الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Post Market In-depth Clinical Evaluation for the Safety and the Current Local Practice of Robotically-Assisted Surgical Devices in Mastectomy

Study Category:

☑ Post-market evaluation study (دراسة تقييم سريري)

☐ Risk analysis report (تقرير تحليل مخاطر)

BACKGROUND

Robotically-assisted surgical device (RAS) is a new technology with great advantages which holds significant promise. Recently, RAS device is widely used in prostatectomy, hysterectomy, and cholecystectomy and general surgical procedures through small incisions in a patient's body. RAS has medical devices marketing authorization (MDMA) in Saudi Arabia for these uses. RAS device may help to minimize the invasive procedure, decrease pain, blood loss, scarring, infection, and recovery time after surgery comparing to traditional surgical procedures. With a massive use and potential advantages of RAS, the robotic system has been used for nipple-sparing mastectomy (NSM). Using robotic nipple-sparing mastectomy (RNSM) could enhance visualization of tissue planes, give better access to areas that are remote and difficult to reach, more precise and hiding the incision in the axilla that enhances the cosmetic outcomes. However, based on our knowledge RAS device in mastectomy is not approved by any regulatory authority such as the FDA and it is off-label. In 2019, the FDA issued a safety communication about using robotically-assisted surgical devices in women's health including mastectomy to warn patients and healthcare providers that the safety and effectiveness of RAS devices for use in mastectomy procedures have not been established. The aim of this report is to evaluate the safety and the current local practice of robotically-assisted surgical devices in mastectomy.

CLINICAL BURDEN

Clinical need of Robotically-Assisted Surgical Devices.

Breast cancer is a serious health concern for women. It is the most common cancer among females in the worldwide. It is the second cause of death among all cancers. According to the World Health Organization about 2.3 million women diagnosed with breast cancer and 685 000 deaths globally in 2020[1]. Each breast contains 15-20 glands called lobes, that are milk-producing glands. Lobes are connected to the nipple by ducts. Breast cancer usually starts in the lobes. In addition, breast contains lymph nodes and vessels that allow cancer to spread to other organs of the body in some cases.

Breast cancer treatment is extremely effective with survival rates of 90% especially when the cancer is detected early. Treatment generally including surgery, radiation therapy, anti-cancer medicines including hormone therapy and chemotherapy [1].

Earlier, mastectomy was widely used to treat breast cancer surgically, which is an operation for removing all the breast. Mastectomy was considered as the ultimate treatment, and it might still be required[1]. However, with advance in surgical technique and medical oncology for breast cancer treatment, Nipple spray mastectomy has developed. It preserves the skin envelope and the nipple areola

complex (NAC), and it followed by immediate breast reconstruction (IBR) by using autologous tissue or implants [2]. Recently, NSM is very common to use in breast cancer even in invasive cancer. NSM is an oncologically safe treatment for breast cancer, and it improves cosmetic outcome of reconstructed breast and patient satisfaction[3]. Despite the benefits of NSM, it is technically challenging methods since the incision is placed at a peripheral border of the breast at the inframammary fold that results in difficulty visualization and access to remote region of the breast from the incision. Sometimes the surgeons need to place their head and neck in unsuitable positions to have better visualization, that results in increasing the mental and physical efforts which leads to have fatigue for the surgeons. Moreover, dissecting and removing huge samples through limited and small size incisions have restricted the number of qualified candidates that go through NSM. The scar of NSM incision on the breast is visible and unavoidable, and it can cause distortion or malposition of the nipple areola complex (NAC). In addition, there are two types of necrosis which are partial thickness-necrosis and full thickness necrosis. Partial thickness-necrosis could be treated with antibiotics, while full thickness necrosis sometimes needs additional surgery for skin or nipple excision and sometimes needs revision of the reconstructed breast. Therefore, necrosis is a major risk of NSM on patient that should be considered[4, 5]. Robotic nipple-sparing mastectomy (RNSM) was developed in order to overcome these challenges of nipple-sparing mastectomy. Robotic technology was evolved to minimize invasive surgery.

