https://orcid.org/0000-0001-7381-7271
https://doi.org/10.15388/vu.thesis.592

VILNIUS UNIVERSITY

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Immediate Prepectoral Implant-Based Breast Reconstruction for Breast Cancer Patients

DOCTORAL DISSERTATION

Medicine and Health Sciences,
Medicine (M 001)

VILNIUS 2024

The dissertation was prepared at Vilnius University and Vienna Medical University between 2019 and 2023. The dissertation is defended on an external basis.

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https://orcid.org/0000-0001-7381-7271
https://doi.org/10.15388/vu.thesis.592

VILNIAUS UNIVERSITETAS

Edvin Ostapenko

Vienmomentė prepektoralinė krūtų rekonstrukcija implantais pacientams, sergantiems krūties vėžiu

DAKTARO DISERTACIJA

Medicinos ir sveikatos mokslai,
medicina (M 001)

VILNIUS 2024

Disertacija rengta 2019–2023 metais Vilniaus universitete ir Vienos Medicinos universitete. Disertacija ginama eksternu.

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Disertaciją galima peržiūrėti Vilniaus universiteto bibliotekoje ir VU interneto svetainėje adresu: https://www.vu.lt/naujienos/ivykiu-kalendorius

CONTENT

1. ABBREVIATIONS

ALND – axillary lymph node dissection
ADM – acellular dermal matrix
BC – breast cancer
Bi-RADS – breast imaging and reporting data system
BCS – breast conservative surgery
BMI – body mass index
CDC – Clavien-Dindo classification
DCIS – ductal carcinoma in situ
DTI – direct-to-implant
ER – estrogen receptor
HER2 – human epidermal growth factor
IBBR – implant-based breast reconstruction
IMF – inframammary fold
LCIS – lobular carcinoma in situ
MRI – magnetic resonance imaging
MBC – metastatic breast cancer
MG – mammography
NSM – nipple-sparing mastectomy
NAC – nipple-areolar complex
NACT – neoadjuvant chemotherapy
OS – overall survival
PMRT – post-mastectomy radiation therapy
PD – paget disease
PR – progesterone receptor
pCR – pathological complete response
QoL – quality of life
RBT – residual breast cancer
RT – radiotherapy
SSM – skin-sparing mastectomy
SLNB – sentinel lymph node biopsy
TNBC – triple-negative breast cancer
US – ultrasound
WHO – World Health Organization

2. INTRODUCTION

In 2020, about 2.3 million women were diagnosed with breast cancer worldwide and 685.000 died. Breast cancer is the most common cancer in women both in the developed and less developed world. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer.[1] In Lithuania, the incidence of this cancer is also increasing rapidly. In 2020, 1,769 new cases (21,7% of all cases) of primary BC were diagnosed with 490 cases of deaths.[2]

The incidence of BC is higher in economically strong countries and in women of higher socioeconomic status, whereas BC mortality is higher in women from poor countries and from lower socioeconomic backgrounds.[3] This may be partly due to raised awareness, improved diagnostic methods and screening programs among economically strong countries.

BC was initially managed with operative extirpation alone, but now requires a multidisciplinary team across various surgical, medical, psychological, and social specialties in order to produce the best outcomes for the patients.[4] In the last 50 years, a lot of effort has been made to improve the surgical treatment modalities, in order not only to prolong the survival, but also to ensure a better quality of life. Halsted mastectomy was replaced by quadrantectomy and conservative mastectomy, which included skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) for BC patients. In contrast to conventional mastectomy, where the complete breast is removed, SSM is characterized by the abscission of the breast tissue within the skin envelope through a small but well-planned skin incision and a minimum amount of skin excision. However, the nipple-areola complex (NAC) is eliminated by SSM. The NSM was therefore developed to remove all breast glandular tissue with total preservation of skin and NAC, it's also a direct result of the development of oncoplastic surgery in BC.[5] In the last century, the numbers of NSM are raising.[6] The reason for this are multifactorial, including better understanding of mastectomy flap perfusion, increased rate of immediate implant-based breast reconstructions (IBBR), genetic testing due to high-risk genetic mutations such as BRCA-1 and BRCA2, as well as raised awareness, and improved diagnosis methods.[7]

As the number of breast cancer are increasing every year, diagnostic and treatment options and patient overall survival are improving, making the quality of life outcomes more important. Breast reconstruction rates have increased also over the last decade in the world. Implant-based breast reconstruction (IBBR) remains the most common reconstructive approach with more than 137,000 procedures during 2020 in the USA.[8] Currently, IBBR

is divided into one-stage or two-stage reconstruction. The one-stage or direct-to-implant reconstruction technique in which a definitive implant is placed following NSM needs only one operative time, fewer recovery days, and follow-up visits.[9] Generally, the two-stage technique involves positioning of a tissue expander in a retro-pectoral pocket after NSM/SSM, followed by exchange with an implant in a second stage.[10]

The selection of the implant plane during breast reconstruction has recently become a subject of debate. Prepectoral IBBR involves filling the space between the pectoralis major muscle and mastectomy skin flap, whereas subpectoral position involves placing the implant between the pectoralis major muscle and chest wall.[11] The prepectoral IBBR technique eliminates the need for an elevation and dissection of the pectoralis muscle, adjacent muscles, and fascia. This preserves the pectoralis major muscle in its anatomical position, resulting in a more natural breast appearance and less postoperative pain.[12] First described in the 1970s, the prepectoral IBBR technique was associated with an unacceptable high rate of complications, including infection, implant exposure, and capsular contracture. To decrease the risk of complications, the procedure was modified to position the implant subpectorally.[13] The subpectoral IBBR was a reliable and safe alternative. In the past few years, prepectoral IBBR has resurged in popularity. Modern iterations have demonstrated improved outcomes for several reasons, including a better clinical understanding of mastectomy flap perfusion, new reconstructive techniques as well as the introduction of new generation implants, which are linked to decreased capsular contracture and have allowed safe and efficacious prepectoral implant placement.[13–16]

However, comparative studies of prepectoral versus subpectoral IBBR are limited and results vary. In addition, patients who will undergo NSM and have ptotic breasts present a technical challenge for surgeons in terms of oncological safety and aesthetic outcomes, especially in immediate prepectoral IBBR.[17,18] Another challenge remained with this procedure in the adjuvant radiotherapy (RT) settings and overall complication rates. Moreover, despite the beneficial effect of saving the NAC on psychosocial well-being, body image, and aesthetic satisfaction, no conclusive evidence exists proving the oncological safety of NSM following immediate prepectoral IBBR.[19,20]

2.1. Study hypothesis

Prepectoral IBBR is a safe modality that should be considered for any BC patient, who is a candidate for immediate IBBR.

2.2. The aim of the study

The aim of this dissertation is to provide the evidence for the oncological safety, to evaluate results of combined treatment and quality of life, and to optimize surgical technique in NSM following immediate prepectoral IBBR for BC patients.

2.3. Objectives

1. To perform a systematic review and meta-analysis for clinical outcomes and efficacy of prepectoral IBBR compared with subpectoral IBBR for BC patients.
2. To evaluate and compare the oncological safety according to the surgical technique in NSM following immediate prepectoral IBBR.
3. To analyse the quality of life using the BREAST-Q scale according to the surgical technique in NSM following immediate prepectoral IBBR.
4. To investigate the efficacy of PMRT according to the surgical technique in NSM following immediate prepectoral IBBR.
5. To determine the main indications for surgical technique in NSM following immediate prepectoral IBBR for BC patients.

2.4. Novelty of the study

To our best knowledge, this was the first clinical study in the EU comparing oncological safety, quality of life, and other outcomes according to the surgical technique in NSM following immediate prepectoral IBBR in BC patients.

Our performed systematic review and meta-analysis of prepectoral implant-based breast reconstruction versus subpectoral implant-based breast reconstruction included 15 studies with 3101 patients and at the moment it is the largest conducted meta-analysis.

3. LITERATURE REVIEW

3.1. Breast cancer epidemiology

BC is the most frequently diagnosed cancer in women worldwide with 2.26 million new cases in 2020.[7] BC incidence is highly correlated with human development. The human development index is a composite measure of life expectancy, education and wealth and is a more useful comparator between countries than income alone. Countries with the highest levels of human development have the highest incidences of breast cancer.[21,22] The global age standardized incidence rate in females is estimated to be 48/100,000, varying from under 30/100,000 in sub-Saharan Africa to over 70/100,000 in Western Europe and North America. Women in older age have high breast cancer incidence.[23] BC is rare before the age of 40, and the incidence increases significantly after that. Worldwide, the incidence of breast cancer in women aged 15–39 years is 14/100 000, while the incidence of breast cancer in women aged 65–69 years is much higher 159/100 000.[24] According to the American Cancer Society, global cancer burden would be 28.4 million cases by 2040, which is ~47% raise compared to 2020 cancer burden.[25] In 2020, breast cancer was responsible for almost 685,000 deaths in females worldwide. Almost two-thirds of those deaths were recorded in less-developed regions. In more developed regions, overall 5-year survival from breast cancer is well over 80%; in comparison, 5-year survival in India is reported as less than 70% and less than 50% in South Africa.[26]

In Lithuania in 2020, BC remains the most commonly diagnosed cancer in women with 1,769 cases (21.7% of all cases), followed by colorectal cancer with 959 cases (11.8%), and uterine body cancer with 803 cases (9.9%). There were also registered 490 BC related deaths. Based on the European age-standardized rate, the mortality rate in Lithuania was 27.8%.[25]

Risk factors that may influence the development of BC includes both modifiable factors (hormone replacement therapy, physical activity, obesity, alcohol, smoking, other drugs) and non-modifiable factors (female sex, age, family history of BC or ovarian cancer, genetic mutations, ethnicity, pregnancy, menstrual period and menopause, previous history of BC, non-cancerous breast diseases, radiation therapy).[27]

Non-modifiable factors

Gender. Being female is the biggest risk factor for breast cancer. Approximately 1 in 8 women in USA (about 13%) will develop invasive breast

cancer in her lifetime.[28] Less than 1% of all breast cancers occurs in men. However, breast cancer in men is an extremely rare disease that tends to be more advanced at the time of diagnosis than in women.[29]

Age. The incidence of breast cancer increases with age, from 1.5/100 000 women aged 20-24 years to a peak of 421/100 000 women aged 75-79 years.[7] In the USA and EU countries, the majority of BC cases are diagnosed aged >50, with the most frequent diagnosis occurring between the ages of 50 and 69 years. The median age at death due to breast cancer is 68 years overall, with a median age at death of 62 years for black women and 69 years for non-Hispanic white women.[30]

History of BC. A personal history of BC is associated with a higher risk of developing renewed cancerous lesions within the breasts.[31] History of any other non-cancerous breast diseases, such as atypical ductal and lobular hyperplasia, are also associated with a higher risk (4–5 times) of developing BC. Benign lesions and a family history of BC are two factors that are strongly associated with BC risk.[32]

Family history. Approximately 13-19% of patients diagnosed with BC report a first-degree relative affected by the same condition.[33] The incidence rate of BC is significantly higher in all of the patients with a family history despite age. A cohort study of over 113,000 women in the UK demonstrated that women with one first-degree relative with breast cancer have a 1.75-fold higher risk of developing this disease than women without any affected relatives. Moreover, the risk becomes 2.5-fold or higher in women with two or more first-degree relatives with breast cancer A family history of ovarian cancer might also induce a greater risk of BC.[34,35]

Genetic mutations. It is estimated that around 5–10% of breast cancers are directly linked to genetic mutations. Two major mutations in the BRCA1 and BRCA2 pathological genes account for about half of the mutations in BC. They are primarily linked to the increased risk of breast carcinogenesis.[36] These mutations that occur are present within every cell in the body, and therefore can be passed on to future generations. Statistically, women are 35–60% more likely to develop ovarian cancer in comparison to the 1.6% seen in the general population.[37] Women who have inherited mutations in the BRCA1 and BRCA2 pathological genes have an average of up to 7 in 10 chances of developing BC by the age of 80. Less common pathological mutations in BC genes include: PALB2, ATM, CHEK2, CDH1, STK11, PTEN, TP53, NF1 and BRIP1 which are characterized by a lower

penetrance compared to BRCA1 or BRCA2.[37–44]

Density of breast tissue. Women with greater breast tissue density are more likely to have BC. Greater density of breasts is observed in females of younger age and lower BMI.[45] Dense breast tissue is linked to markedly reduce mammographic sensitivity and a higher interval cancer rate. A recent study showed that mammographic breast density BI-RADS D is associated with an approximately two-fold increased risk of breast cancer compared to have BI-RADS density B in the general population women.[46]

Race. Generally, the BC incidence rate remains the highest among white non-Hispanic women. However, the overall incidence of BC is slightly lower in black women than in white women, black women have the highest 5 year breast cancer mortality rate for each known stage at diagnosis.[47,48] In the USA, BRCA mutations are more common in people of Ashkenazi Jewish origin (Eastern Europe) than in other racial and ethnic groups. Ashkenazi Jewish women also have a risk of mutation in the BRCA1 and BRCA2 genes that is approximately 20 times higher than in the general population (approximately 1 in 40).[49–51]

Reproductive history. Women who started menstruating before the age of 12 years have had more menstrual cycles because they started menstruating earlier and have a slightly higher risk of developing BC.[52,53] Breast cancer risk is approximately 20% higher among girls that begin menstruating before age 11 than those that begin at age 13. In addition, women who experience menopause at age 55 or older have about a 12% higher risk compared to those who do so between ages 50-54.[54] Early age of first full-term birth is highly protective against late-onset breast cancers, but each pregnancy, including the first one, increases the risk of early-onset BC. Additional important factors relating to pregnancy are breast feeding and number of pregnancies. A longer duration of breast feeding is correlated with a lower risk of BC.[55] However, the first full-term pregnancy at an early age is associated with a reduced risk of BC.[56]

Previous radiotherapy. Women who have received radiotherapy to the chest or breasts before the age of 30 (for example, treatment for Hodgkin's lymphoma) have a higher risk of developing BC later in life.[57] A recent meta-analysis showed that radiotherapy for breast cancer is associated with a small but significantly increased risk of second cancers of the lung, esophagus, and soft tissues.[58]

Modifiable factors

Alcohol consumption. Alcohol is considered to be causally related to BC risk, with 7–10% increase in risk for each 10 (tilde; 1 drink) alcohol consumed daily by adult women.[59] This association is observed in both premenopausal and postmenopausal women. The mechanism behind these findings is likely related to the ability of alcohol to increase the levels of estrogen in the blood.[60]

Obesity. Overweight and obesity are associated with an overall increased risk of BC. The link between increased body mass index (BMI) and BC is found primarily in post–menopausal women that form estrogen positive BC.[61] Before menopause, a woman's ovaries produce most of the estrogen, while adipose tissue accounts for only a small proportion. After menopause, most of the estrogen comes from adipose tissue.[62]

Smoking. Some studies have found that long-term heavy smoking may be associated with a slightly higher risk of breast cancer. The 2014 US Surgeon General's report on smoking stated that there is "convincing but insufficient" evidence that smoking increases the risk of BC.[63] Thus, not only active but also passive smoking significantly contributes to the induction of pro–carcinogenic events. Based on studies, greater risk was seen in women who started smoking before their first pregnancy (up to 21% higher risk) and in those who were heavy, long–term smokers.[64]

Physical activity and nutrition. Recent studies have shown that there is an association between increased physical activity and lower risk of BC.[65,66] Exercise has been linked to reduced estrogen levels, which could also play an important role in reducing BC risk. Most of the studies showed, that vitamin D deficiency was directly related to BC, while total vitamin D and supplemental vitamin D intakes had an inverse relationship with this outcome.[67,68]

Oral contraceptives. Most studies have shown that women who take oral contraceptive pills have a slightly higher risk of breast cancer than women who never take them.[69] After stopping the pill, this risk returns to normal within 10 years. Hormone replacement therapy (HRT): Combined HRT hormone therapy after menopause increases the risk of breast cancer. This risk usually increases after about 4 years of use.[70]

Breast implants. Breast implants do not increase the risk of breast cancer.

However, they may increase the risk of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).[71] This lymphoma seems to be more common in women with implants with textured (rough) rather than smooth surfaces.

