov (NCT04537312) and the investigational plan was approved by The Ohio State University IRB 2020C0094 (18 August 2020). Any amendments to the trial protocol will be submitted to the IRB for approval.

The results of the study will be reported at appropriate scientific conferences. We plan to publish the trial results in a scientific, peer-reviewed journal. A full deidentified individual patient data set of the trial will be made available after trial completion and publication on request to the corresponding author.

Correction notice This article has been corrected since it was published. The name of author has been corrected to William E Carson.

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Contributors The first author of this paper (KUP) initially designed the study protocol. KUP, AS and RJS contributed to initial planning of the trial. AS, RJS, MC and SS contributed to initial preliminary data collection. Each co-author (KUP, SL, AS, MC, SS, DA, VG, WC and RJS) contributed to subsequent development of the protocol. KUP and SL wrote the initial draft of the manuscript. All authors (KUP, SL, AS, MC, SS, DA, VG, WC, RJS) approved the final version of this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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