The application of robotic-assisted nipple-sparing mastectomy (R-NSM) has allowed mastectomy to be performed via a small incision. These procedures allow to enhance the accurate visualization of breast tissue and give better access to areas that are remote and difficult to reach through traditional open nipple-sparing mastectomy incisions. The RNSM is performed through a very small axillary wound around 2.5–6-cm or over the extra-mammary lateral chest, with immediate breast reconstruction (IBR). In addition, the scars wound is short and invisible that associated with excellent patients' satisfaction especially of inconspicuous scar location, and increase the desire of patients to go through RNSM for scarless operation[6, 7]. Figure 1 demonstrates the skin incision types and locations of robotic nipple sparing mastectomy (R-NSM) versus traditional nipple sparing mastectomy (NSM)[8]. The main purpose of RNSM is to reach outstanding technical and cosmetic outcome with the same oncologic concept of standard mastectomy. Furthermore, RNSM is associated with low complication of nipple areola complex necrosis rate because incision placement over the skin flap of breast and far away from nipple areola complex [8]. This is one of the most significant advantages of RNSM.

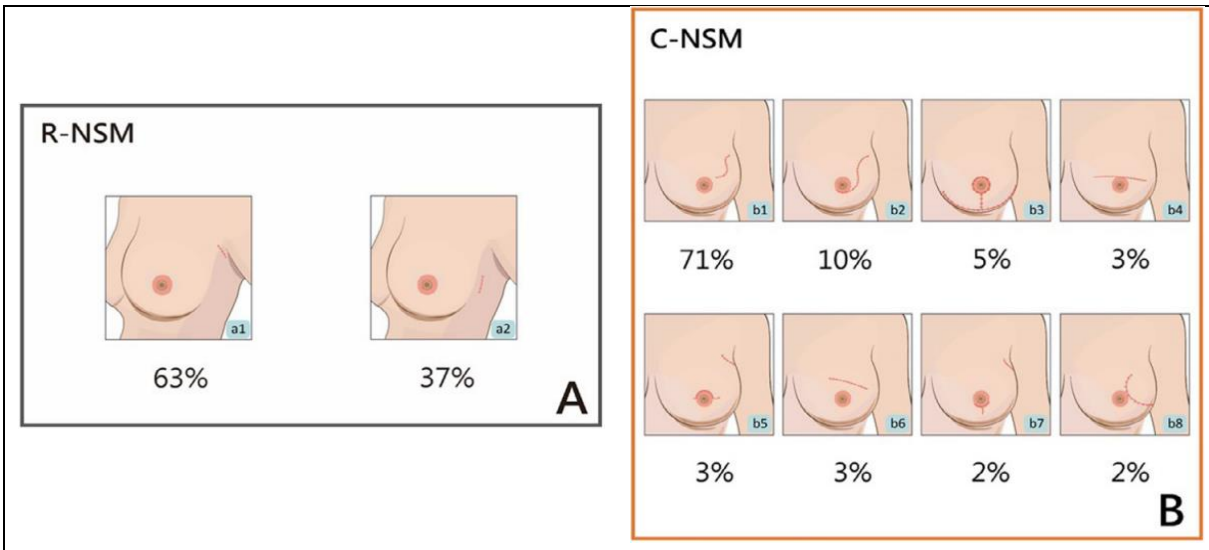

Figure 1: The incision types and locations of RNSM versus NSM. (A) The types and locations of incisions for R-NSM, B) The types and locations of incisions for C–NSM

R-NSM was first described and reported by Toesca et al. RNSM was conducted by using a small axillary incision to perform both the resection and immediate implant reconstruction. The results have been promising. There were no major outcomes including hematoma, seroma, necrosis or infection were observed for any case. This study proved the feasibility and the safety of the RNSM technique [9]. Another study was reported by Sarfati et al. using RNSM on 33 patients with 63 procedure. The result showed that there were no major complications were observed except for three infections occurred, one case leading to implant. The preliminary data of this study illustrated the feasibility, the safety and the reproducibility of RNSM procedure[10]. Since then, many studies were done on the RNSM to prove it is safe and feasible.

Although RNSM is a promising and potential technique, long-term data and further studies are needed to confirm the oncological safety and the cosmetic stability of the result. In addition, the main limitations of using robotically-assisted surgery device in mastectomy are off-label, highly cost, and specialized skills required.

EVALUATION OUTCOMES

Part 1: Clinical paper review

1.1 An overview of search criteria

A systematic review was conducted to evaluate the safety and the current local practice of robotically-assisted surgical devices in mastectomy, and to calculate the most common complications

associated with the robotic nipple sparing mastectomy. Using a defined inclusion criterion, a total of 104 article were obtained and screened, which result in 23 articles, as shown in **figure 2**.