Other Drugs. Other drugs that might constitute potential risk factors for breast cancer include antibiotics, antidepressants.[72–74] Between 1940 and 1971, some pregnant women in the USA were given diethylstilbestrol (DES) to prevent miscarriage. Women who have used DES or whose mothers have used DES while pregnant are at an increased risk of BC group.[75]

3.2. Breast cancer diagnosis

Early detection and monitoring of patients are the main aspects of BC therapy. For the diagnosis of BC, there are mandatory tests for the detection of the primary tumor and for the assessment of the spread of BC as well as additional tests that can be performed to confirm the diagnosis of BC. BC could be diagnosed by monitoring patients with imaging techniques or symptoms such as pain or a palpable mass. It has been shown that monitoring healthy subjects could contribute to the detection of small tumors, which could lead to the progression of BC. Among various techniques, imaging techniques have emerged as powerful tools for detection and monitoring the response to therapy in patients with BC.

Mammography – is the most important and fundamental tool in breast imaging. Mammography uses a low x–ray tube voltage, typically 25 kV, resulting in images with high resolution and contrast, with microcalcifications 100um and smaller clearly visible. It is irreplaceable in detecting calcifications in breast tissue. Mammogram images can detect up to 75% of cancers up to one year before the cancer becomes palpable.[76] However, its ability to detect abnormalities in dense breasts and masses close to the chest is limited. The mammography also exposes females to radiation, it is not recommended as the preferred option for young females. Most cancer organizations recommend prophylactic mammography every 1 year for women aged 40 years and older – 50 to 69 years.[49,77,78,79]

Breast tomosynthesis – has the potential to overcome the primary limitation of standard two-dimensional mammography, a masking effect to overlapping fibroglandular breast tissue, improving diagnostic accuracy by differentiating

benign and malignant features, and increasing lesion conspicuity, particularly in dense breasts.[80] In diagnostic setting, tomosynthesis also allows for improved lesion localization and characterization over conventional imaging, which potentially improves the accuracy and improved workflow efficiency.[81]

Breast ultrasound – is applicable in females of all ages suspected of breast diseases. Breast ultrasound has been proven to be an exceptionally effective tool for imaging palpable abnormalities in the breast. It distinguishes cystic from solid masses and demonstrates features of solid masses that would denote the mass as suspicious and warrant biopsy. Ultrasound is a particularly useful diagnostic modality in dense breast tissue, often detecting breast cancers obscured on mammography.[82] Furthermore, if biopsy is required, ultrasound is the ideal imaging tool to guide subsequent procedures, further enhancing its utility in breast cancer diagnosis. US is also widely used as a second-look tool in patients with abnormalities found on MRI.[83]

Magnetic Resonance Imaging (MRI) – is the most sensitive modality for BC detection with excellent sensitivity and good specificity. This method is indicated to assess the response to neoadjuvant chemotherapy and to detect the spread of disease in invasive carcinoma with axillary lymph node metastases, local recurrence and residual carcinoma, and multifocal or bilateral breast cancer. MRI is more useful than mammography and US when staging multifocal and multicentric disease or when DCIS is present.[84] Unfortunately, MRI has a significant false positive rate, is not always available, and is significantly more expensive than mammography or ultrasound.[85–87]

Breast biopsy – if breast cancer is suspected, the next step is to sample the abnormal area to confirm the diagnosis. Regardless of whether the lump can be felt or not, the biopsy should be obtained using a needle biopsy with the help of an imaging study (such as mammography, ultrasound, or MRI) to assure that the lump has been adequately biopsied. A fine needle aspiration may be sufficient to establish a diagnosis of breast cancer, though a core needle biopsy, which utilizes a larger-gauge needle, is often preferable as it provides a larger sample to better characterize certain features of the cancer.[88]

Positron emission tomography with computer-aided tomography (PET-CT) – is a combination of PET (a nuclear medicine technique) and CT that produces highly detailed views of the body. The improved spatial resolution and sensitivity of PET scanners dedicated to breast (positron emission mammography) has allowed its clinical application in the study of primary

tumors. In detection of distant metastases, this imaging tool may have a better accuracy in detecting lytic bone metastases compared to bone scintigraphy.[89] PET-CT is also recommended when advanced-stage disease is suspected, and conventional modalities are inconclusive. PET-CT has high sensitivity and specificity to detect locoregional recurrence and is recommended in asymptomatic patients with rising tumor markers.[90] Using PET to evaluate advanced breast cancer, a met analysis of 5 studies (547 patients) demonstrated a sensitivity for breast cancer of 0.97 (95% confidence interval, 0.93–0.99) and a specificity of 0.95 (95% confidence interval, 0.90–0.97).[91]

Bone X-Ray – uses ionizing radiation, it is an inexpensive, fast and accessible exploration—that allows detection of the presence of lytic lesions (with greater than 50% destruction of the mineralized bone), blastic lesions, mixed lesions or complications, such as pathological fractures.[92] However, the use of the classical metastatic bone series to systematically exclude the presence of metastasis has not been recommended for years given its low diagnostic yield.

Genetic testing – is a powerful tool that allows for the detection of germline mutations in individuals at high risk of BC and, in select cases, those who already have a diagnosis of BC, which in turn aids in the individualization of treatment. BRCA1 and BRCA2 germline mutations play important roles in the development of breast and ovarian cancer in particular, as well as in other cancers such as pancreatic and prostate cancer and melanoma. Recent studies suggest that other cancer susceptibility genes, including ATM, CHEK2, PALB2, and RAD51C, confer differential risk of BC.[93–95]

To estimate the spread of the disease a chest radiography and routine laboratory blood tests are sufficient for staging in a patient with clinical stage I or II breast cancer and on specific symptoms of metastatic disease. For suspected advanced (stage IIIB/C or IV) disease, the National Comprehensive Cancer Network guidelines recommend ether chest, abdomen, and pelvis CT or chest CT with abdomen and pelvis MRI as well as bone scan or sodium fluoride PET/CT.[96]

3.3. Breast cancer types

BC according to relation to the basement membrane is divided into: non-invasive BC and invasive BC.

Non-invasive BC

It's a type of cancer that has not extended away from the lobule or ducts where it situated. Non-invasive breast cancer can be classified to ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). If cancers arise in the ducts of the breast (the tubes that carry milk to the nipple when a woman is breastfeeding) and do not grow outside of the ducts, the tumor is called DCIS. DCIS cancers do not spread beyond the breast tissue. However, DCIS may progress into invasive cancers if not treated.[97,98] Most women are able to be treated with removal of the cancerous area (quadrantectomy) followed by radiation therapy. Surgical removal of the cancerous are alone may be an option, particular for older women with a very small are of hormone receptor positive, low-grade disease that is completely removed. Women with DCIS who are being treated with quadrantectomy do not need their lymph nodes checked for spread of tumor.[99,100]

Ductal carcinoma in situ (DCIS) was rarely diagnosed before the advent of breast screening, yet it now accounts for up to 25% of detected "breast cancers". Generally, patients diagnosed with DCIS have an excellent long-term breast-cancer-specific survival of around 98% after 10 years follow-up.[98]

Lobular carcinoma in situ (LCIS) isn't BC and it less common than DCIS. LCIS is a rare condition where you have abnormal cells in the terminal duct lobular units, whereas ductal lesions appeared most often in the mammary ducts. However, LCIS is a marker that you have greater risk for developing BC than those who don't have LCIS. The relative risk of invasive carcinoma after LCIS diagnosis is approximately 9 to 10 times that of the general population.[101]

Invasive BC

The majority of breast cancers are referred to as invasive BC because they have grown or "invaded" beyond the ducts or lobules of the breast into the surrounding breast tissue. Invasive breast cancer can be also classified to invasive ductal carcinoma and invasive lobule carcinoma. The most frequent is invasive carcinoma of no special type (NST), also known as invasive ductal carcinoma NST, and this comprises 40–75% of cases.[102] Invasive ductal cancer trends to grow as a cohesive mass and it appears as discrete abnormalities on mammograms. While, invasive lobular carcinoma tends to permeate the breast in a single-file nature, which explains why it remains clinically occult and

often escapes detection on mammography or physical examination until the disease is extensive. Invasive lobular carcinoma accounts for 10% of BC.[103]

Rare invasive BC

Adenoid cystic carcinoma – is a rare form of BC that accounts for <0.1% of all BC.[104] It has a unique dual-cell pattern and is indistinguishable from ACC arising from salivary tissue. Most cases present as a painful, palpable mass in the outer quadrants of the breast, and must be diagnosed via core needle biopsy or surgical excisional biopsy. Unlike most other breast cancers, ACC rarely metastasizes to the axillary lymph nodes, and therefore dissection is not recommended in the management of this disease.[104]

Mucinous carcinoma – a rare form of BC that accounts for 2-4% of all BC. Mucinous breast carcinoma is characterized by a large amount of extracellular mucin.[105] There are two main subtypes of MC: pure (PMC), which is more frequent, and mixed (MMC). It has a better prognosis compared to other breast malignant neoplasia such as ductal or lobular variants.[105]

Papillary carcinoma – a rare form of BC that accounts for 0.5% to 1% of all BC.[106] These tumors lack the myoepithelial cell layer (MCL) within the papillae or at the periphery of the tumor with areas showing stromal invasion or invasion into lymphovascular spaces. It is usually seen in postmenopausal age group. Bloody nipple discharge is a relatively common presenting sign, occurring in 22–34% of cases or may present as a palpable mass. Though the frequency of axillary node metastasis is low, treatment often involves mastectomy and axillary node dissection.[106]

Tubular carcinoma – is a distinct, relatively rare low-grade neoplasm, accounting for approximately 1–4% of invasive breast cancers.[107] It is composed of well-differentiated tubular structures with open lumina, typically one layer thick surrounded by abundant stroma. This tumor is nearly always estrogen (ER) and progesterone receptor (PR)-positive, and mostly human epidermal growth factor receptor type 2 (HER2)-negative. Tobular carcinoma is associated with an excellent prognosis.

Medullary breast cancer – is a rare and distinct subgroups of BC accounting for less than 5% of all invasive BC.[108] This unique histologic subtype has very strict criteria for diagnosis, including complete circumscription, the syncytial growth pattern of at least 75% of the tumor, intermediate to high nuclear grade,

an associated diffuse lymphocytic infiltrate and a lack of intraductal components.[108]

Metaplastic breast cancer – is a rare form of BC that accounts for only 0.5% of all BC.[109] The cancerous epithelium becomes non-glandular through metaplastic differentiation. The current WHO identifies different histological patterns of MBC: low-grade, adenosquamous carcinoma, fibromatosis-like metaplatic carcinoma, squamous cell carcinoma, spindle cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, mixed metaplatic carcinoma, and myoepithelial carcinoma.[110] Compared with the other hystotypes of BC, MBC most commonly shows a triple-negative phenotype, due to the absence of expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. MBC carries the worst prognosis in comparison to other BC types and plays a significant role in global BC mortality.[111]

Other rare BC

Inflammatory breast cancer – is a rare form of BC that accounts for only 2–4% of all BC.[112] Inflammatory breast cancer (IBC) typically presents with breast skin symptoms such as erythema and edema of the breast skin. IBC is also characterized by rapid progression and higher metastatic potential. Despite it's low incidence, IBC contributes to 7–10% of BC caused mortality with median overall OS 3.5 years shorter than non-IBC.[113]

Phyllodes tumor – are rare neoplastic lesions that are comprised of both stromal and epithelial components, and the account for approximately 0.3–1% of breast tumors in women.[114] Phyllodes tumors are subdivided into benign (60–75%), borderline (15–20%), or malignant (10–15%). Approximately 9–27% of patients with malignant phyllodes tumor have metastasis to distant organs with spreading hematogenously to most frequent sites as lungs, bones, brain, and liver.[115,116]

Paget's disease – is a rare malignant tumor that represents 1–3% of all BC.[117] The main symptoms are: skin changes including scaling, redness, and itching of the nipple and areola. The nipple changes later progress to ulcerations and erosion and may occur alone or in conjunction with and underlying palpable mass. If Paget's disease (PD) is clinically suspected, mammography and biopsy are recommended. According to underlying malignancy, PD can be divided into three groups: PD with invasive ductal carcinoma, PD with ductal

carcinoma in situ, and PD of the nipple without concurrent BC.[118] The treatment of choices is mastectomy, even though partial mastectomy followed by radiotherapy had shown good results. This type of BC is associated with low rate of metastasis and favorable prognosis.[119]

3.4. Molecular subtypes of breast cancer

Breast cancer is a genetically and clinically heterogeneous disease with multiple subtypes. The classification of these subtypes has evolved over the years. The most common and widely accepted classification of breast cancer is from an immunohistochemical perspective, based on the expression estrogen receptor (ER), progesterone receptor (PR) and over-expression and/or amplification of the human epidermal growth factor (HER2).[103,120]

Accordingly, the following four subtypes of breast cancer are widely recognized: luminal A, luminal B, HER2-positive, and triple-negative.[120] A Ki67 antigen is a cellular marker of proliferation and is an excellent marker for providing information on cell proliferation. The proliferative activities determined by Ki67 reflect the aggressiveness of the cancer along with response to treatment and time to recurrence. The need for molecular classification is to categorize patients who may benefit from target therapy, such as hormone therapy and anti HER2 therapy. Luminal A tumors are characterized by the presence of ER and/or PR and the absence of HER2 (*Table 1*), and have a low expression of cell proliferation marker Ki-67 (less than 20%).[121] Clinically they are low grade, slow growing, and have the best prognosis with less incidence of relapse and higher survival rate. Luminal B tumors are of higher grade and worse prognosis compared to Luminal A. They are ER positive and can be PR negative and have a high expression of Ki67 (greater than 20%). These tumors may benefit from hormonal therapy along with chemotherapy. The elevated Ki67 makes them grow faster than luminal A and worse prognosis. The HER2-positive group constitutes 10–15% of BC and is characterized by high HER2 expression with absence of ER and PR. They grow faster than the luminal ones and the prognosis has improved after the introduction of HER-2 targeted therapies.[122] The HER2-positive subtype is more aggressive and fast growing. Within this, two subgroups can be distinguished: luminal HER2 (E+, PR+ HER+ and Ki67: 15–30%) and HER2-enriched (HER2+, E+, PR-, Ki67>30%).[123] They have a worse prognosis compared to luminal tumors. Triple-negative (TNBC) BC is ER-negative, PR-negative, and HER2-negative. They constitute about 20% of all BC. It is most common among women under 40 years of age, and in African-American women. TNBC is characterized by its aggressiveness, early relapse, and a

greater tendency to present in advanced stages. Histologically, it is a poorly differentiated, highly proliferative, heterogeneous neoplasm, including subsets of variable prognosis.[124]

Table 1. Characteristics of subtypes of BC.

	Luminal A	**Luminal B**	**Luminal B HER2+**	**Non-Luminal B HER2+**	**TNBC**
Frequency (%)	50	10	10	18	15
ER/PR status	ER/PR positive	ER/PR positive	ER/PR positive	ER/PR negative	Most ER/PR negative
PR	Yes	Some cases	Some cases	Some cases	No
HER	No	No	Yes	Yes	No
Ki67	Low	High	High	High	High

The staging of BC based on the International Classification of Malignant Tumors 2018 TNM version 8 is presented. The classification is based on the TNM staging system, where T - is the primary tumor size, N - is number of lymph nodes with cancer, and M – whether the cancer has metastasized or spread to other organs of the body.[125]

TNM staging, published by the American Joint Committee on Cancer, uses both clinical and pathologic information of tumor size (T), the status of regional lymph nodes (N), and distant metastases (M). The staging combines these factors and stratifies the disease into one of 5 stages (0, I, II, III, and IV). In the latest edition (AJCC-TNM8), the information on grade and ER, PR, and HER2 has also been incorporated to form the prognostic staging. This prognostic staging overcomes the limitation of evaluation of the anatomical disease extent alone and takes into account biological parameters that have predictive and prognostic value, and it provides more accurate prognostic information than the former staging systems.[126]

3.5. Breast anatomy

Blood is supplied to the breast from the following vessels:

- Thoracoacromial artery
- Internal mammary perforators (second to fifth)
- Lateral thoracic artery
- Thoracodorsal artery

- Terminal branches of the intercostal perforators.

