CLINICAL TRIAL REPORT



Robot-assisted Nipple Sparing Mastectomy: Recent Advancements and Ongoing Controversies

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Abstract

Purpose of review The purpose of this review is to summarize the recent technical advancements in RNSM, describe the ongoing teaching programs, and discuss the ongoing controversies.

Recent findings Robot-assisted nipple sparing mastectomy (RNSM) is the newest addition to the armamentarium of surgical techniques for patients who require a mastectomy. The potential benefits of using the da Vinci® Robotic Surgical System (Intuitive Surgical, Sunnyvale, CA) are the small 3D camera and lighting offering superior visualization, the Endowrist robotic instruments offering greater range of motion, and surgeon being at a seated position at the console rendering a more ergonomic operating position.

Summary RNSM can potentially help overcome the technical difficulties of performing a conventional NSM. Further studies are needed to elucidate the oncologic safety and cost-effectiveness of RNSM.

Keywords Robot-assisted Nipple Sparing Mastectomy · Robotic mastectomy · Nipple sparing mastectomy · Breast Cancer Surgery

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Introduction

Nipple-sparing Mastectomy (NSM) with reconstruction has been demonstrated to have superior psychosocial and sexual well-being patient reported outcomes (PRO) when compared to traditional mastectomy [1, 2]. However, utilization of NSM in the US is low, estimated to be approximately 10-15% [3]. This is due to multiple factors: 1) total mammary glandular excision is technically challenging due to poor visualization through incisions which are also large and cosmetically unsightly; 2) as compared to conventional mastectomy there is a higher rate of surgical complication (specifically mastectomy skin flap necrosis) which can delay adjuvant cancer treatments and impact reconstruction that can range from temporary wound issues to total implant loss requiring multiple reoperations; 3) NSM is ergonomically taxing for surgeons and consumes greater operating time; 4) lack of technical skill. To address these challenges, robot-assisted NSM (RNSM) has been used internationally since 2015, with recent advances in its technical and oncologic safety, ongoing teaching programs, and controversies reviewed in the present article [4, 5].

Technical Considerations

In essence, the operation of RNSM is not vastly different than conventional NSM in that the goal of the operation is to remove the breast tissue and mound in its entirety while preserving the mastectomy skin flap [6•]. Rather than the surgeon's hands directly performing the dissection, the robotic arms are utilized for dissection. The main technical differences lie in the incision placement, creation of the working space, and the use of CO2 gas insufflation for retraction. Once the robot is docked, the conduct of the operation and dissection planes are similar to those of a conventional NSM.

Among robotic surgical systems, Si or Xi (da Vinci system; Intuitive Surgical, Sunnyvale, USA) multiport systems were initially used, while recently the single-port (SP) device is also used for mastectomy. In multiport systems, more working space is required for robot docking, creating blind spots due to the rigid three-dimensional camera scope. These systems can also lead to inadvertent neurapraxia due to the patient's position and cause interruption in operation due to collisions between devices and patient's arms [7, 8]. To address these issues, investigation began using the SP surgical robot system. SP system may provide better visualization, increased range of motion, improved efficiency, and a smaller patient cart than multiport. It consists of 4-instrument drives to one instrument arm and enables approach through 25 mm single cannula, reducing incision size to 20—55 mm [8]. It features a flexible 3-dimensional camera and robotic arms with two joints, preventing potential collisions. It also includes a third robotic arm with Cardiere or Maryland forceps, which is useful for counter-retraction of tissue. It has various camera modes and clutches providing more detailed movements and visualization, as well as a smaller patient cart than the multiport system [8, 9]. However, the SP system has lower grasping power and its long elbow may interfere with effective counter-retraction [10, 11]. Surgeons need to have experience with and be familiar with the system to maximize its benefits and minimize risks or complications.