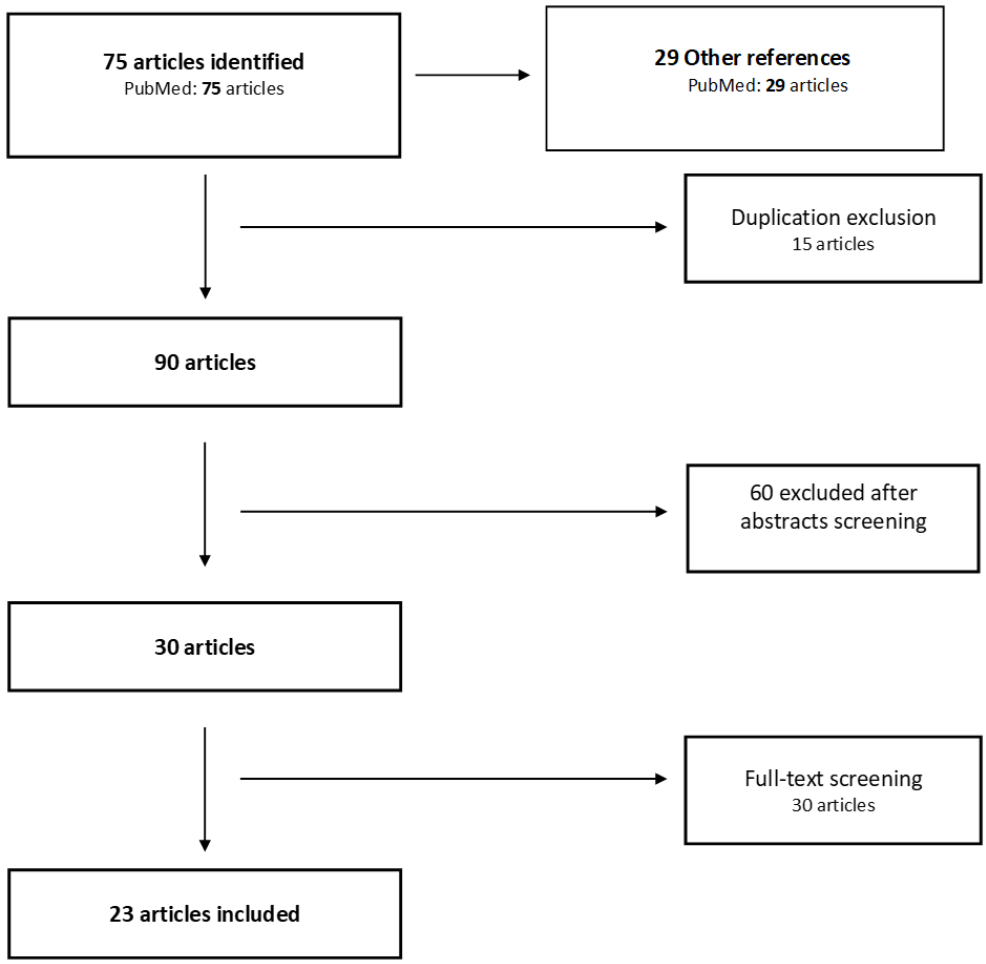

Figure 2: Schematic representation of the search findings

2.1 Results of the clinical paper review

Clinical paper review for safety and effectiveness of using Robotic Nipple Sparing Mastectomy

A total of 23 studies described the overall postoperative complications rate of nipple sparing mastectomy (NSM) and robotic nipple sparing mastectomy (RNSM) in tables 1,2 to determine the safety and effectiveness of using robotically-assisted surgical devices. Table 1 shows the studies included in the analysis and their characteristics for NSM technique, it can be seen that the total cases who went through nipple sparing mastectomy is 4035. The proportion of seroma complaints are 2.5%, hematoma are 1%, necrosis are 8%, infection are 2, delayed wound healing are 0.5% and capsular contraction are

1% out of 4035 cases. It can be observed that necrosis complaints have the highest percentage of the whole complications of NSM.

In addition, table 2 described RNSM data, the total cases who went through robotic nipple sparing mastectomy is 711. The proportion of seroma complaints are 3%, hematoma are 3%, necrosis are 3%, infection are 3, delayed wound healing are 1% out of 711 cases. Regarding to capsular contraction, there is no data about it and it doesn't mention in any article that reported about RNSM.