Overall, at least 60% of the blood supply is from superomedial perforators which come off the internal mammary artery. The breast also has profuse venous drainage divided into the superficial and deep veins. The nipple-areolar complex (NAC) has robust and overlapping vascularity from different arterial sources. The internal mammary artery (IMA) perforators are the dominant blood supply to the nipple, especially the second, third, and fourth perforators used in superomedial pedicle based mastopexies. The lateral thoracic and thoracoacromial arteries supply the breast and the nipple's superolateral aspect, and the intercostal arteries supply the anteromedial and anterolateral aspect of the breast. The superficical veins are found along the anterior surface of the fascia.

Sensory innervation to the breast is derived from branches of the intercostal nerves T3–T5. Other nerves that supply sensory innervation include the lower cervical plexus.

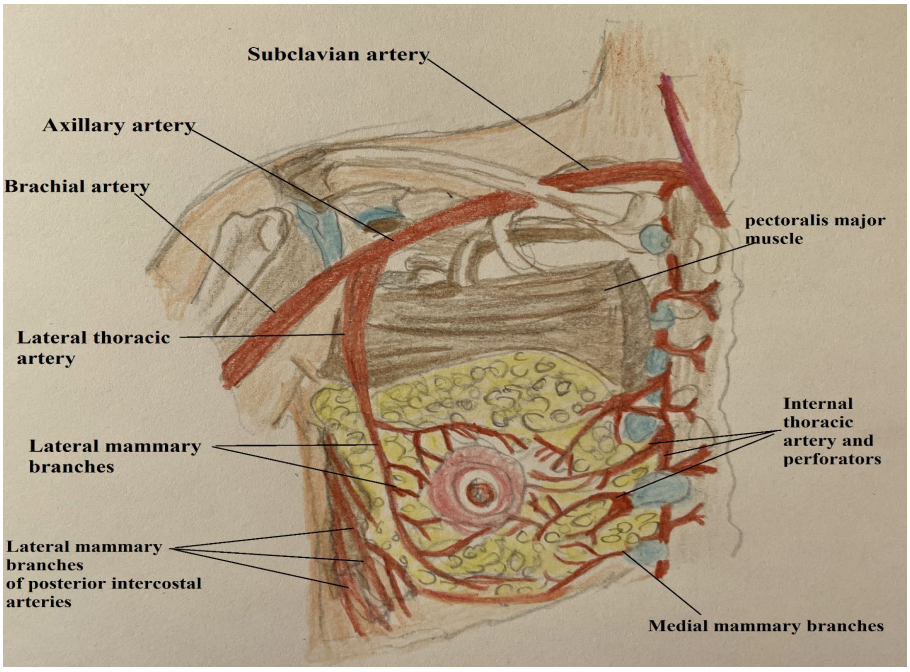

Fig. 1. The anatomy of the arteries of the breast.

The degree of ptosis can be categorized by the Regnault classification, which assesses the breast according to the relative position of the nipple to the inframammary fold (IMF). Grade 1 or mild ptosis is when the nipple is at the level of the fold. Grade 2 or moderate ptosis is when the nipple is below the

level of the fold, but it is not at the most dependent part of the breast. Grade 3 or severe ptosis is when the nipple is below the fold and is the most dependent part of the breast. Pseudoptosis is when the nipple is above or at the level of the fold, most of the breast is well below the fold, and the nipple to IMF distance is usually more than 6cm.[127]

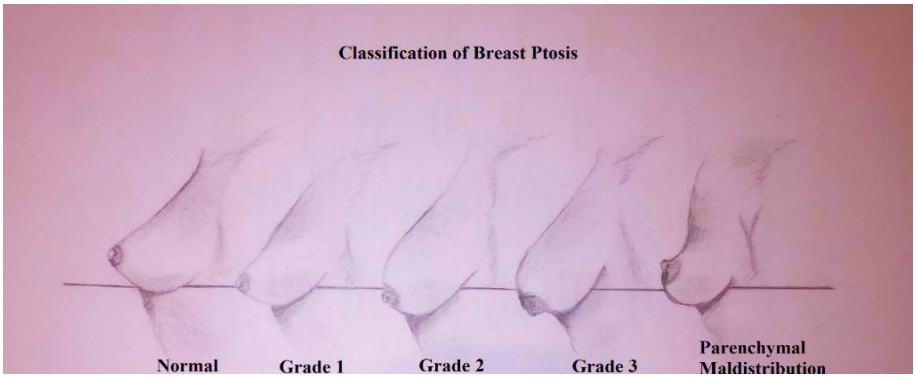

Fig. 2. Regnault classification of breast ptosis.

3.6. Breast cancer treatment

3.6.1. Surgery

During the first half of the 20th century, women diagnosed with BC were commonly treated by radical mastectomy, as first described by William Stewart Halsted in 1894.[128] However, surgical treatment of BC has evolved significantly from the original surgical technique described by Halsted. Following a clinical trial in which the Halsted mastectomy was compared to the less invasive quadrantectomy, no differences were reported in terms of local recurrence, disease-free or overall survival between the two groups.[4] As a result, Umberto Veronesi was the first in the world to state that the radical mastectomy appeared to involve unnecessary mutilation in patients with breast cancer of less than 2 cm and no palpable axillary nodes.[129] To date, the Prof. Veronesi BCS is routinely considered for BC treatment worldwide.[130]

Breast-conserving surgery (BCS)

BCS also called quadrantectomy or lumpectomy enables the removal of the cancerous tissue with simultaneous preservation of intact breast tissue. Breast conservation is a legacy of Umberto Veronesi who laid the groundwork for the preservation of the body image of women affected by breast cancer

(BC) with the Milan I study in the 1970s.[129] Breast conservative surgery (BCS) has two aspects: oncological safety of tumor resection with free margins and aesthetic preservation of the breast. This techniques have become increasingly popular as a strategy for improving aesthetic outcomes and extending the option of breast conservation therapy.[131]

BCS also called quadrantectomy involves excision of the tumor, including a 2- to 3- cm margin, pectoralis fascia, as well as the overlying skin. On the other hand, quadrantectomy indicates a less generous tissue excision with a 1-cm margin. The majority of early-stage tumors do not necessitate a quadrantectomy and thus will not be further described in detail.[132]

The incision choice for a quadrantectomy is based on numerous factors. It may be located within the Langer lines over the mass, whenever technically or cosmetically feasible, or a radial incision, particularly in the case of a large tumor. Regardless of the incision location, it is crucial to keep in mind the possibility of a future mastectomy. Following the incision, subcutaneous flaps are formed surrounding the tumor. Once removed, it is vital to orient the specimen, particularly if the need for re-excision arises in the future. Intraoperative specimen imaging is then performed to verify the presence of the biopsy clip and any preoperatively placed markers. If a close margin is suspected or indicated, many surgeons will excise an additional 0.5 to 1.0 cm of tissue to accompany the specimen. “Shave margins” or an excising an additional 1 mm of tissue, have been shown to reduce margin positivity and re-excision rates possibly.[133,134] It is also common practice to place radiopaque clips in the tumor cavity to guide future radiation treatment as well as follow-up imaging.[135]

Oncoplastic surgery

Oncoplastic surgery it’s a breast-conserving surgery, performed in combination with reconstructive surgery. This technique become increasingly popular as a strategy for improving aesthetic outcomes and extending the option of breast conserving therapy. The essential differences between OBS and conventional BCS are that OBS can provide larger volumes of excised tissue, less required re-excision rates, and reduced rates of positive margins. The main goals of OBS are complete excision of the tumor, obtaining negative surgical margins, achieving excellent cosmetic outcomes, and if possible oncological surgery with concurrent reconstruction.[136] Oncoplastic breast surgery technique are generally classified according to the breast size, location of the expected tumor resection, and the ratio of breast volume to resection volume. They are divided into II types of breast oncoplastic surgeries:

Breast oncoplastic surgery type I. Oncoplastic technique include basic segmental mastectomy technique that require excision of less than 20% of the breast volume in small to moderate-sized breasts with minimal ptosis. The objective is tumor excision without skin resection, and to repair partial breast defects effectively to reduce the risk of deformity that will occur with the effect of RT. The main principles are the localization of the tumor, planning the incision, dissecting the subcutaneous flap widely beyond the tumor, identifying the tumor, removing the specimen, undermining the breast anterior to the pectoralis fascia, marking the tumor cavity, and closure of the defect with mobilized tissue pillars.[136–138]

Breast oncoplastic surgery type II. Oncoplastic techniques are applied in cases that require excision of 20% to 50% of the breast volume and are often accompanied by skin excision. The strength of this technique lies in obtaining a negative margin by allowing large amounts of breast tissue to be resected, and preventing radiation toxicity, especially in women with large breast sizes. Breast cancer-related lymphedema may occur in patients with macromastia, especially after axillary surgery and RT, with inadequate lymphatic drainage and limited effect of gravity on the lymphatics. Reduction mammoplasty, which prevents or reduces breast lymphedema after RT is an option for patients with macromastia. One of the greatest contributions of level-2 technique to BCS is that they are often safe to resect multicentric tumors. Thus, tumor beds that are brought together with the safe margin obtained by resection and reduction, can be converted into a single boost area that RT can be safely applied.[137,138]

Lymph node dissection

Lymph system is often the first place cancer spreads. Lymph node procedures include:

Sentinel lymph node biopsy: is a minimally invasive procedure used to assess the stage of disease in breast cancer patients. SLB is characterized by shorter operation and hospitalization times and lower post-operative morbidity. The removal of 1–3 sentinel lymph nodes is recommended.[139]

Axillary lymph node dissection: it is recommended to remove at least ten axillary lymph nodes.[140] This standard operation is often accompanied by prolonged lymphedema, hand function and sensory disturbances.

One of the major technical advances in breast surgery was the introduction of sentinel lymph node biopsy (SLNB) to replace the conventional axillary node dissection described by Guliano et al. in 1994.[141] Since Halsted first described radical mastectomy, axillary lymph node dissection (ALND) has been accepted as a means to assess nodal burden while providing regional disease control. However, given the significant morbidity of this surgery including risk of lymphedema, which occurs in about 2–56% of patients, and injury to major neurovascular structures like the thoracodorsal and long thoracic nerves, efforts were made to adopt an approach that was as effective, but less morbid.[142] In the mid-1990s, Giuliano and colleagues showed that the sentinel lymph node biopsy (SLNB) was effective at staging the clinically node negative axilla while limiting the morbidity of the more extensive axillary lymph node dissection.[141]

At present, SLNB is the standard of care for axillary staging in clinically node-negative patients. When SLNB is performed, and axillary lymph nodes are found to be negative, multiple studies have shown that no further surgery is needed.[141,143] If SLNB is positive, standard of care was to proceed with axillary lymph node dissection (ALND). Nowadays, new clinical studies showed that ALND can be safely omitted. This included the Z0011 trial, which showed that patients with T1-T2 invasive primary breast cancer with clinically negative axilla, 1 or 2 sentinel lymph nodes containing metastases, and who had breast-conserving surgery followed by whole-breast irradiation, had noninferior overall survival outcomes if ALND was omitted.[144]

In patients who did receive neoadjuvant chemotherapy, ACOSOGZ1071 showed that SLNB can be safely performed in cN1 patients, as long as two or more SLNs are examined, as this practice keeps the false negative rate to <10%. Of note, further analysis of this trial showed that there was improved sentinel node identification when using both blue dye and radioactive colloid (93.8%), compared to either blue dye alone (78.6%) or radioactive colloid alone (91.4%).[145]

Mastectomy

Mastectomy may be necessary for women who have had radiation to be affected side or for women with a relatively small breast in the setting of a large primary breast cancer, extensive calcifications, or multicentric disease. For women with a large primary breast cancer without extensive associated malignant calcifications, neoadjuvant chemotherapy may downstage the primary cancer and make breast conservation possible.

Types of mastectomy procedures include:

***Halsted mastectomy* –** removal of the whole breast, all of the axillary lymph nodes, and the chest wall muscles (m. pectoral major, m pectoralis minor). For many years, Halsted radical mastectomy was the type of breast cancer surgery used most often, but it is rarely used now.

***Modified radical mastectomy* –** removal of the whole breast tissue, fascia m. pectoralis major and underarm lymph nodes**.**

***Simple mastectomy* –** removal of the whole breast tissue and fascia m. pectoralis major.

***Conservative mastectomy* –** skin-sparing mastectomy (SSM), nipple-sparing mastectomy (NSM).

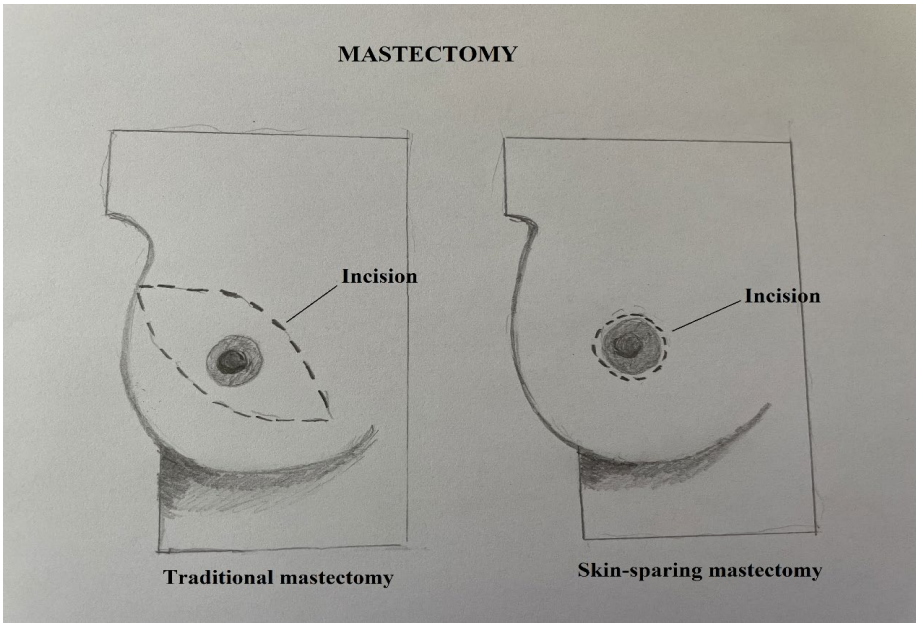

Fig. 3. Mastectomy types.

Skin-sparing mastectomy

Toth and Lappert first coined the term skin-sparing mastectomy (SSM) in 1991.[146] Instead of removing a large ellipse of skin, the SSM procedure removes the breast while preserving the skin envelope. The skin incision includes the nipple-areola complex (NAC) and should be amenable for axillary

dissection. This technique allows better breast shape after reconstruction, reduces the area of skin necessary on myocutaneous flaps, and reduces the need for contralateral breast surgery to achieve symmetry. SSM has become increasingly popular by facilitating immediate breast reconstruction.[147]

SSM's skin incision is more limited compared with NSM or simple mastectomy and typically involves a circular incision at the areola border, thereby excising the NAC. Skin flaps are created with excision of the underlying breast tissue, and skin flap viability is important to facilitate breast reconstruction. Preservation of the skin envelope facilitates preservation of the inframammary fold and enhanced overall breast shape. Furthermore, the circular scar at the areolar border ultimately becomes more hidden in the future with nipple reconstruction or nipple tattooing. The incision can allow access to the axilla for lymph node biopsy or dissection. At times the incision may require extension to facilitate exposure to the axilla. Complications of SSM include infection, hematoma, and skin flap necrosis. Risk factors for skin flap necrosis include smoking, previous or adjuvant breast irradiation, diabetes, and high BMI.[148]

Indications for SSM include multicentric disease; invasive carcinoma associated with an extensive intraductal component; extensive ductal carcinoma in situ (DCIS) not amenable to breast conservation; invasive disease not amenable to breast conservation because of size; tumor that extends to and involves the NAC; breast cancer prevention in high-risk patients; or women with breast cancer or DCIS who are ineligible for radiation therapy.[149] Furthermore, if nipple preservation cannot be performed because of breast ptosis, large breast size, then SSM offers a viable option for mastectomy in these patients. Skin involvement with tumor that cannot be resected with small extension of the SSM incision would be a contraindication. Other considerations and possible contraindications include previous breast or chest irradiation, adjuvant radiation, smoking, high body mass index (BMI), and delayed reconstruction.[150]

Nipple-sparing mastectomy

The first report of nipple-sparing mastectomy (NSM) came from Hinton et al. in 1990, who stated that NSM achieved comparable results as radical mastectomy.[151] However, widespread acceptance of NSM by surgeons was prolonged because of initial concerns regarding local recurrence and procedure complications.