The incision for RNSM is typically hidden along the mid-axillary line although some do perform the operation through a small upper outer quadrant incision [12]. One of the first steps in RNSM is creating an ample 'working space' to dock the robotic arms. Unlike the abdomen wherein due to a natural cavity the working space can be easily established, in the breast the surgeon must create this optimal working space by dissecting the relatively avascular subcutaneous plane similar to a conventional mastectomy. Once the optimal working space is created, the robotic arms are docked and the remaining breast skin flap is retracted. Since the first technical description of RNSM, various techniques were explored by international investigators to create optimal retraction of the skin flaps [4, 5]. For instance, surgeons in South Korea explored the feasibility of performing RNSM using a gasless technique [12, 13]. Instead of CO₂ insufflation, the investigators used the modified Chung's retractor which is mounted to the table to maintain a working space. The premise was that by omitting the use of CO_2 gas they would be able to avoid any potential subcutaneous emphysema or hypercarbia following insufflation. However, due to the ischemic skin changes secondary to retraction, the technique is no longer widely used. The most common technique currently utilized for creating a working space is through CO₂ insufflation [12].

Typically, the robotic system is undocked from the patient for removal of the breast specimen and the reconstruction proceeds without the robot. Implant-based reconstruction after RNSM can occur in a similar technique as after open NSM while using the lateral axillary incision [14]. Performing the reconstruction portion using the robotic surgical system is under investigation [15, 16]. Due to the lateral location of the breast incision, investigators exploring autologous tissue-based flap reconstruction (e.g. deep inferior epigastric perforator flap) after RNSM are using thoracodorsal artery and vein as the target for microvascular anastomosis [16]. While the feasibility of performing these operations have been demonstrated in a single institution setting, larger studies are needed to determine the technical learning curve, safety, and aesthetic outcomes before widespread use.

Learning Curve

The learning curve for RNSM, as with any surgical procedure, can vary depending on the experience and skill level of the individual surgeon including their proficiency with the robotic system. In a pilot study published by Toesca et al. there was rapid operating time reduction after two or three cases [17]. Subsequent studies have suggested that surgeons may require around 20–25 cases to become proficient with robotic mastectomy, although the time required to reach this point may depend on the surgeon's pre-existing experience and comfort with the technology [18, 19]. Similarly, a study of 85 cases focusing on learning curve of RNSM concluded that the operative time significantly decreased after 20 to 30 procedures and the time needed to reach proficiency decreased as the number of cases increased [20].

RNSM Training Programs

There are various international training programs for RNSM designed to teach surgeons already in practice. Surgeons without prior training in robotic systems should first become familiar with the robotic system. Ad hoc clinical observation programs were the most common teaching tool initially offered. These took place at hospitals or surgical centers that had the technology and expertise to perform RNSM. Surgeons observed several procedures, gaining familiarity with the technique and learning its nuances [21]. Later, this training was combined with other forms such as cadaveric or simulation training, to provide a comprehensive learning experience, as observing is important, but not a substitute for hands-on training [22–24].

In 2021, a formal training program was introduced due to the need for standardized training, given the increasing interest in case-observership and proctoring requests internationally [22]. The first programs included cadaveric and animal lab training, based on the experience of the first surgeons starting their learning curve in previous years, and were supplemented by live surgery observation [22–24]. RNSM skill laboratory training programs were piloted using cadaveric and porcine models and suggested two phases of programs, including procedure design, lectures, procedures, questionnaires, feedback and participant discussion.

Cadaveric studies offer valuable opportunity for surgeons to practice and hone their skills in a realistic and safe environment before performing the procedure on actual patients. Surgeons practice performing the procedure using a robotic surgical system on cadaveric specimens typically prepared to simulate the tissue characteristics of the breast, and may include various lesions and abnormalities to simulate different breast conditions [23]. It's worth noting that cadaveric studies have limitations, as cadavers and cadaveric tissue do not respond to surgery in the same way as live patients. Therefore, additional forms of education should be used to ensure that surgeons are adequately prepared to perform the procedure on patients.