All data were collected to compare between postoperative complication of NSM and RNSM. The significance level for a study is set to 5%, that means above 5% indicated as a significant difference and less than 5% indicated as no significant difference between the complications of NSM and RNSM. As illustrated in figure 3, hematoma occurred more often in RNSM (3%) than in NSM (2%) but this difference was not significant. Moreover, seroma also occurred more often in RNSM (3%) than in NSM (1%) but this difference was not significant too. However, Necrosis occurred more often in NSM (8%) than in RNSM (3%) this difference was significant because is more than 5%. Finally, infection and delayed wound healing occurred 3% and 1% in RNSM and 2% and 0.50% in NSM.

As a result, there is no significant difference in postoperative complication rates between NSM and RNSM. However, Nipple necrosis rate was significantly lower in the RNSM group than in the NSM group. In conclusion, RNSM technique might have some advantages in terms of lower nipple necrosis**.**

Table 1: Common complications of Nipple Sparing Mastectomy Technique

Nipple Sparing Mastectomy								
Ref	Study design	Number of cases	Seroma	Hematoma	Necrosis	Infection	Delayed wound healing	Capsular contraction
8	Case-control	270	N/A	N/A	41	6	N/A	N/A
11	Case-control	62	5	1	3	N/A	5	N/A
12	Retrospective	369	0	0	39	1	N/A	8
13	Retrospective	142	0	3	34	7	N/A	N/A
14	Retrospective	65	N/A	N/A	9	8	N/A	N/A
15	Retrospective	2023	80	24	135	24	N/A	N/A
16	Retrospective	123	N/A	0	16	N/A	0	N/A
17	Retrospective	97	4	2	12	2	N/A	1
18	Retrospective	55	2	0	N/A	1	18	2
19	Prospective	384	N/A	5	24	16	N/A	N/A
20	Case series	34	0	1	0	1	1	1
21	Retrospective	411	13	3	4	15	N/A	33
Total		4035	104	39	317	81	24	45
Percentage			2.5%	1%	8%	2%	0.5%	1%

Table 2: Common complications of Robotic Nipple Sparing Mastectomy Technique

Robotic Nipple Sparing Mastectomy								
Ref	Study design	Number of cases	Seroma	Hematoma	Necrosis	Infection	Delayed wound healing	Capsular contraction
8	Case-control	41	N/A	N/A	1	3	N/A	N/A
11	Case-control	54	3	1	1	N/A	5	N/A
22	Prospective	29	0	0	0	0	N/A	N/A
1	Cohort	27	N/A	3	1	4	N/A	N/A
4	Prospective	94	5	2	1	2	0	N/A
7	Prospective	15	N/A	N/A	0	N/A	1	N/A
23	Retrospective	23	N/A	N/A	0	N/A	1	N/A
24	Prospective	63	0	0	0	3	N/A	N/A
25	Prospective	78	0	6	2	1	N/A	N/A
26	Prospective	39	1	1	2	N/A	2	N/A
27	Prospective	94	5	4	1	2	N/A	N/A
28	Prospective	138	7	4	2	9	N/A	N/A
29	Retrospective	16	1	0	1	0	0	N/A
Total		711	22	21	21	24	N/A	0
Percentage			3%	3%	3%	3%	1%	N/A