An NSM involves the removal of the entirety of the breast tissue, including ductal tissue at the NAC, but with preservation of the nipple-areolar

dermal layer. Therefore, the skin envelope of the breast is left intact and facilitates breast reconstruction. Incisions for NSM vary among surgical practices but include inferolateral, radial extension, inframammary fold, and "omega" incisions. Inframammary or inferolateral incisions are frequently approximately 10 cm in length but can be less to facilitate adequate exposure. Breast glandular tissue is dissected away from subcutaneous fat, attempting to preserve the dermal and sub-dermal vascular arcades. The NAC is elevated in a superficial plane via sharp dissection, avoiding thermal damage from electrocautery. The nipple is then everted and the retro-areolar tissue is transected and sent for frozen pathology. If intra-operative pathology reports are positive for malignancy, the nipple areolar complex is excised. Following removal of remaining breast tissue, immediate or delayed reconstruction is possible depending on confidence in mastectomy flap viability and NAC vascularity.

The NCCN guidelines suggest that NSM is oncologically safe provided the following indications are respected: early stage, biologically favorable, invasive breast cancer or DCIS at least 2 cm from the nipple, imaging findings indicating no nipple involvement, nipple margin assessed and found to be clear, no nipple discharge and no Paget's disease. However, with extension of eligibility criteria for NSM for patients, NSMs have increased in popularity significantly in recent years.[152]

Contraindications of NSM include clinical or imaging evidence of tumor or disease involvement of the NAC, locally advanced tumors with skin involvement, and inflammatory breast cancer. Additional concerns and possible contraindications include active smokers, uncontrolled diabetes, or other immunosuppressive therapy that could complicate wound healing.[153] However, many women without nipple involvement with disease are eligible for this procedure. Women who have axillary involvement with invasive disease have a history of breast radiation or who will require postoperative radiation are still candidates for nipple preservation. Women who initially present with stage II or III breast cancer who undergo NAC with a good response are increasingly eligible for NSM. There is no specific tumor size that is a contraindication. Furthermore, previous requirements of a certain distance from tumor to nipple are no longer relevant. However, obtainment of a negative tumor margin at the nipple remains key.[154]

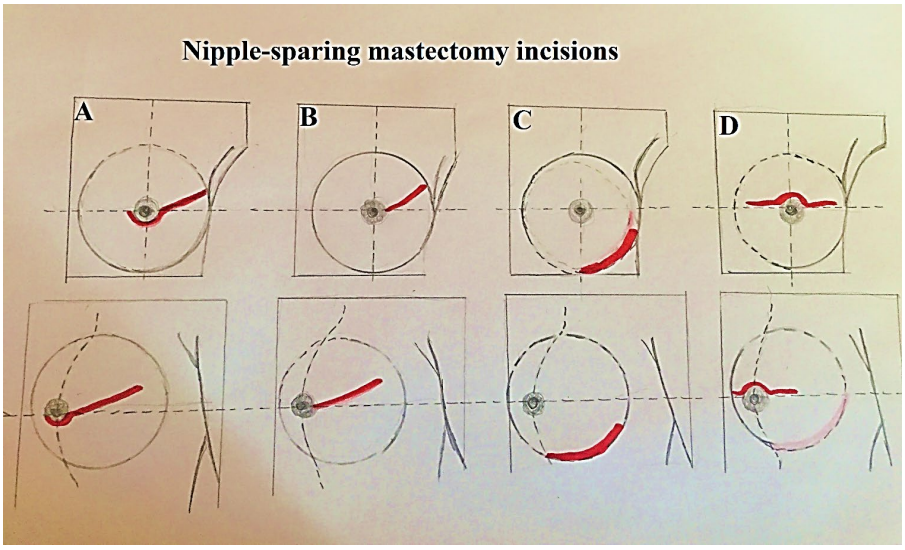

Fig. 4. Nipple-sparing mastectomy incision types: (A) inferolater, (B) radial, (C) inframammary fold (D) omega.

Reconstructive breast surgery

Breast reconstruction has seen an increase by 75% between 2000 and 2020, with 137,808 breast reconstruction procedures performed in 2020.[7] The goal of breast reconstruction is to recreate a breast mound to restore form and psychosocial function. Considerable advances have been made in breast reconstruction where the principles of both reconstructive and cosmetic surgery have merged with the goal of optimizing patient outcomes and minimizing the effects of a mastectomy. Improved knowledge of breast anatomy and its circulation as well as advances in mastectomy and reconstruction technique have enhanced our ability to preserve the entire breast skin envelope and all of the breast subunits including the nipple areola complex without sacrificing oncologic principles.[155]

Autologous reconstruction

The first reported case of autologous breast reconstruction was by Verneuil in 1887 who used a pedicle-based off the opposite breast.[156] Nowadays, a variety of flaps from various donor sites have been described that have provided women with excellent outcomes and a high quality of life. There are a variety of donor sites for autologous reconstruction; however, the most commonly utilized are:

Latissimus dorsi (LD) musculocutaneous flap – was first described by Tassini in 1906, but the technique did not gain popularity in breast reconstruction until the 1970s.[157] Unlike most autologous reconstructions, the latissimus is often used in combination with underlying prostetic implant and involves recruitment of adjacent tissue without microvascular transfer. The latissimus myocutaneus flap can be used in both the delayed or immediate reconstruction, with impalnts or expanders. LD flaps are viable options for patients who have undergone radiotherapy, who are not candidates for abdominal flap-based reconstruction. LD flaps can be used for chest wall coverage or as salvage therapy after a previous breast reconstruction has failed. The most common complication in latissimus autologous breast reconstruction is seroma formation.[158]

Transverse Rectus Abdominis Musculocutaneous (TRAM) – is the one of the most common method of autologous breast reconstruction. TRAM flaps can be used as a pedicled or free flap. The abdomen as a tissue source was first described by Holmstroem, who reported his experience with the free transverse rectus abdominis musculocutaneous (TRAM) flap in 1979.[159] Interestingly, it was not until Hartrampf et al. described the pedicled TRAM flap in 1982 that the abdomen became the preferred donor site for autologous breast reconstruction.[160] Advantages of the TRAM flap are that it accomplishes reconstruction with autogenous tissue, leaves an acceptable donor scar and serves as a simultaneous abdominoplasty. Disadvantages are a high tissue-to-blood supply ratio, protracted recovery with abdominal discomfort, potential for hernia from weakness from the abdominal wall.[161]

Deep Inferior Epigastric Perforator (DIEP) **–** first described in 1989 by Koshima and Soeda,[162] the DIEP flap was popularized for use in breast reconstruction by Allen and Treece.[163] It has since become the gold standard in autologous reconstruction. The DIEP flap allows for the ease of transfer of skin and fat from the abdomen for the reconstruction of a new breast without the sacrifice of rectus muscle or fascia. The ideal patient is a non-obese, non-smoker, with an adequate lower abdominal pannus. DIEP flap offers the same advantages as the TRAM flap, but the donor site has few complication by preserving rectus muscle. The hernia rates for DIEP flaps (0–3.6%) are lower than for either free TRAM (3–10%) or pedicled TRAM flaps (1–15.6%). The main complications are partial or total flap loss, and fat necrosis of flap.[164,165]

Superficial inferior epigastric artery flaps (SIEA) – is an axial

adipocutaneous flap based on the superficial inferior epigastric vessels and was first described in 1971 by Antia and Buch for the repair of a soft tissue defect of the face.[166] Robert Allen Sr reported the first use of the SIEA flap for partial and total breast reconstruction. The SIEA flap has the same indications and contraindication as the DIEP flap. The major disadvantages of the SIEA flap are inconsistent vascular pedicle anatomy and small diameter of the vascular pedicle for the free flap transfer of the whole abdominal tissue.[167]

Thoracodorsal artery perforator flaps (TDAP) – is one of the relatively new technique in breast reconstruction. This pedicled flap retains the benefits of perforator flaps as regards minimal donor site morbidity without the need for microvascular anastomosis. It is raised as a fasciocutaneous flap based on a medial or lateral branch of the thoracodorsal arteries, drained by two venae comitantes.[168]

Inferior and Superior gluteal artery perforator flaps (IGAP, SGAP) – the gluteal region was first used in breast reconstruction by Orticochea in 1973.[169] With the popularization of perforator flap surgery, and refinements in technique for flap harvest to spare the sacrifice of gluteus maximus muscle, both the superior gluteal artery perforator (SGAP) flap and the inferior gluteal artery perforator (IGAP) flap were developed. The SGAP flap was initially described by Allen and Tucker in 1995 for breast reconstruction.[170] The superior gluteal artery arises from the internal iliac artery and exits the pelvis superior to the piriformis muscle. The inferior gluteal artery is a terminal branch of the internal iliac artery. Typically the length of the IGAP pedicle is longer than that of the SGAP. This option have been developed especially for patients in whom the abdominal tissue is not available or sufficient. The selection between a superior gluteal artery perforator (SGAP) and an inferior gluteal artery perforator (IGAP) flap should be based on patient's individual characteristic including the distribution of gluteal fat tissue and the preference of the donor site scar. The main disadvantage of the free GAP flap, especially the IGAP flap, is the tedious dissection of the perforator.[171] Care should be taken to check the pulsation of the perforator frequently during dissection to ensure that it remains intact.

Transverse Upper Gracillis (TUG) – in 2002, Peek et al described the use of a free longitudinal gracilis perforator flap in the breast reconstruction.[172] The TUG is perfused by a branch of the medial circumflex artery and its venae that reliably perfuse the gracilis muscle and the ipsilateral medial upper thigh skin and fat. The ideal patients are women with small to moderate breast size (only

250–400 cc per flap) and excess adiposity in their medial thighs. The main disadvantages of this technique are relatively short pedicle, reported between 5–7 cm, excessive tension on the skin may result in wound dehiscence and scar migration with reported rates as high as 27% and 78%. One potential complication that deserves special attention is risk for lower extremity lymphedema.[173]

Profunda Artery Perforator flaps (PAP) – the first profunda artery perforator flap was described by Allen et al. for autologous breast reconstruction.[174] The flap initially was introduced in 1980 as the pedicled posterior thigh myocutaneous flap by Hurwitz and Walton. The PAP flap offers several advantages including an inconspicuous donor site scar, large vessels with consistent anatomy that match up well with the internal mammary vessels, a long pedicle, and a muscle-sparing alternative to the gracilis-based flaps. It is based on perforating arteries off the profunda femoris vessel that course through the adductor magnus (AM) muscle to supply the skin and fat of the proximal posterior thigh. The main disadvantages of this technique are that as the incision lies just inferior to the gluteal crease, some patients may find this painful while sitting. Additionally, the width of the skin paddle may be limited due to the transverse orientation of the scar. Finally, the posterior cutaneous nerve of the thigh may be sacrificed during dissection that alters sensation to the posterior thigh.[175]

Implant-based breast reconstruction

Early attempts at reconstruction with autologous techniques were frequently unsuccessful, not reproducible, or were associated with significant donor-site morbidity. As such, concurrent with the growth in autologous techniques, the development of prosthetic and synthetic reconstructive options became sought after, and growth in this field became considerable. Robert Gersuny was the first to describe the paraffin injection as a breast filler in 1889.[176] Anticipating success, surgeons quickly began experimenting with other injectable, such as paraffin, vegetable oils, lanolin, silicone, beeswax, petroleum jelly and etc.[177] However, results were short-lived as reports of "paraffinomas" and other serious complications such as pulmonary embolism, skin necrosis, fistulas began to surface in 1911, leading to subsequent black-listing by the U.S. Food and Drug Administration.[178]

The first attempt at breast reconstruction with an implant was performed by Vincent Czerny in 1895 with implantation of a lipoma to reconstruct a lumpectomy defect.[179] The introduction of silicone implants by Cronin and

Gerow, who developed these prostheses in 1961 and used them clinically from 1962, brought about a revolution in the field of the breast reconstruction.[180] The earliest prosthetic breast reconstruction were carried out as one-stage reconstructions, this technique lost it's popularity in the early 1980s as Chedomir Radovan introduced the tissue expander, offering new possibilities for both immediate and delayed breast reconstructions.[181] Today, tissue expanders have an important role in breast reconstruction and come in various textures, shapes, and sizes to cater to the patient.

Nowadays, implant-based breast reconstruction (IBBR) remains the most common reconstructive approach.[182] This type of reconstruction is considered safe, confer psychosocial benefits, results better aesthetic results and reliable; furthermore, it can be performed in women with a wide variety of comorbid conditions.[183] One-stage immediate breast reconstruction (IBR) is a method to reconstruct a definitive breast mound at the time of oncologic resection without the need for tissue expansion or tissue expander/implant exchange.

Preoperative and intraoperative evaluations commonly guide surgeons' decision to perform IBBR.

Prepectoral implant-based breast reconstruction

Prepectoral IBBR involves filling the space between the pectoralis major muscle and mastectomy skin flap. First described in the 1970s, the prepectoral IBBR technique was associated with unacceptably high rate of complications, including infection, implant exposure, capsular contracture.[13] To decrease the risk of complication, the procedure has been modified to position the implant subpectorally. The subpectoral IBBR was a reliable and safe alternative. In the past few years, prepectoral IBBR technique have become "re-popularized" as a less-invasive alternative to subpectoral breast reconstruction. Modern iterations have demonstrated improved outcomes for several reasons, including a better clinical understanding of mastectomy flap perfusion, new reconstructive technique as well as the introduction of new generation implants, which are linked to decreased capsular contracture and have allowed safe and efficacious prepectoral implant placement.[15,16,184]

Initially, prepectoral breast reconstruction was reported in small series that employed both immediate implant and two-stage expander reconstructions using a variety of ADMs and meshes with low complications rates.[185] While surgical procedures vary, the majority of techniques utilize some form of ADM or mesh to control implant position, tailor the implant pocket and mitigate excessive pressure from implants on inferior mastectomy flaps. Most commonly this involves either an anterior sling or a complete

implant wrap. Prepectoral implant reconstruction without ADM or mesh has also been reported with low complications rates.[186,187]

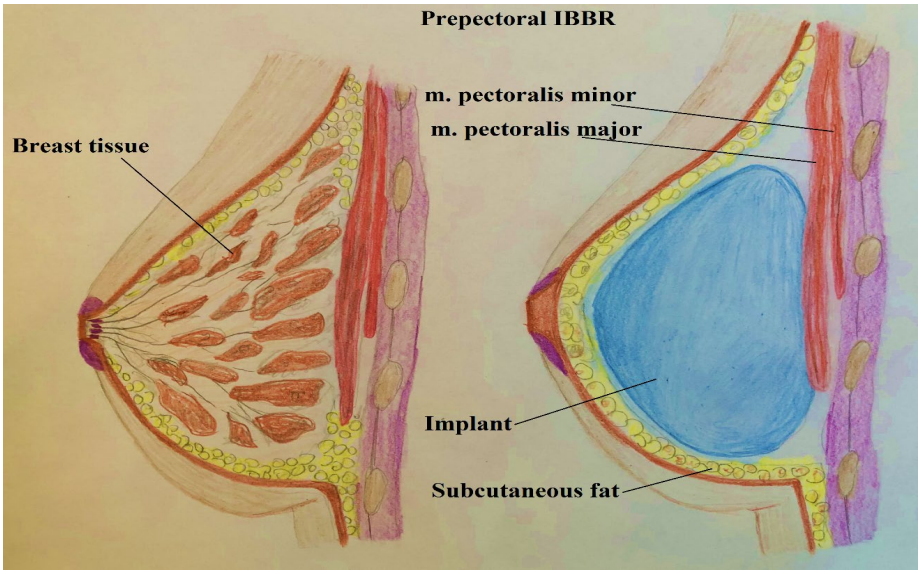

Fig. 5. Prepectoral implant-based breast reconstruction

Subpectoral implant-based breast reconstruction

Subpectoral IBBR involves filling the space between the pectoralis major muscle and chest wall. The subsequent shift from prepectoral to subpectoral plane in the 1970s offered and increased coverage of the implant and the effective prevention of unacceptably high rate of complications, including infection, implant exposure and skin necrosis[182]. Newer subpectoral IBBR operative techniques led to initially pleasing results.