Especially after the COVID-19 pandemic, most training programs are now based on simulation training using breast simulation models such as Mastotrainers, which are less resource intensive than cadavers. The Mastotrainer includes a silicone breast model with realistic tissue density and texture, and different lesions and abnormalities that can be included to simulate various breast conditions. Handson training with the system, didactic lectures, workshops, and live-surgeries are provided by manufacturer of robotic surgical systems (Intuitive Surgical). Moreover, academic institutions and professional organizations offer training programs. For instance, KoREa-BSG organizes an annual congress to provide regular education programs to any breast surgeon interested in RNSM, and participates in cadaveric workshops, such as Catholic International Bioskills Education Center (CIBEC) Week, which is hosted annually for minimal invasive surgery with high quality fresh cadavers (http://www.medioffice.or.kr/conference/main.php?cidx= 194). A web-page based system to help beginning surgeons with their first case may also be useful (http://koreabsg. com/?act=main). One of the advantages of these formal programs is the opportunity for mentorship and support from experienced colleagues to ensure that the surgeon can ask questions and receive feedback during the learning process.

Finally, surgical competency is not only based on the number of cases, but also on the ability to understand the correct indications and contraindications, manage the complexity of cases, and handle any potential complications. RNSM is not suitable for every patient, and that the surgeon should be familiar with the specific indications and contraindications [25].

Surgical Safety

The evidence for the surgical safety of the Robotic Nipple-Sparing Mastectomy (RNSM) has been reported. Nipple necrosis is considered the most serious complications after NSM. From the early experience of the Korea Robot-endoscopy Minimal Access Breast Surgery Study Group (KoREa-BSG), among 82 cases of RNSM, nipple ischemia was found in 9 cases (10.9%), with only 1 case (1.2%) requiring nipple excision [26]. Another observational study concerning the feasibility of RNSM using single port (SP) system suggested that the incidence of nipple necrosis was approximately 1%, which was consistent with the initial experience [27]. Recently, results from a randomized controlled trial (RCT) revealed that there was no difference in the number or type of perioperative complications between RNSM and open NSM [28]. This study reported that there was no skin or nipple necrosis among the 40 patients undergoing RNSM. A pooled analysis, the Surgical and Oncologic Outcomes after Robotic Nipple Sparing Mastectomy and Immediate Reconstruction (SORI) study using international multicenter patient-level data indicated that there was a significantly lower rate of nipple necrosis in the RNSM than in the open NSM (2.2% vs. 7.8%. p=0.002) [29]. Small axillary or lateral incisions for RNSM seem to have positive effects on maintaining blood supply for the viability of the nipple [30].

With regard to other surgical complications, Houvenaeghel et al. reported that there was no significant difference for breast complications (such as hematoma, skin-flap suffering, and seroma) between RNSM and open NSM [31]. Another meta-analysis, which included 49 studies comparing the postoperative complication of RNSM with open NSM, showed that there was no significant difference regarding hematoma, infection, wound seroma, and implant loss. [32].

Taken together, the early data is promising with regards to the surgical safety of RNSM. To confirm the surgical safety of RNSM, the Korea-BSG and Korean Breast Cancer Study Group initiated a prospective multicenter cohort study entitled Mastectomy with Reconstruction Including Robotic Endoscopic Surgery (MARRES, NCT04585074). The inclusion criteria for this study are adult women aged 19 or older with breast cancer or a high risk of breast cancer who have scheduled therapeutic or risk-reducing mastectomy and want immediate reconstruction. The primary endpoints of this study are the postoperative complication rates within 30 postoperative days and the Clavien-Dindo grade of complications within 180 postoperative days. Since April 2020, more than two thirds of the target accrual (2000 patients) has been recruited, and an interim analysis is expected to be reported in April 2025. This study will provide a high level of evidence about the surgical outcomes of RNSM compared to conventional NSM.

Cosmesis and Quality of Life

A Phase III RCT demonstrated that women who underwent robotic mastectomy maintained their preoperative healthrelated quality of life more than those who underwent open NSM [28]. With an emphasis on improving PRO and quality of life following cancer treatment, the study evaluated the patients' conditions one year post-operatively by measuring BREAST-Q, Hopwood's body image scale, patient satisfaction with the nipple-areolar complex and subjective nipple sensitivity. The change in Q-score and satisfaction with the breasts increased in the robotic group. Scores in psychological well-being significantly improved after robotics, although the paired differences were not statistically significant. Scores in physical and sexual well-being decreased initially, but after one year, both domains had returned to their preoperative levels in the robotic arm only. In all categories of responses to the body image scale (BIS) questionnaire, patients who underwent RNSM reported significantly less distress regarding changes in appearance and body related to treatment. Furthermore, the sensitivity of the nipple-areolar complex was mostly preserved after RNSM. While the results of this RCT is encouraging, a multivariate analysis of small sample size found no significant difference between RNSM And open NSM and reported unfavorable satisfaction results [31].