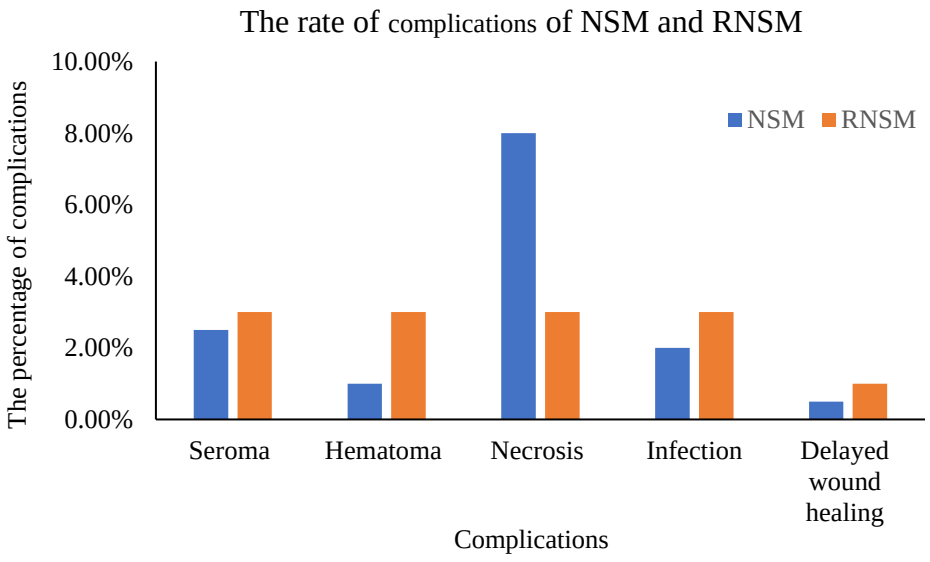

Figure 3: Comparing the postoperative complications between NSM and RNSM

Part 2: Clinical experience review

2.1 International regulatory organizations opinions

The US FDA released a safety communication by February 2019 about caution when using robotically-assisted surgical devices in women's health including Mastectomy for healthcare providers and patients with breast cancer who are considering to go under mastectomy using robotically-assisted surgical devices. The FDA issued this safety communication because it is crucial for health care providers and patients to be aware and understand that the safety and effectiveness of using robotically-assisted surgical devices in mastectomy has not been established. The data and preliminary evidences of using robotically-assisted surgical devices in mastectomy are limited. The FDA updated the safety communication by august 2021 to remeined the healthcare provider and patients that the safety and effectiveness of using robotically-assisted surgical devices in mastectomy has still not been established. The FDA has not granted any robotically-assisted surgical device in mastectomy marketing authorization. The labeling for robotically-assisted surgical devices in mastectomy have not been evaluated by the FDA. In addition, The FDA will inform public if important new information becomes available[30].

2.2 The opinion of global specialized societies

Specialized international plastic surgery societies also investigated the safety of the using robotic assisted surgery in mastectomy. The American Society of Plastic Surgeons (ASPS) has members who are Neil Tanna, MD, and Armen Kasabian, MD and their team utilized the Robotically-assisted surgical device to conduct North America's first robotic-assisted in nipple-sparing double-mastectomy with breast reconstruction. They did a procedure through a 3-4 cm incision in mid-axillary line located away from the breast. The scar of the incision only becomes apparent when the patient raises her arm. In their opinion they believe that the place of the incision that far away from the breast will be better to preserve the nipple, areola and skin envelope. However, robotic mastectomy procedure is not suitable for all mastectomy patients. For instant, it is not appropriate for women who go under skin-flap reduction, because the only way to conduct a skin reduction is to cut away extra skin, and that needs placing an incision directly on the breast. Robotic mastectomy procedure is ideal for smaller-breasted women. Robotic surgery will be a promising tool in mastectomy that hold a relevant surprise in the future[31].

2.3 The opinion of Saudi users

Surgeons from many Saudi healthcare providers were asked to fulfil an evaluation check to demonstrate the opinion regarding the safety and the current local practice of robotically-assisted surgical device in mastectomy. A survey was prepared and sent to more than 130 hospitals around KSA including

public, private, and other types of healthcare providers. The survey consists of 3 questions about the safety and the current local practice of the device. A number of 4 responses were received. All the healthcare providers that answered the survey don't use or perform robotically-assisted surgical devices in mastectomy. Hence, robotically-assisted surgical devices in mastectomy is not applied in Saudi Arabia, and there is no risk related to RAS.

Part 3: Overall conclusion

In this study, robotically-assisted surgical devices in mastectomy was evaluated through a number of directions; which are clinical paper review, clinical experience review, and through considering the Saudi user's opinions.

The major findings of this study indicate that RNSM technique might be a promising tool in terms of lower nipple necrosis rate comparing to traditional NSM. However, there is no significant difference in other postoperative complication rates between NSM and RNSM. In addition, RNSM technique improves the cosmetic outcomes because it is performed through a very small axillary wound around 2.5–6-cm the scars wound is short and invisible that results in increasing the desire of patients to go through RNSM.

Although RNSM has some advantages, long-term data and further studies are needed to confirm the oncological safety and the cosmetic stability of the result. The main limitations of using robotically-assisted surgery device in mastectomy which are RAS is not approved by FDA or any regulatory for mastectomy, it is off-label, highly cost, and specialized skills required.