Nowadays, there are several subpectroal IBBR techniques. Total subpectoral IBBR techniques, with implant placement under the pectoralis muscle and serratus muscle and/or fascia have traditionally been perceived to be the "safest" with regards to rates of postoperative complications such as seroma, infection and implant loss.[188] However, limited expansion of the inferior pole to mimic the natural curvature of the breast as well as additional morbidity with serratus elevation led to the introduction of dual-plane procedures.[188]

During the "dual-plane" subpectroal IBBR technique, the pocket is created by releasing the muscle and the implant is covered inferiorly with the advancement of the lower pole skin flap. A variety of options for dual-plane implant placement currently exist, most commonly utilizing an adjunctive

scaffold, such as ADM or mesh, to define the inframammary fold, provide inferolateral implant support and contour, as well as preventing window shading of the pectoralis muscle.[189]

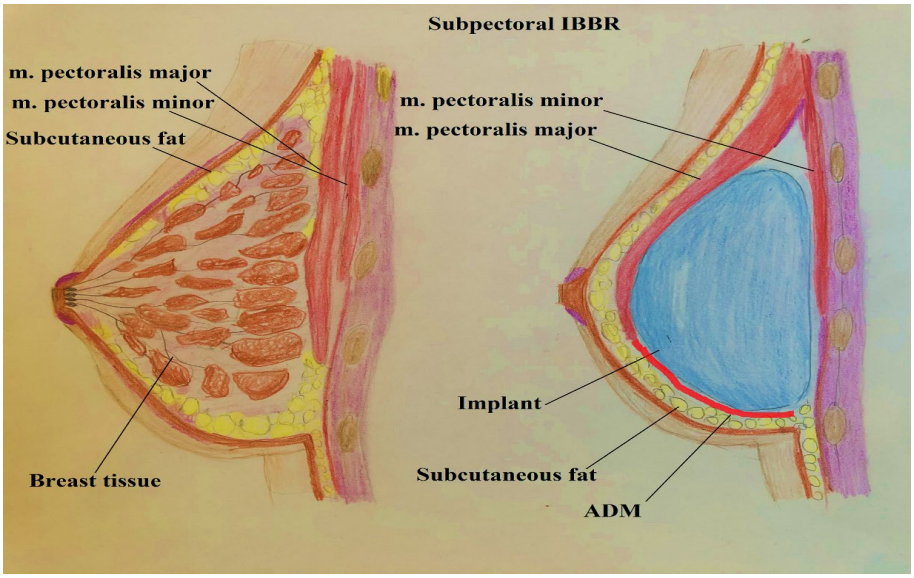

Fig. 6. Subpectoral implant-based breast reconstruction.

3.6.2. Radiotherapy

Radiotherapy has a significant role in local disease control. It's typically provided after surgery and/or chemotherapy. It is performed to ensure that all of the cancerous cells remain destroyed, minimizing the possibility of breast cancer recurrence. Further, radiation therapy is favorable in the case of metastatic or unrespectable breast cancer. The risk of cancer recurrence decreases by about 50% at 10 years, and the risk of breast cancer death reduces by almost 20% at 15 years when radiation therapy follows BCS.[190] Choice of the type of radiation therapy depends on previous type of surgery or specific clinical situation; most common techniques include breast radiotherapy (always applied after BC), chest-wall radiotherapy (usually after mastectomy), and 'breast boost' (a boost of high-dose radiotherapy to the place of tumor bed as a complement of breast radiotherapy after BCS).[191]

Patients generally treated with postmastectomy radiation include those who have 4 or more positive axillary nodes, T3 tumor size, positive resection margins, and locally advanced or inflammatory breast cancer. Radiation is also recommended for patients who have 1–3 positive nodes and other risk factors

for local–regional recurrence, such as lymphovascular invasion, young age, high-grade tumors, or hormone receptor–negative breast cancer.[192]

The radiation may adversely affect the cosmetic outcome of the immediate reconstruction and there is some concern that reconstructed breast may result in technical difficulties in the delivery of radiation therapy. If breast reconstruction is delayed until after radiation, however, the mastectomy skins is often compromised, and the shape of the native breast skin envelope lost. Delayed breast reconstruction with implants following postmastectomy radiation can result in wound healing problems, capsular contracture with subsequent implant displacement, and painful constriction against the chest wall.[15,193] To evaluate capsular contracture after IBBR we can use Baker classification.

Table 2. Bakker classification

Grade	Description
BAKER I	Capsular contracture is asymptomatic. The breast is soft and natural. Implant is not palpable
BAKER II	Capsular contracture presents with minor cosmetic symptoms. Breast is solid. Implant is palpable, but not visible
BAKER III	Capsular contracture presents with obvious cosmetic symptoms. Breast is hardened. Implant is palpable and visible
BAKER IV	Capsular contracture causes the breast to become hard and deformed and painful. Implant is palpable and clearly visible

3.6.3. Chemotherapy

Chemotherapy is a systemic treatment of BC and might be either neoadjuvant or adjuvant. Choosing the most appropriate one is individualized according to the characteristics of the breast tumor; chemotherapy might also be used in the secondary breast cancer. Neo-adjuvant chemotherapy (NAC), initially indicated to downstage tumors to achieve the option of breast conserving surgery, has lately become common practice in the primary treatment of breast cancer. Its effects are equal to adjuvant chemotherapy and can therefore be used in all patients with an indication for postoperative chemotherapy. Patients with large tumors and tumors with a poor prognosis such as HER2-positive and triple-negative breast cancers (TNBC) are most appropriate candidates for NAC.[194] The main advantage of NAC is the opportunity to assess response in predicting pathological complete response (pCR).[195] pCR is a strong prognostic marker for improved disease and overall

survival and it is used as a surrogate clinical endpoint for long term outcome.[196] Therefore, NAC has become an important treatment strategy to reliably identify women at both higher and low risk. In general, it is difficult to predict pCR in the absence of invasive surgical techniques, as it depends on several factors such as biological subtype, the used chemotherapy regimen and anatomic stage.

Currently, treatment includes a simultaneous application of schemes 2–3 of the following drugs—carboplatin, cyclophosphamide, 5-fluorouracil/capecitabine, taxanes (paclitaxel, docetaxel), and anthracyclines (doxorubicin, epirubicin).[197,198] The choice of the proper drug is of major importance since different molecular breast cancer subtypes respond differently to preoperative chemotherapy. The aim of adjuvant chemotherapy is to prolong survival by treating latent micrometastases. BC patients with axillary lymph node metastases or high risk for recurrence should receive chemotherapy such as antracycline containing regimen or TC regimen (docetaxel and cyclophosphamide) or AC followed by taxane (docetaxel or paclitaxel) regiment as adjuvant chemotherapy.[199] Generally, both neoadjuvant and adjuvant chemotherapy are not a contraindication to IBBR and does not increase the complication rate or affect cosmetic outcomes.

3.6.4. Hormone therapy

Hormone therapy might be used either as a neoadjuvant or adjuvant therapy in patients with Luminal–molecular subtype of BC. Hormone therapy aims to lower the estrogen levels or prevents breast cancer cells to be stimulated by estrogen. Drugs that block ERs include selective estrogen receptor modulators (SERMs) (tamoxifen) and selective estrogen receptor degraders (SERDs) (fulvestrant) while treatments that aim to lower the estrogen levels include aromatase inhibitors (AIs) (letrozole, anastrazole, exemestane.[200,201] If there is concern about an increased risk of osteoporosis or aromatase inhibitor intolerance, tamoxifen can be prescribed. Until recently, tamoxifen was recommended for all premenopausal patients.[202]

Studies have shown that between 5 and 10 years of hormone therapy in HR+ breast cancers significantly improves survival. In premenopausal women, hormone therapy options are tamoxifen alone or a luteinizing hormone-releasing hormone analogue combined with tamoxifen or an aromatase inhibitor (AI).[203] Tamoxifen is a selective estrogen receptor modulator that is a partial ER agonist, blocking the activation of ER by estrogen in the breast but acting as an agonist on ER of the endometrium and

skeleton. Tamoxifen was first given to women with breast cancer in the early 1970s, and it has saved countless lives.[204] Recent studies in premenopausal women show that, compared with tamoxifen alone, a combination of luteinizing hormone-releasing hormone or oophorectomy and tamoxifen or AIs produces an even greater improvement in survival, although this comes with a greater incidence of adverse events.[205]

3.6.5. HER2-targeted therapy

The emergence of anti-HER2 therapies has led to significant improvements in prognosis and outcome for patients with HER2+ breast cancers. Anti-HER2 therapy might be used either as a neoadjuvant or adjuvant therapy. The major drugs include trastuzumab, pertuzumab, trastuzumab deruxtecan, lapatinib, and neratinib.

Trastuzumab, a recombinant humanized monoclonal antibody, targets an extracellular domain of HER2, preventing its dimerization with other HER receptors to halt cancer growth.[206] Pertuzumab, another monoclonal antibody, acts on a different extracellular domain of HER2 and halts dimerization particularly of HER2 with HER3, the most growth-promoting dimerization of the HER family of receptors.[207] Combinations of trastuzumab and pertuzumab with chemotherapy are more effective than either drug alone with chemotherapy.[208] Lapatinib is a dual tyrosine kinase inhibitor of both HER2 and HER1 (EGFR) that was approved by the US FDA for use in combination with the chemotherapy drug capecitabine.[209] Lapatinib can also be given together with trastuzumab , and this combination provides a more complete blockade of HER signaling than either alone.[210] Neratinib, a tyrosine kinase inhibitor, is a pan-HER inhibitor, licensed and currently recommended by the UK's National Institute for Health and Care Excellence in the technology appraisal guidance TA612 for use as extended adjuvant treatment following trastuzumab in patients with ER+/HER2+ breast cancer.[211] Trastuzumab emtansine (T-DM1), also known as ado-trastuzumab emtansine, is an antibody–drug conjugate in which trastuzumab is linked to the cytotoxic agent DM1. T-DM1 was approved by the FDA in 2013 for the treatment of HER2+ metastatic breast cancer and in 2019 for patients with HER2+ early breast cancer who have residual disease following neoadjuvant trastuzumab and a taxane.[212] Trastuzumab deruxtecan is an antibody–drug combination comprising trastuzumab and a cytotoxic topoisomerase I inhibitor and has broader antitumor activity than T-DM1, including efficacy against low HER2-expressing tumors.[213] There is a series of other anti-HER2 drugs in development and early clinical trials.

4. MATERIAL AND METHODS

4.1. Systematic review and meta-analysis of prepectoral vs subpectoral IBBR

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards[214] and the a priori protocol was registered in the PROSPERO database (CRD42022312094).

Literature search and search criteria

The systematic review was conducted using PubMed and the Cochrane Library for studies published between January 1, 2011, and December 31, 2021. The inclusion criteria were as follows: (1) reporting follow-up for at least 1 year; (2) the article described implant-based breast reconstructions with implant places either prepectorally or subpectorally; (3) publication was from January 1, 2011, to December 31, 2021; (4) the full text was available; (5) reporting of relevant outcomes, i.e. postoperative complications; and (6) studies published in English.

The exclusion criteria were as follows: (1) studies evaluating < 60 patients; (2) abstracts; (3) patients undergoing other breast reconstruction operations; and (4) insufficient data or not meeting our inclusion criteria.

Data extraction

Data for the analysis of prepectoral implant-based breast reconstruction (IBBR) versus subpectoral implant-based breast reconstruction (IBBR) were extracted independently by two reviewers (E.O. and F.F.); disagreements were resolved through discussion. The data extracted from each study, including year of publication, country of origin, patient demographics such as gender, mean age, follow-up time, operative details, type of breast reconstruction, and main outcomes, were collated using a standardized form. Attempts were made to contact the corresponding author to clarify missing data in any of the included studies.

Risk-of-Bias and Publication Bias Assessment

We assessed for risk of bias using the Cochrane Risk of Bias In Nonrandomized studies of Interventions (ROBINS-I) tool.[215] The assessment

was recorded as low, moderate, serious, critical risk of bias or no information. The degree of bias was measured using the Egger bias test.

4.2. Immediate prepectoral IBBR technique

Ethics

The ethics committee of the Medical University of Vienna approved this study (no. 1597/2021). All study-related procedures were performed in accordance with the Declaration of Helsinki.

Patients and study design

This retrospective design study included all BC patients who underwent prepectoral implant based-breast reconstruction (IBBR) after nipple sparing mastectomy (NSM) performed at the Department of General surgery, Medical University of Vienna between March of 2017 and November of 2021. Inclusion criteria were as follows: patients were 18-years-old or older, patients received only inverted-T or IMF operation technique. The exclusion criteria for the study were patients who received other mastectomy technique or over implant based-breast reconstruction, pregnancy, and contraindication for operative treatment. After exclusion of 36 patients, who met at least one exclusion criteria, 98 patients were included in the study and were divided into 2 groups regarding the surgical method (inverted-T vs. IMF technique). An inverted-T technique was preferable for the ptotic breasts, whereas an IMF technique was preferable for the nonptotic breasts. The results of the two groups were compared.

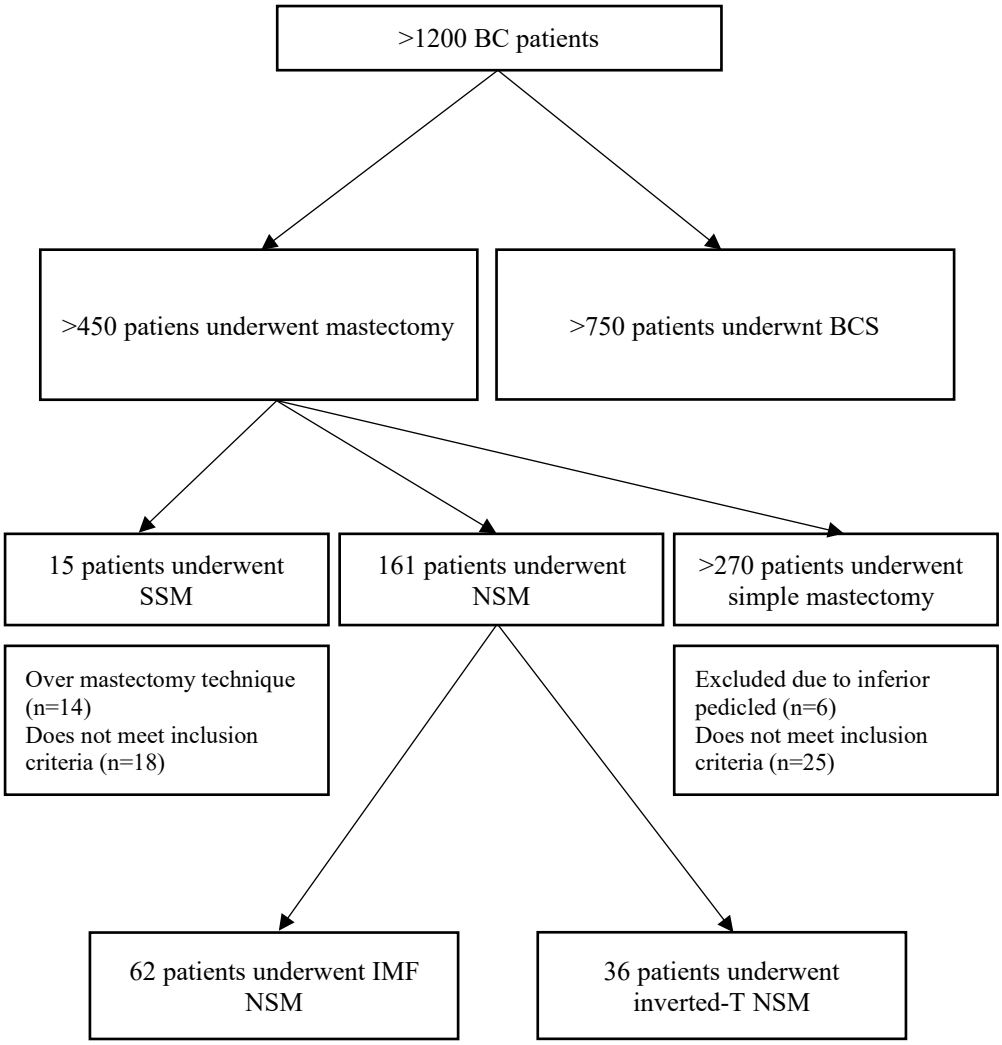

Fig. 7. Flowchart of the study.