One of the major advantages of RNSM is the smaller (3-5 cm) wound and its inconspicuous extra-mammary location and the PROs after RNSM were high [33]. International studies that include postoperative cosmetic outcome evaluations demonstrated that the overall satisfaction rate was superior in the RNSM group compared to open NSM. Furthermore, the RNSM group reported higher satisfaction scores with regard to nipple-areolar position, scar appearance, scar length, and incision location [34]. However, no statistically significant difference was observed between the two groups in terms of breast appearance when dressed or undressed, symmetry of bilateral breast size, or shape.

Oncologic Safety

While time will take for the oncological safety data of RNSM to mature, early studies have found that the procedure is safe and oncologically equivalent to traditional open surgery. Current and recently completed clinical trials are summarized in Table 1. In 2019, an update study on the first 29 cases of robotic nipple-sparing mastectomy was published by Toesca et al., reporting the oncological outcomes. The mean follow-up was short at 20 months. One patient died due to brain metastases, and the overall survival at 12 months, 24 months, and projected at 24 and 60 months, was 98% (CI 86-100%) [35]. An updated RCT in 2021 by Toesca et al. reported results of 40 open and 40 robotic NSM. The most significant results of the trial included cosmetic and PRO as stated above; however, oncological results were also reported, with a median follow-up of 3.5 years (42 months). Disease-free survival was 93% and 92% (p = 0.76), and overall survival was 96.7% and 96.2% (p = 0.91), both comparable between the two techniques [25, 28]. Furthermore, a pooled-analysis on robotic mastectomy was published in 2022, enrolling 755 RNSMs in 659 women, most of whom were treated for cancer and underwent immediate reconstruction. The authors, in addition to demonstrating a statistically significant reduction of nipple-necrosis that confirmed surgical advantages, reported the oncological outcomes. The disease-free survival and overall survival of robotic

Table 1	Recent clinical trial records on RNSM from Clinicaltrial.gov w	vebsite. [†] Status of the record is as of April 4th, 2023

Clinicaltrial.gov Identifier	Sponsor	Estimated enrollment	Primary outcome	Indication	Allocation	Status [†]
NCT03440398	European Institute of Oncology (Italy)	82	Patient satisfaction (BREAST-Q)	Breast cancer or prophylaxis	Randomized	Active, not recruiting
NCT03892980	Intuitive Surgical (USA)	145	Conversion to open NSM, incidence of adverse events	Prophylaxis only	Single arm	Recruiting
NCT04108117	Severance Hospital (South Korea)	300	Locoregional recurrence-free survival	Breast cancer or prophylaxis	Single arm, retro- spective pooled analysis	Active, not recruiting
NCT04537312	The Ohio State University (USA)	20	Feasibility of en bloc removal of breast	Breast cancer or prophylaxis	Single arm	Recruiting
NCT04585074	Severance Hospital (South Korea)	2000	Postoperative com- plication	Breast cancer or prophylaxis	Single arm	Recruiting
NCT04866992	University of Texas Southwestern Medical Center (USA)	10	Feasibility of en bloc removal of breast	Breast cancer or prophylaxis	Single arm	Completed
NCT05245812	University of Texas Southwestern Medical Center (USA)	90	Completion with SP system, periop complications	Breast cancer or prophylaxis	Single arm	Recruiting
NCT05251285	Intuitive Surgical (France, Italy)	50	Intraop and postop complications	Porphylaxis	Single arm	Recruiting
NCT05448963	Chang Gung Memorial Hospi- tal (Taiwan)	30	Surgical perfor- mance of SP sys- tem (conversion to open, addition of ports)	Breast cancer or prophylaxis	Single arm	Recruiting
NCT05490433	Yonsei University (South Korea)	790	5-year disease-free survival rate	Stage 0-III breast cancer	Randomized	Not yet recruiting
NCT05720039	Intuitive Surgical (USA)	200	Conversion to open, adverse event, positive surgical margin	Breast cancer or prophylaxis	Randomized	Not yet recruiting

mastectomy patients were not inferior to open mastectomy patients (p = 0.15 and p = 0.60) after propensity score matching [29].

is 790, and the anticipated completion date of the study is June 2030.