Furthermore, a survey about the safety and the current local practice of robotically-assisted surgical device in mastectomy was prepared and sent to more than 130 hospitals around KSA. the result of the questionnaire showed that robotically-assisted surgical devices in mastectomy is not conducted in Saudi Arabia, and there is no risk related to RAS.

In conclusion, RNSM could be a promising new producer for breast cancer patients who go through mastectomy. Also, RNSM could decrease morbidity and improve cosmetic outcomes even further in the future.

SFDA RECOMMENDATIONS

Based on the study findings, the following actions are recommended:

- Request from the manufacturer of device to develop awareness plan for the users of device at healthcare providers to instruct them to use the device only as intended by manufacturer.

- Follow-up with the manufacturers to ensure that the robotically-assisted surgical devices manufacturers have implemented the actions of the awareness plan.

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For further information or inquiries related to this study, you may contact us at: cia.md@sfda.gov.sa

REFERENCES

1. WHO | World Health Organization. https://www.who.int/. Accessed 14 Dec 2021
2. Ng T, Knowles S, Brackstone M, Doherty C (2019) Mastectomy flap necrosis after nipple-sparing mastectomy and immediate implant-based reconstruction: An evaluation of tumescence and sharp dissection technique on surgical outcomes. Breast J 25:1079–1083
3. Sarfati B, Honart J-F, Leymarie N, Rimareix F, Al Khashnam H, Kolb F (2018) Robotic da Vinci Xi-assisted nipple-sparing mastectomy: First clinical report. Breast J 24:373–376
4. Selber JC (2019) Robotic Nipple-Sparing Mastectomy: The Next Step in the Evolution of Minimally Invasive Breast Surgery. Ann Surg Oncol 26:10–11
5. Hwang RF, Hunt KK (2020) The Emergence of Robotic-assisted Breast Surgery: Proceed With Caution. Ann Surg 271:1013–1015
6. Moon J, Lee J, Lee DW, Lee HS, Nam DJ, Kim MJ, Kim NY, Park HS (2021) Postoperative pain assessment of robotic nipple-sparing mastectomy with immediate prepectoral prosthesis breast reconstruction: a comparison with conventional nipple-sparing mastectomy. Int J Med Sci 18:2409–2416
7. Toesca A, Invento A, Massari G, et al (2019) Update on the Feasibility and Progress on Robotic Breast Surgery. Ann Surg Oncol 26:3046–3051
8. Lai H-W, Chen S-T, Mok CW, Lin Y-J, Wu H-K, Lin S-L, Chen D-R, Kuo S-J (2020) Robotic versus conventional nipple sparing mastectomy and immediate gel implant breast reconstruction in the management of breast cancer- A case control comparison study with analysis of clinical outcome, medical cost, and patient-reported cosmetic results. J Plast Reconstr Aesthet Surg 73:1514–1525
9. Toesca A, Peradze N, Manconi A, et al (2017) Robotic nipple-sparing mastectomy for the treatment of breast cancer: Feasibility and safety study. Breast 31:51–56
10. Sarfati B, Struk S, Leymarie N, et al (2018) Robotic Prophylactic Nipple-Sparing Mastectomy with Immediate Prosthetic Breast Reconstruction: A Prospective Study. Ann Surg Oncol 25:2579–2586
11. Parcells A, Spiro S (2020) Exploration of Robotic Direct to Implant Breast Reconstruction. Plast Reconstr Surg Glob Open 8:e2619
12. Woodward S, Willis A, Lazar M, Berger AC, Tsangaris T (2020) Nipple-sparing mastectomy: A review of outcomes at a single institution. Breast J 26:2183–2187
13. Laporta R, Longo B, Sorotos M, Farcomeni A, Patti C, Mastrangeli MR, Rubino C, Santanelli di Pompeo F (2017) Breast reconstruction following nipple-sparing mastectomy: clinical outcomes and risk factors related complications. J Plast Surg Hand Surg 51:427–435
14. Olson J, Anderson LA, Ying J, Zhang M-M, Agarwal JP (2017) Nipple Sparing Mastectomy in Patients With Prior Breast Scars: Is It Safe? Ann Plast Surg 78:22–27