Inverted-T technique

This group included BC patients who underwent prepectoral implant-based breast reconstruction after nipple sparing mastectomy (NSM) between March of 2017 and November of 2021. 40 patients were included to this group. After the surgery, 33 Breast-Q questionnaires were completely filled in and analyzed. Mean age of patients where 46.14 ± 11.15 years (from 34 to 68 years). Inclusion criteria were as follows: patients were 18-years-old or older, patients received only inverted-T incision. The exclusion criteria for the study

were patients who received other mastectomy technique, over implant based-breast reconstruction or autologous reconstruction, pregnancy, and contraindication for operative treatment.

IMF technique

This group included BC patients who underwent prepectoral implant-based breast reconstruction after nipple sparing mastectomy (NSM) between September of 2017 and May of 2021. 62 patients were included, to the final analyses. After the surgery, 53 Breast-Q questionnaires were analyzed (85% response rate), of which 51 (82% response rate) were completely filled in. Mean age of patients where 45.17 ± 10.30 (from 41 to 78 years). Inclusion criteria were as follows: patients were 18-years-old or older, patients received only IMF technique. The exclusion criteria for the study were patients who received other mastectomy incisions, over implant based-breast reconstruction or autologous reconstruction, pregnancy, and contraindication for operative treatment.

Patient's characteristics and clinical data

All patient characterics were obtained from their medical records and prospectively collected database. Demographic and clinicopathological characteristics (age, current smoking, radiotherapy, and chemotherapy exposure) and oncological characteristics (pathology of tumor, BRCA carrier status, tumor stage, axillary nodal stage, metastasis stage, estrogen receptor status, progesterone receptor status, and human epidermal growth factor receptor 2 status) were recorded.

Operative characteristics including prophylactic or therapeutic indication, single- or two-stage approach, implant location, NSMs operation technique (inverted-T vs. IMF), axillary management (axillary lymph node dissection or sentinel node biopsies), grade of breast ptosis (evaluated according to the Regnault classification,[127] and follow-up time were recorded.

Post-reconstruction complication rates were subsequently evaluated. The outcomes of interest were any complications including breast infection, seroma, hematoma, skin and NAC necrosis, capsular contracture (graded using the four-grade Baker scale;[216] only II, III, and IV Baker grading scale were considered in the study), implant loss (removal of implant was classified as implant loss), local and distant recurrence. Postoperative complications were defined as any deviations from a normal postoperative course during the hospitalization time. To assess the impact of postoperative radiation on various

complication rates, analyses were performed, separating patients into post-mastectomy radiation therapy (PMRT) and non-PMRT groups.

Follow-up schedule

Patients who underwent immediate prepectoral IBBR were scheduled for follow-up visits annually every year.

The minimum follow-up was ranged from 12 to 60 months. Breast mammograms, chest and abdominal CT, and bone density tests were conducted annually in both groups. If patients underwent follow up visits outside of the original study institutions, data was still obtained directly from the patient or their physicians by phone review. Photographs were taken also before surgery and at follow-up visits at 6, 12, 24, 36, 48 and 60 months postoperatively.

Quality of life evaluation

To assess patients' quality of life, they were asked prospectively to complete the Breast-Q questionnaire after breast reconstruction.[217] These domains were scored from 0 to 100, with a larger number indicating more satisfaction or better quality of life. The domains are also meant to function independently from each other, so domains that were not completed were not scored were excluded from analysis. BREAST-Q scores were collected on average 2 years after breast reconstruction. Change scores were calculated for each domain by calculating the difference between the two groups. Patients completed the following Breast-Q post-reconstruction subscales:

(1) Sexual well-being (***Supplementary Content 1***), which consists of an assessment of the following parameters: sexually attractive in your clothes, comfortable/at ease during sexual activity, confident sexually, satisfied with your sex-life, confident sexually about how your breast area looks when unclothed, sexually attractive when unclothed. Each of the following points is scored from 0 to 5. Where 1 – none of the time, 2 – a little of the time, 3 – some of the time, 4 – most of the time, 5 – all of the time. For each scale, item responses were summed and transformed into scores, ranging from 0 (worst) to 100 (best).

(2) Satisfaction with breast (***Supplementary Content 2***), which consists of an assessment of the following parameters: how you look in the mirror clothed, how comfortably your bras fit, being able to wear clothing that is more fitted,

how you look in the mirror unclothed. Each of the following points is scored from 0 to 4. Where 1 – very dissatisfied, 2 – somewhat dissatisfied, 3 – somewhat satisfied, and 4 – very satisfied. For each scale, item responses were summed and transformed into scores, ranging from 0 (worst) to 100 (best).

(3) Psychosocial well-being (***Supplementary Content 3***), which consists of an assessment of the following parameters: confident in a social settings, emotionally able to do the things that you want to do, emotionally healthy, of equal worth to other women, self-confident, feminine in your clothes, accepting of your body, normal, like other women, attractive. Each of the following points is scored from 0 to 5. Where 1 – none of the time, 2 – a little of the time, 3 – some of the time, 4 – most of the time, 5 – all of the time. For each scale, item responses were summed and transformed into scores, ranging from 0 (worst) to 100 (best).

(4) Physical well-being (***Supplementary Content 4***), which consists of an assessment of the following parameters: pain in the muscles of your chest, difficulty lifting or moving your arms, difficulty sleeping because of discomfort in your breast area, tightness in your breast area, nagging feeling in your breast area, tenderness in your breast area, sharp pains in your breast area, aching feeling in your breast area, throbbing feeling in your breast area. Each of the following points is scored from 1 to 3. Where 1 – none of the time, 2 – some of the time, 3 – all of the time. For each scale, item responses were summed and transformed into scores, ranging from 0 (worst) to 100 (best).

Clavien-Dindo classification

Complications were classified using the Clavien-Dindo classification (CDC) of surgical complications;[218] it is a simple and well-validated classification of surgical complications and allows an objective and reproducible approach for comprehensive surgical outcome assessment, which can help the evaluation and comparison of surgical outcomes among different surgeons, centers, and therapies. For the purposes of this study, CDC grades I and II were classified as minor complications, and CDC grades III and greater were classified as major complications; this included minor wound healing problems that only required dressing changes.

Surgical technique

Nipple-sparing mastectomy

IMF Technique

Preferable method for cup A-B sized breast, ptosis grade 0-I. We start the dissection with antibiotics regularly and then infiltrating 1% Xylocain (25ml in 500cc 0.9% saline) between the subcutaneous tissue and the breast to reduce skin damage.

Ordinarily, we used the inframammary fold (IMF) for the incision laterally from the medioclavicular line and leads up to 5 cm to medially along the IMF. If the inframammary fold has to be lowered this has to be included in the primary planning of the incision. After the incision, we searched the right plane, which is just above the fascia of scarpa. This fascia splits into two distinct parts: the anterior lamella, which becomes the superficial fascia between the subcutaneous tissue and breast parenchyma, and the posterior lamella, which grows to the pectoralis fascia. At the point where both fascia's divert we found the inframammary fold (IMF), which should not be destroyed in order to diminish implant malposition. Next, we dissected between skin and superficial lamella following the fascia. We stopped the preparation around 2 cm towards the nipple, dissected the fascia at this margin end, and followed it back again at the inner part down to the IMF. Finally, the resulting fascial flap covered the implant.

After this step, dissection was continued directly to the posterior lamella of the fascia at the pectoralis muscle. This reduces bleeding during second part of the dissection between skin and breast. The breast parenchyma was removed from the pectoralis muscle due to dissection between the posterior lamella and pectoralis muscle alongside the footprint of the breast. Subsequently, the breast tissue was detached from the skin. For this dissection between the subcutaneous skin and breast parenchyma, we used the scissors (cold dissection) to avoid thermal injury. We tracked the breast with two Kocher clamps, and then started sharp dissection. After finishing the dissection between the skin flap and breast parenchyma, retroareolar tissue sample was taken and examined by frozen section with marked margins. In cases of no atypical cells or cancer cells, the nipple can be spared. Finally, the remaining breast tissue was dissected.

Inverted-T Technique

Preferable method for cup C-D sized breast, ptosis grade II-III. The patients we marked preoperatively while standing for NSM through inverted-T incision with a new preplanned position for the NAC. After de-epithelialization, the skin was carefully lifted from the breast parenchyma. The NAC was harvested as a full-thickness skin graft and grafted to the new position, depending on the preoperative sternum-nipple distance and intraoperative findings. Regarding preparation, we performed the surgery with no differences from non-ptotic breasts.

Immediate prepectoral implant-based breast reconstruction

Upon completion of the mastectomy, we performed prepectoral direct-to-implant reconstruction. The plane of the mastectomy must be correct, between the superficial dermis fascia and Cooper ligaments. The pocket should fit the used implant size, which should be measured first by a ruler, than by a sizer. If a synthetic mesh was not used, the implant was inset into the prepared prepectoral pocket. If synthetic mesh was used (TiLOOP Bra Pocket), we sutured the mesh to the upper pole and the lateral pole and inserted the implant. The mesh was wrapped around the prosthesis at the medial and lower borders, and then we closed everything with 4/0 resorbable white color and 4/0 monifilamnet (Monocryl® or V-Lock®).

4.3. Statistical analysis

All statistical analyses were conducted using the statistical program IBM SPSS Version 24 (IMB Corp., Armonk, NY, USA) and STATA Version 16.0 (Stata Corporation, College Station, Texas). Clinical characteristics of two groups were compared to demonstrate adequate matching and described using descriptive statistics. Mean, median and standard deviation were calculated. Odds ratios (OR) and its associated 95% confidence interval (CI) were measured. Statistical heterogeneity was tested using Chi-square and inconsistency (I^2) statistics. I^2 value ranging from 0% to 100%, were used to quantify the effect of heterogeneity. I^2 value of greater than or equal to 40% represented significant heterogeneity and pooled odds ratios (OR) were estimated using a random-effect model (DerSimonian and Laird method).[219] When no statistical heterogeneity was observed (I^2 value of lower than 40%), a fixed effects model (Mantel-Haenszel method)[220] was used. Publication bias

was evaluated using Egger regression tests. $\chi 2$/Fisher's exact test were used to evaluate associations between categorical values and complications rates.

Numerical variables among the groups were analyzed and compared either with independent-samples t test or Mann-Whitney U test depending on the normality. To determine the independent effect of reconstruction technique (Inverted-T vs IMF) on the odds of capsular contracture for the patients who received PMRT, we constructed a multivariable logistic regression model. Kaplan-Meier method was used to estimate and additional pointwise 95% confidence intervals for several timepoints of interest. OS was assessed from the date of surgery to death from any cause. OS curves were estimated using the Kaplan-Meier method, and the long-rank test was used to assess the significance of differences in OS between subgroups. Odds ratios, 95% confidence intervals, and p values were calculated for each outcome. P value < 0.05 was considered to indicate statistical significance.

5. RESULTS

5.1. Systematic review and meta-analysis of prepectoral vs subpectoral IBBR

Study Screening

The study flow diagram is depicted in (Fig. 8). In total, 440 studies were initially identified; after duplicates were removed, the titles and abstracts of 428 studies were screened. Of these, 400 studies were excluded, and the full texts of the remaining 28 studies were obtained for further evaluation. After reading the full texts, 13 studies were excluded for various reasons, including incorrect comparisons, short follow-up time, and inappropriate numerical data necessary for statistical analysis. Ultimately, 15 studies were included in this meta-analysis.[218-232]

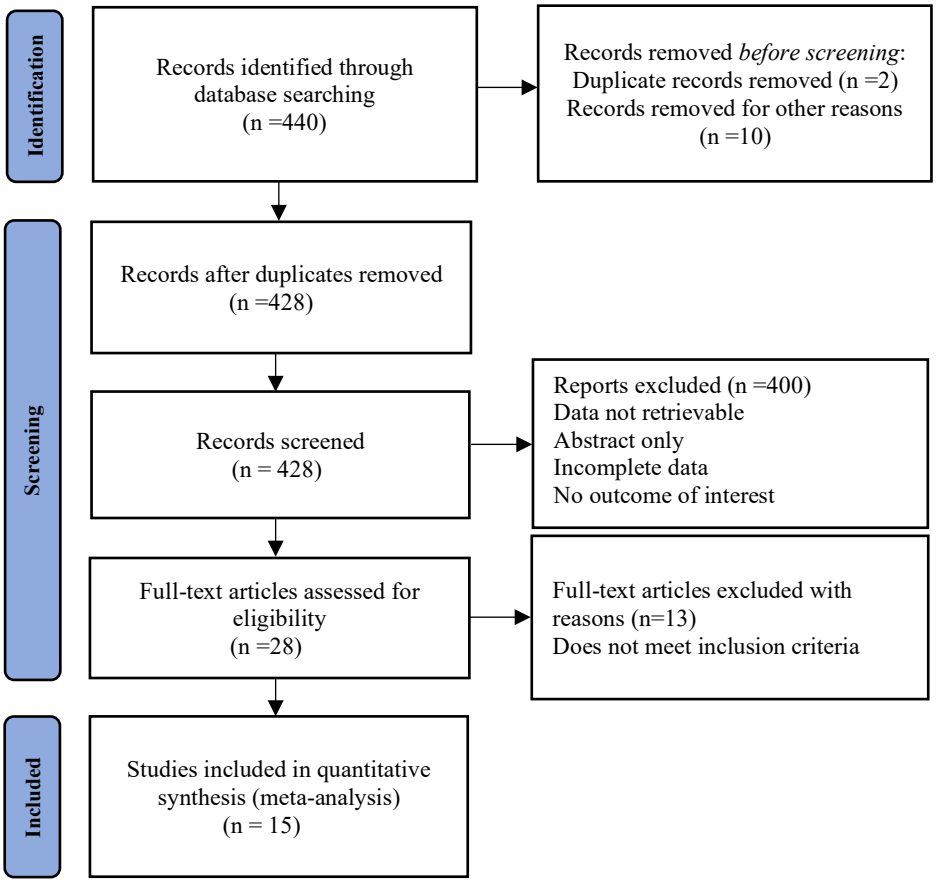

Fig. 8. Flow diagram of literature search and selection of included studies for meta-analysis[217]

Study Characteristics

Table 3. The characteristics of included studies for analysis of prepectoral IBBR versus subpectoral IBBR[221]

Author, Year, Country	Study type	Patients			BMI(kg/m^2)		Mean age		Outcomes	Mean Follow-up
		Cohort	SR	PP	SR	PP	SR	PP		
Nicholas J. Walker et al.[222] 2021, USA	R	195	103	92	27.8	30.2	55.5	53.0	Complication rate, quality of life	13
Oscar J. Manrique et al.[223] 2018, USA	R	169	69	100	26.3	25.3	34.2	35.3	Complication rate	17.7
Diego Ribuffo et al.[224] 2020, Italy	R	642	509	207	24.6	25.3	55.7	56.2	Complication rate	22.1
Jung Young Yang et al.[225] 2019, Korea	R	79	47	32	21.2	23.5	46.4	48.9	Complication rate	12
Mihir N. Chandarana et al.[226] 2018, UK	R	130	69	61	25.1	27.3	50	51	Complication rate	12
Oscar J. Manrique et al.[227] 2019, USA	R	85	42	33	24.9	25.8	47	54	Complication rate, quality of life	20.6
Fabinshy Thangarajah et al.[228] 2019, Germany	R	63	29	34	24.4	24.7	49.3	49.9	Complication rate, quality of life	18
Caroline A. King et al.[229] 2021, USA	R	405	202	203	23.7	24.0	45.9	46.5	Complication rate	24
Sarah J. Plachinski et al.[230] 2021, USA	R	186	103	83	28.1	26.1	49.9	47.8	Complication rate	18.5
Gianluca Franceschini et al.[231] 2021, Italy	R	177	95	82	24.7	23.9	44	47	Complication rate, quality of life, recurrence rate	18
Catherine J. Sinnott et al.[232] 2018, USA	R	374	100	274	25.2	29.0	46.9	52.4	Complication rate, recurrence rate	25.5
Kassandra P. Nealon et al.[233] 2020, USA	R	256	142	114	25.6	27.4	50.7	52.7	Complication rate, recurrence rate	24.4
Shayda J. Mirhaidari et al.[234] 2019, USA	R	129	67	62	26.4	27.2	48	54	Complication rate, recurrence rate	24
Leonardo Cattelani et al.[235] 2017, Italy	P	86	45	39	26.1	24.9	52.3	52.9	Complication rate, quality of life	12
Marco Bernini et al.[236] 2015, Italy	P	63	29	34	23	23	51	47	Complication rate, quality of life, recurrence rate	25

SR:subpectoral IBBR; PP: prepectoral IBBR; R: retrospective comparative study; P: prospective comparative study.