It is important to note that larger scale trials with longer follow up are needed to evaluate the oncological outcomes of RNSM, as well as updated follow-up data from the cohorts of the previous studies. Ideally RCTs with a primary endpoint of disease-free survival are needed to confirm that RNSM is not inferior to open NSM. KoREa-BSG is planning a RCT for evaluating disease-free survival as a primary endpoint of RNSM, set to begin recruiting in the near future (ClinicalTrials.gov Identifier: NCT05490433). This ROM (Robot-assisted vs. Open Nipple-sparing Mastectomy With Immediate Breast Reconstruction) trial will provide prospective results for 5-year survival rates, as well as postoperative complication rates and cost-effectiveness of RNSM (Table 1). The estimated number of accrual patients

Ongoing Controversies

Controversies have grown in the US after isolated reports of surgeons performing RNSM outside of a clinical trial and without the use of a US Food and Drug Administration (FDA)-approved Investigational Device Exemption (IDE) [36, 37]. Combined with the inferior outcomes in minimally invasive radical hysterectomy for cervical cancer [38], the FDA issued a "safety communication" in February 2019 and August 2021 cautioning the use of robotically assisted platforms for mastectomy. [39•] Furthermore, some argue that mere technical capability and low perioperative morbidity does not justify the use of robotics in NSM given lack of data on oncologic safety. [40, 41] The use of the da Vinci surgical system (da Vinci Surgical System, Intuitive Surgical, Sunnyvale, CA) is not FDA approved for use in breast surgery in the United States [39•].

To address these concerns, there are several prospective ongoing studies in the US including a study sponsored by Intuitive Surgical (NCT03892980) and investigator-initiated studies (NCT04866992) [21, 42]. The company sponsored study (NCT03892980) includes 2 primary outcomes (Table 1). The primary effectiveness outcome includes conversion of the case to open NSM and the primary safety outcome includes the incidence of adverse events within 42 days of the surgery. Oncologic outcome (e.g. occurrence or recurrence of breast cancer) is an additional outcome measure. Long-term oncologic safety information such as disease free survival will take a significant follow up period to mature. However, the current oncologic RNSM experience is promising given the ability to perform a complete mastectomy with low residual breast tissue after RNSM combined with the experience with the International collaboratives. [43, 44••, 45, 46].

Lastly, cost is a main criticism of using the robotic system in any surgical setting in the US [47]. Due to the high amortization cost of a robotic system coupled with a relatively low reimbursement for a typical mastectomy case renders the RNSM a financially costly operation for the institution [21]. What remains unknown and important to investigate is the cost-effectiveness of performing RNSM. The rate of nipple and skin necrosis after conventional NSM ranges widely and can be upwards of 30%. One can hypothesize, that if the RNSM creates optimal less traumatized skin flaps, decreasing the rate of nipple and skin necrosis and rate of additional operations due to poor cosmetic outcomes then ultimately it may be a cost-effective operation compared to open NSM.

Conclusion

In conclusion, RNSM has been evolving since its first introduction in 2015. Multiple ongoing studies are exploring its safety, efficacy, and cost-effectiveness. To date, RNSM has been associated with low perioperative morbidity, improved cosmetic outcomes, and retained nipple sensitivity. Although the FDA has not approved the use of robotics in the US due to safety concerns, further studies exploring the oncologic safety and cost-effectiveness of RNSM may contribute essential data for advancing the surgical care of patients undergoing NSM.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/ national research committee standards, and international/national/institutional guidelines).

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