15. Munhoz AM (2017) Outcome Evaluation after 2023 Nipple-Sparing Mastectomies: Our Experience. Plast Reconstr Surg 140:348e-349e
16. Kim JH, Chun YS, Park HK, Kim SE, Kim YW, Cheon YW (2020) Inframammary Fold Incision Can Reduce Skin Flap Necrosis in Immediate Breast Reconstruction With Implant and Conjoined Fascial Flap. Ann Plast Surg 85:488–494
17. Lee J-H, Choi M, Sakong Y (2021) Retrospective analysis between complication and nipple areola complex preservation in direct-to-implant breast reconstruction. Gland Surg 10:290–297
18. Valero MG, Moo T-A, Muhsen S, Zabor EC, Stempel M, Pusic A, Gemignani ML, Morrow M, Sacchini V (2020) Use of bilateral prophylactic nipple-sparing mastectomy in patients with high risk of breast cancer. Br J Surg 107:1307–1312
19. Roh TS, Kim JY, Jung BK, Jeong J, Ahn SG, Kim YS (2018) Comparison of Outcomes between Direct-to-Implant Breast Reconstruction Following Nipple-Sparing Mastectomy through Inframammary Fold Incision versus Noninframammary Fold Incision. J Breast Cancer 21:213–221
20. Parvez E, Martel K, Morency D, Dumitra S, Meguerditchian AN, Dionisopoulos T, Meterissian S, Basik M, Boileau J-F (2020) Surgical and Oncologic Outcomes of Nipple-Sparing Mastectomy for a Cohort of Breast Cancer Patients, Including Cases with High-Risk Features. Clin Breast Cancer 20:353–358
21. Lagendijk M, Desantis S, Nakhlis F, Duggan M, Calvillo KZ, Carty M, Chun Y, Caterson S, Golshan M, Dominici LS (2020) Impact of surgical complications on patient reported outcomes (PROs) following nipple sparing mastectomy. Am J Surg 220:1230–1234
22. Donnely E, Griffin MF, Butler PE (2020) Robotic Surgery: A Novel Approach for Breast Surgery and Reconstruction. Plast Reconstr Surg Glob Open 8:e2578
23. Bishop SN, Selber JC (2021) Minimally invasive robotic breast reconstruction surgery. Gland Surg 10:469–478
24. Houvenaeghel G, Cohen M, Ribeiro SR, Barrou J, Heinemann M, Frayret C, Lambaudie E, Bannier M (2020) Robotic Nipple-Sparing Mastectomy and Immediate Breast Reconstruction With Robotic Latissimus Dorsi Flap Harvest: Technique and Results. Surg Innov 27:481–491
25. Rajappa SK, Kumar R, Garg S, Ram D (2018) Robotic nipple-sparing mastectomy: The first experience from Indian subcontinent. Breast J 24:1114–1115
26. Morrow M (2021) Robotic mastectomy: the next major advance in breast cancer surgery? Br J Surg 108:233–234
27. Lai H-W, Lin S-L, Chen S-T, Lin Y-L, Chen D-R, Pai S-S, Kuo S-J (2018) Robotic nipple sparing mastectomy and immediate breast reconstruction with robotic latissimus dorsi flap harvest - Technique and preliminary results. J Plast Reconstr Aesthet Surg 71:e59–e61
28. Houvenaeghel G, Barrou J, Jauffret C, et al (2021) Robotic Versus Conventional Nipple-Sparing Mastectomy With Immediate Breast Reconstruction. Front Oncol 11:637049
29. Lai H-W, Chen S-T, Lin S-L, Lin Y-L, Wu H-K, Pai S-H, Chen D-R, Kuo S-J (2018) Technique for single axillary incision robotic assisted quadrantectomy and immediate partial breast reconstruction with robotic latissimus dorsi flap harvest for breast cancer: A case report. Medicine (Baltimore) 97:e11373
30. Caution When Using Robotically-Assisted Surgical Devices in Women's Health including Mastectomy and Other Cancer-Related Surgeries: FDA Safety Communication | FDA. https://www.fda.gov/medical-devices/safety-communications/caution-when-using-robotically-assisted-surgical-devices-womens-health-including-mastectomy-and. Accessed 13 Dec 2021
31. First robot-assisted breast recon in U.S. a success | ASPS. https://www.plasticsurgery.org/for-medical-professionals/publications/psn-extra/news/first-robot-assisted-breast-recon-in-us-a-success. Accessed 21 Dec 2021