Characteristics of the studies, including sample size, operative technique, and outcomes, are provided in (*Table 3*). All 15 studies that reported clinical outcomes were observational studies. Eight studies were from the United States; four studies from Italy; one study from Korea; one study from United Kingdom; and one study from Germany. The sample size ranged from 63 to 642 patients. Fifteen studies included 3101 patients, where 1642 (52.9%) underwent subpectoral IBBR. The follow-up time ranged from 12 to 60 months. The mean follow-up interval was 19.12 months. The mean BMI was significantly higher in the prepectoral IBBR compared to the subpectoral IBBR (25.6 vs 23.4; P<.01). (*Table 3*).

Risk-of-Bias and publication bias assessment

Publication bias was not detected for any of the outcomes investigated in the meta-analysis comparing prepectoral and subpectoral IBBR. Publication bias analysis was not performed for animation deformity and recurrence rates due to shortage of study numbers. Bias in the selection of participants, bias in measurement classification of interventions, bias due to deviation from intended interventions, and bias in selection of the reported result were generally low (***Supplementary Content 5****).*

Overall complication

All fifteen studies reporting the overall complications were included in the meta-analysis. The overall complication rates for breasts undergoing prepectoral IBBR was 25.08% (366 of 1459) and subpectoral IBBR was 29.65% (487 of 1642). As shown in (Fig. 9A), no significant difference in overall complication rates between prepectoral and subpectoral IBBR was found, with pooled (odds ratio [OR], 0.83; 95% CI, 0.64-1.09; P=.19). The pooled analysis was performed using a random-effects model because moderate heterogeneity (P=.02, I2= 49%) among the studies was found.

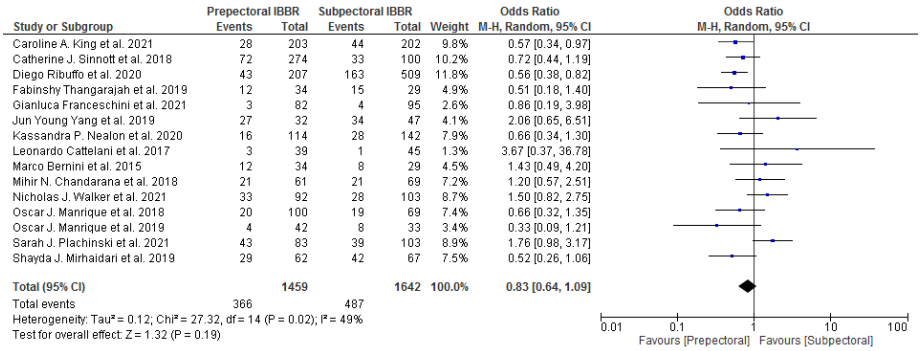

Fig. 9A. Forest plots comparing prepectoral vs subpectoral IBBR for overall complications[217]

Seroma

Twelve studies[222–228,230,232–234,236] in the meta-analysis reported seroma rates. As shown in (Fig. 9B), no significant difference in seroma rates between prepectoral and subpectoral IBBR was found, with pooled (OR, 1.21; 95% CI, 0.59-2.51; P=.60). The analysis was performed using a random-effect model, as substantial heterogeneity (P=.0007, I2=71%) among the studies was found.

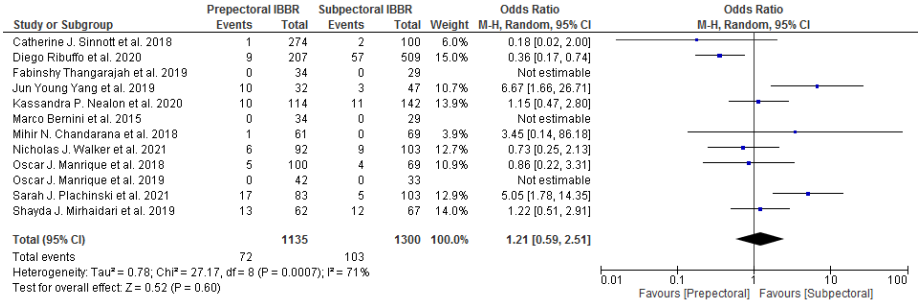

Fig. 9B. Forest plots comparing prepectoral vs subpectoral IBBR for seroma[217]

Hematoma

Thirteen studies[222–230,232–234,236] reporting data for hematoma rates were included in the meta-analysis. As shown in (*Fig. 9C*), no significant difference in hematoma rates between prepectoral and subpectoral IBBR was found, with pooled (OR, 0.76; 95% CI, 0.49-1.18; P=.22). The analysis was performed using a fixed-effect model, as minimal heterogeneity (P=.25, I2=20%) among the studies was found.

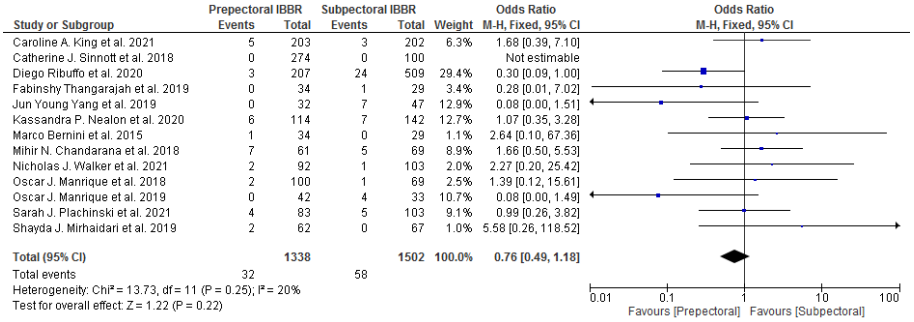

Fig. 9C. Forest plots comparing prepectoral vs subpectoral IBBR for hematoma[217]

Capsular Contracture

Teen studies[223–230,232,233,236] in the meta-analysis reported the capsular contracture rates. As shown in (*Fig. 10A*), our pooled analysis showed that subpectoral IBBR had significantly higher rates of capsular contracture compared to prepectoral IBBR, with pooled (OR, 0.54; 95% CI, 0.32-0.92; P=.02). The analysis was performed using a random-effect model, as substantial heterogeneity (P=.02, I2=53%) among the studies was found.

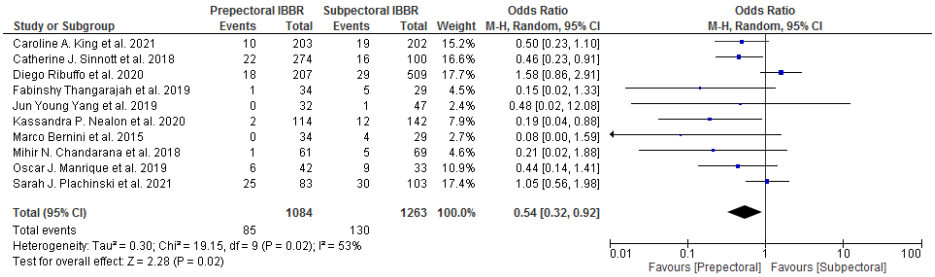

Fig. 10A. Forest plots comparing prepectoral vs subpectoral IBBR for capsular contracture[217]

Prosthesis Failure

All fifteen studies reporting prosthesis failure were included in the meta-analysis. As shown in (*Fig. 10B*), our pooled analysis showed that subpectoral IBBR had significantly higher rates of prosthesis failure compared to prepectoral IBBR, with pooled (OR, 0.61; 95% CI, 0.44-0.84; P=.002). The pooled analysis was performed using a fixed-effects model because no significant heterogeneity among the studies was found (P=.77, I2= 0%).

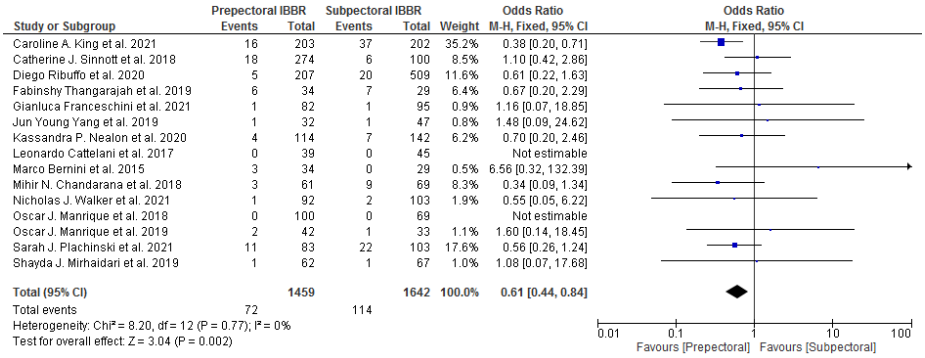

Fig. 10B. Forest plots comparing prepectoral vs subpectoral IBBR for prosthesis failure[217]

Infection

Thirteen studies[222–228,230–234,236] reporting data for infection rates were included in the meta-analysis. As shown in (*Fig. 10C*), no significant difference in infection rates between prepectoral and subpectoral IBBR was found, with pooled (OR, 0.87; 95% CI, 0.63-1.20; P=.39). The pooled analysis was performed using a fixed-effects model because no significant heterogeneity among the studies was found (P=.79, I2= 0%).

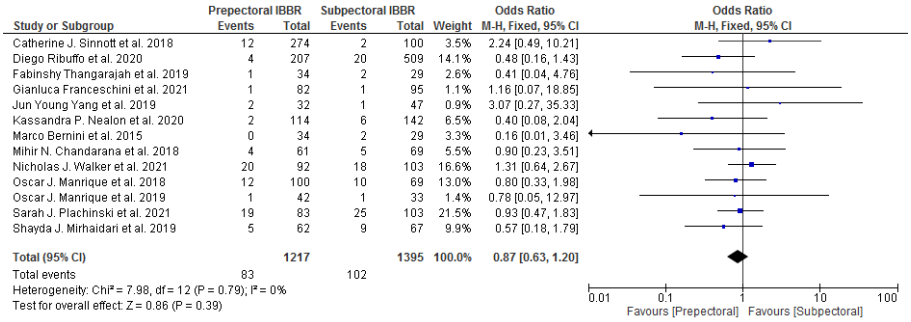

Fig. 10C. Forest plots comparing prepectoral vs subpectoral IBBR for infection[217]

Skin Flap Necrosis

Twelve studies[222,223,225–228,230–234,236] reporting data for skin flap necrosis were included in the meta-analysis. As shown in (*Fig. 11A*), no significant difference in skin flap necrosis rates between prepectoral and subpectoral IBBR was found, with pooled (OR, 0.70; 95% CI, 0.45-1.08; P=.11). The

pooled analysis was performed using a fixed-effects model because no significant heterogeneity among the studies was found (P=.61, I2= 0%).

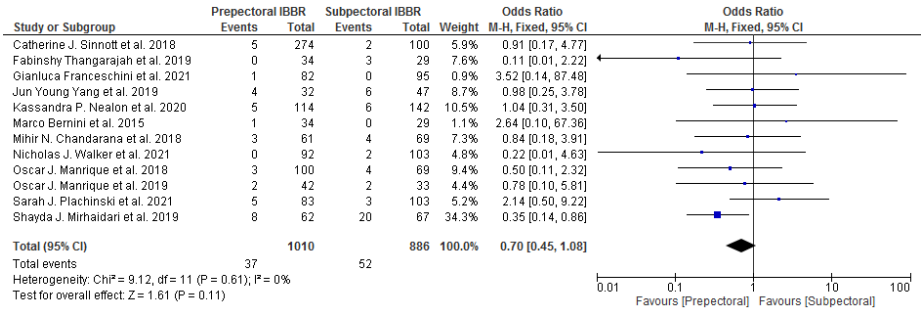

Fig. 11A. Forest plots comparing prepectoral vs subpectoral IBBR for skin flap necrosis[217]

Animation Deformity

Four studies[224,225,229,230] reporting animation deformity were included in the meta-analysis. As shown in (*Fig. 11B*), our pooled analysis showed that subpectoral IBBR had significantly higher rate of animation deformity compared to prepectoral IBBR, with pooled (OR, 0.02; 95% CI, 0.00-0.25; P=.002). The analysis was performed using a random-effect model, as substantial heterogeneity (P=.01, I2=73%) among the studies was found.

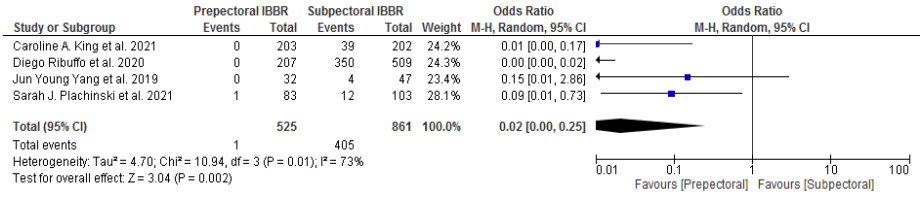

Fig. 11B. Forest plots comparing prepectoral vs subpectoral IBBR for animaton deformity.[217]

Oncological Safety

Four studies[231–233,236] reporting recurrence were included in the meta-analysis. The recurrence rates for breasts undergoing prepectoral IBBR were 2.77% (14 of 504) and subpectoral IBBR was 1.91% (7 of 366). As shown in (*Fig. 11C*), no significant difference in recurrence rates between prepectoral and subpectoral IBBR was found, with pooled (OR, 1.31; 95% CI, 0.52-3.39; P=.55). The pooled analysis was performed using a fixed-effects model because no significant heterogeneity among the studies was found (P=.67, I2=

0%). However, there were large diffrences in the mean follow-up time between the two groups (prepectoral, 20.4 [16-25] months; subpectoral, 27.6 [20-35.4] months).

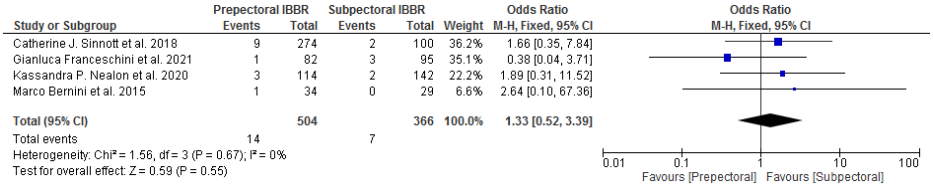

Fig. 11C. Forest plots comparing prepectoral vs subpectoral IBBR for recurrence rate.[217]

Quality of Life

Six studies[222,223,228,231,235,236] reporting patient's quality of life were included in the meta-analysis. Two[222,231] of these studies used postoperative quality of life measuring (QoL): (1) aesthetic satisfaction; (2) skin sensibility; (3) compromised relationship life; (4) sports before surgery; (5) sports after surgery; (6) chronic pain in the pectoral region, and (7) impaired arm motility. Franceschini et al.[231] reported significant difference in aesthetic satisfaction (p<.001), skin sensibility (p=.025) and chronic pain in the pectoral region (p<.001) in favor of prepectoral IBBR. Four[227,228,235,236] of these studies assessed quality of life using the BREAST-Q, a module measuring post reconstruction satisfaction on five subscales: (1) sexual well-being; (2) satisfaction with the breast; (3) psychosocial well-being; (4) physical well-being; and (5) satisfaction with the outcome. For each scale, the items responses were summed and transformed into a score, ranging from 0 to 100. Of the four studies that reported comparative BREAST-Q data, only two measured the five subscales. Four of the included studies presented data regarding "satisfaction with breast" subscale. Overall, the scores on "satisfaction with breast" were good for both reconstruction techniques with 77.3% in the prepectoral IBBR group and 71.1% in the subpectoral IBBR group. As shown in (*Supplementary Content 6A*), no significant difference in "satisfaction with breasts" subscale between prepectoral and subpectoral IBBR was found, with pooled (mean difference [MD], 6.55; 95% CI, -1.94-15.04; P=.13). The pooled analysis was performed using a random-effects model because considerable heterogeneity among the studies was found (P=.0002, I2= 85%). Similarly, no significant difference was found in the subscales: satisfaction with outcome (*Supplementary Content 6B*), sexual well-being (*Supplementary Content 6C*), psychosocial well-being (*Supplementary Content 6D*), and physical well-being (*Supplementary Content 6E*).

Patients and baseline clinopathologic characteristics

A retrospective chart review identified 98 patients who underwent nipple-sparing mastectomy (NSM) and prepectoral IBBR between March 2017 and November 2021. NSM was mostly performed as a treatment for invasive breast cancer without suspected NAC invasion, consequently most of operations were therapeutic. The patients' demographic and clinical characteristics are summarized in (*Table 4*). IMF technique was performed in 62 (63.3%) patients, whereas the remaining 36 (36.7%) patients underwent inverted-T technique. The patients in the two groups had similar age at the time of surgery (46.14 ± 11.15 vs. 45.17 ± 10.30; p=.766). The mean follow-up period was longer for the inverted-T group, but the difference was not statistically significant (31.24 ± 14.11 vs. 30.84 ± 12.13; p=.912). Almost all the prepectoral reconstructions in the two groups were performed with a single-stage, direct-to-implant approach (91.7% vs. 80.6%; p=.243). Synthetic mesh was used for IBBR in 13 (13.2%) patients (11.1% vs. 14.5%, p=.763). The rate of neoadjuvant chemotherapy (47.2% vs 38.7%; p=.524), adjuvant radiotherapy (36.1% vs. 25.4%; p=.359), lymph node biopsy (63.9% vs. 71%; p=.504), and axillary lymph node dissection (33.3% vs. 22.6%; p=.342) were not significantly different among the two groups.

Table 4. Demographic and clinical characteristics.[237]

Characteristic	Inverted-T (%)	IMF (%)	Total (%)	P value
No. of patients	**36 (36.7)**	**62 (63.3)**	**98**	
Mean age* ± SD, y	**46.14 ± 11.15**	**45.17 ± 10.30**	**45.5 ± 10.77**	**0.766**
Mean follow-up, mo	**31.24 ± 14.11**	**30.84± 12.13**	**31.12 ± 14.15**	**0.912**
Reconstruction				
Unilateral	**13 (36.1)**	**32 (51.6)**	**45 (46)**	**0.149**
Bilateral	**23 (64)**	**30 (48.4)**	**53 (54)**	**0.149**
Prophylactic	**3 (8.3)**	**9 (14.5)**	**12 (12.2)**	**0.523**
Therapeutic	**33 (91.7)**	**53 (85.5)**	**86 (87.8)**	**0.523**
Single-stage	**33 (91.7)**	**50 (80.6)**	**83 (84.7)**	**0.243**
Two-stage	**3 (8.3)**	**12 (19.4)**	**15 (15.3)**	**0.243**
Mesh usage	**4 (11.1)**	**9 (14.5)**	**13 (13.3)**	**0.763**
T stage (TNM)				
pTis	**4 (11.1)**	**12 (19.35)**	**16 (16.3)**	**0.392**
pT1a	**5 (13.9)**	**8 (12.93)**	**13 (13.3)**	**1.00**

Characteristic	Inverted-T (%)	IMF (%)	Total (%)	P value
pT1b	**7 (19.4)**	**11 (17.74)**	**18 (18.4)**	**1.00**
pT1c	**9 (25)**	**16 (25.8)**	**25 (25.5)**	**0.496**
pT2	**6 (16.7)**	**9 (14.51)**	**15 (15.3)**	**0.778**
pT3	**3 (8.3)**	**2 (3.22)**	**5 (5.1)**	**0.353**
No tumor	**2 (5.5)**	**4 (6.45)**	**6 (6.1)**	**1.00**
N stage (TNM)				
pN0	**23 (63.9)**	**45 (72.6)**	**68 (69.4)**	**0.375**
pN1	**7 (19.4)**	**14 (22.6)**	**21 (21.4)**	**0.802**
pN2	**4 (11.1)**	**1 (1.6)**	**5 (5.1)**	**0.06**
pN3	**2 (5.5)**	**2 (3.2)**	**4 (4.1)**	**0.623**
M stage (TNM)				
M0	**35 (97.2)**	**61 (98.4)**	**96 (98)**	**1.00**
M1	**1 (2.7)**	**1 (1.61)**	**2 (2)**	**1.00**
Estrogen receptor				
Positive	**26 (72.2)**	**43 (69.4)**	**69 (70.4)**	**0.630**
Negative	**10 (27.8)**	**19 (30.6)**	**29 (29.6)**	**0.630**
Progesterone receptor				
Positive	**20 (55.6)**	**38 (61.3)**	**58 (59.2)**	**0.671**
Nhegative	**16 (44.4)**	**24 (38.7)**	**40 (40.8)**	**0.671**
HER2/neu receptor				
Positive	**10 (27.8)**	**19 (30.6)**	**29 (29.6)**	**0.821**
Negative	**26 (72.2)**	**43 (69.4)**	**69 (70.4)**	**0.821**
Chemotherapy, n				
Neoadjuvant	**17 (47.2)**	**24 (38.7)**	**41 (41.8)**	**0.524**
Adjuvant	**15 (41.7)**	**17 (27.4)**	**32 (32.7)**	**0.181**
Radiotherapy, n				
Adjuvant	**13 (36.1)**	**16 (25.4)**	**29 (29.6)**	**0.359**
Axillary management				
Axillary lymph node dissection	**12 (33.3)**	**14 (22.6)**	**26 (26.5)**	**0.342**
Sentinel node biopsy	**23 (63.9)**	**44 (71)**	**67 (68.4)**	**0.504**
No axillary surgery	**1 (2.8)**	**4 (6.4)**	**5 (5.1)**	**0.649**
Grade of ptosis				
0	**1 (2.8)**	**26 (42)**	**27 (27.6)**	**0.0001**
1	**1 (2.8)**	**23 (37)**	**24 (24.5)**	**0.0001**
2	**12 (33.3)**	**10 (16.2)**	**22 (22.4)**	**0.08**
3	**22 (61.1)**	**3 (4.8)**	**25 (25.5)**	**0.0001**

* – Age at surgery.

Complications

The procedural complications are summarized in (*Table 5*). Among the 98 patients, 25 (25.5%) had at least one complication. NAC necrosis was one of the most common postoperative complications occurring in a total of 4 patients (8.3% vs. 1.61%; p=.139). In the inverted-T group, three (8.3%) patients experienced NAC necrosis, which included three cases of -partial NAC necrosis, and one case of -full NAC necrosis. The IMF group had 1 (1.61%) -partial NAC necrosis. The overall infection rate in two groups was 5.1% (5.5% vs 4.84%, p=1.00), seroma rate in two groups was 3.06% (5.5% vs 1.61%, p=.552). There was no statistically significant difference between this groups. The rates of hematoma (2.7% vs. 0%; p=.367) and skin necrosis (2.7% vs. 4.84%; p=1.00), were also comparable between the two groups.

Implant loss was observed in a total number of 4 patients of which 3 patients were from the inverted-T group (8.3% vs. 1.61%; p=.139). Two losses occurred after infection and complete NAC necrosis (both after adjuvant radiotherapy). One further patient had the implant removed following local cancer recurrence. In the IMF group, one patient (1.61%) had the implant removed because of full skin necrosis over the suture line. Capsular contracture was not significantly associated with age and chemotherapy.[237]

Table 5. Postoperative complications.[237]

Complication	Inverted-T (%) (n=36)	IMF (%) (n=62)	Total (%) (n=98)	P value
Overall complication	**10 (27.8)**	**15 (24.2)**	**25 (25.5)**	**0.811**
Hematoma	**1 (2.7)**	**0**	**1 (1.02)**	**0.367**
Skin necrosis	**1 (2.7)**	**3 (4.84)**	**4 (4.08)**	**1.00**
NAC necrosis*	**3 (8.3)**	**1 (1.61)**	**4 (4.08)**	**0.139**
Seroma	**2 (5.5)**	**1 (1.61)**	**3 (3.06)**	**0.552**
Infection	**2 (5.5)**	**3 (4.84)**	**5 (5.1)**	**1.00**
Implant loss	**3 (8.3)**	**1 (1.61)**	**4 (4.08)**	**0.139**
Capsular contracture	**2 (5.5)**	**5 (8.06)**	**7 (7.14)**	**1.00**
Baker II	**0**	**2 (3.22)**	**2 (2.04)**	**0.538**
Baker III	**1 (2.7)**	**3 (4.84)**	**4 (4.08)**	**1.00**
Baker IV	**1 (2.7)**	**1 (1.61)**	**3 (3.06)**	**1.00**
Oncological safety				
Local recurrence, n	**2 (5.5)**	**3 (4.84)**	**5 (5.1)**	**1.00**

Complication	Inverted-T (%) (n=36)	IMF (%) (n=62)	Total (%) (n=98)	P value
Distant recurrence, n	**1 (2.7)**	**1 (1.61)**	**2 (2.04)**	**1.00**
Clavien-Dindo classification				
0	**21 (58.3)**	**47 (75.8)**	**68 (69.4)**	**0.110**
1	**6 (16.7)**	**8 (12.91)**	**14 (14.3)**	**0.766**
2	**5 (13.9)**	**4 (6.45)**	**9 (9.2)**	**0.282**
3	**4 (11.1)**	**3 (4.84)**	**7 (7.1)**	**0.417**
3	**4 (11.1)**	**3 (4.84)**	**7 (7.1)**	**0.417**

*NAC – nipple-areola complex.

Adjuvant radiotherapy

In subgroup analysis, a higher incidence of complications was evident in the RT vs. non-RT groups. 17.9% patients from the RT group developed capsular contracture following RT compared to 4.29% in the non-RT groups, which was statistically significant (p=.04). In addition, all five capsular contracture cases in the RT group were Baker grade 3 or 4 compared with only one of three cases in the non-RT group (p=.07). The rate of implant loss after final prepectoral IBBR due to complications was 1.42% in the non-RT group, and 10.7% in the RT group, the results were statistically significant (p=.05). Two implant losses occurred after infection and complete NAC necrosis and one patient had the implant loss after full skin necrosis in the RT group, and one further patient in the non-RT had implant loss following local cancer recurrence. The rates of hematoma (1.42% vs. 0%; p=1.00), skin necrosis (2.9% vs. 7.14%; p=.321), seroma (2.9% vs. 3.6%; p=1.00), and infection (4.3% vs. 7.14%; p=.622) were comparable between the two groups (*Table 6*).[237]

Table 6. Postoperative complications based on adjuvant RT.

Complication	Non-RT (%)	RT (%)	Total (%)	P value
Overall complications	**16 (22.9)**	**9 (32.1)**	**25 (25.5)**	**0.442**
Skin necrosis	**2 (2.9)**	**2 (7.14)**	**4 (4.08)**	**0.321**
Hematoma	**1 (1.42)**	**0**	**1 (1.02)**	**1.00**
NAC necrosis*	**3 (4.3)**	**1 (3.6)**	**4 (4.08)**	**1.00**
Seroma	**2 (2.9)**	**1 (3.6)**	**3 (2.94)**	**1.00**

Complication	Non-RT (%)	RT (%)	Total (%)	P value
Infection	**3 (4.3)**	**2 (7.14)**	**5 (5.1)**	**0.622**
Implant loss	**1 (1.42)**	**3 (10.7)**	**4 (4.08)**	**0.05**
Capsular contracture	**3 (4.3)**	**5 (17.9)**	**8 (8.16)**	**0.04**
Baker II	**2 (2.9)**	**0**	**2 (2.04)**	**0.505**
Baker III	**1 (1.42)**	**3 (10.7)**	**4 (4.08)**	**0.07**
Baker IV	**0**	**2 (7.14)**	**2 (2.04)**	**0.08**
Oncological safety				
Local recurrence, n	**3 (4.3)**	**2 (7.14)**	**5 (5.10)**	**0.622**
Distant recurrence, n	**1 (1.42)**	**1 (3.6)**	**2 (2.04)**	**0.419**
Clavien-Dindo classification				
0	**52 (74.3)**	**16 (57.1)**	**68 (69.4)**	**0.144**
1	**9 (12.9)**	**5 (17.9)**	**14 (14.3)**	**0.534**
2	**6 (8.5)**	**3 (10.7)**	**9 (9.2)**	**0.712**
3	**3 (4.3)**	**4 (14.3)**	**7 (7.1)**	**0.102**

*NAC – nipple-areola complex.

Oncological outcome

The median follow-up periods were 31.24 ± 14.11 months for the inverted-T group and 30.84 ± 12.13 months for the IMF group. We observed no significant differences between the two groups (inverted-T vs IMF) with LR (5.5% vs 4.84%; P=1.00), or DM (2.7% vs 1.61%, p=0.1) rates. Local recurrence was defined as biopsy-proven cancer recurrence in the ipsilateral chest wall, breast skin, or nipple-areola complex. Regional recurrence was defined as a recurrence in the ipsilateral axillary, internal mammary, or supraclavicular lymph nodes. Any other site of recurrence was considered to be DM. Patients with initial RR or DM were excluded from the LR group.

Of the 62 patients in the IMF group, 3 of patients (4.84%) experienced local recurrence, of the 36 patients in the inverted-T group, 2 of patients (5.5%) experienced local recurrence. There was also no significant differences in terms of age at diagnosis, clinical and pathologic stages, and subtype between the two groups in this subset of the population. No association was found between the operation technique and local recurrence.

The median time from surgery to local recurrence was 14 months. These patients who developed local cancer recurrence had a median age of 37 years

(range, 26-44 years). The median primary tumor size was 2.2 cm (range, 0.7–3). The primary tumor histologic feature was invasive ductal carcinoma in 4 cases, and ductal carcinoma in situ in 1 patients. Each group had one patient with distant recurrence (2.7% vs 1.61%, p=0.1). The primary tumor histologic feature in both cases was invasive ductal carcinoma, with molecular subtype in inverted-T group luminal B HER2-positive, and IMF group TN. In luminal B HER-positive DM occurred – brain, and in TN – lungs. The median time from surgery to DM in inverted-T group was 14 months and in IMF group 17 months. The three-year overall survivals were 97.4% in inverted-T group and 98.5% in IMF group.

Aesthetic outcome

The post-reconstruction module of the BREAST-Q questionnaires were completed with an average of two years after completing final reconstruction, including any needed revisions. Among the 98 women, the Breast-Q scores on all domains were high for both groups. *Table 7* demonstrate the mean scores for the two groups after final reconstruction for the domains of satisfaction with the breast, psychosocial well-being, physical well-being, and sexual well-being.[237]

Table 7. Breast-Q: Postoperative assessment.[237]

Postoperative Breast-Q evaluation	Inverted-T (%)	IMF (%)	Total %	P value
atisfaction with breast	**72.14 ± 21.37**	**77.58 ± 21.43**	**74.95 ± 21.35**	**0.364**
sychosocial well-being	**81.36 ± 15.51**	**77.10 ± 17.39**	**78.97 ± 16.50**	**0.162**
exual well-being	**63.91 ± 22.77**	**68.61 ± 22.78**	**65.35 ± 23.42**	**0.113**
hysical well-being	**56.42 ± 25.24**	**61.80 ± 30.08**	**58.65 ± 28.09**	**0.696**

T-inverted group had higher mean change score for the domain satisfaction with breast when compared with IMF technique, however the difference was not significant. Scores for the domain psychosocial well-being were completed with an average of two years after completing final reconstruction, and there were no significant differences in mean scores between the two groups (p=.162). IMF group were more satisfied with their breast over the inverted-T group, but there was also no significant difference in BREAST-Q scores (p=.364). Participants who experienced at least 1 complication were found to have significantly low scores for the domain sexual well-being.

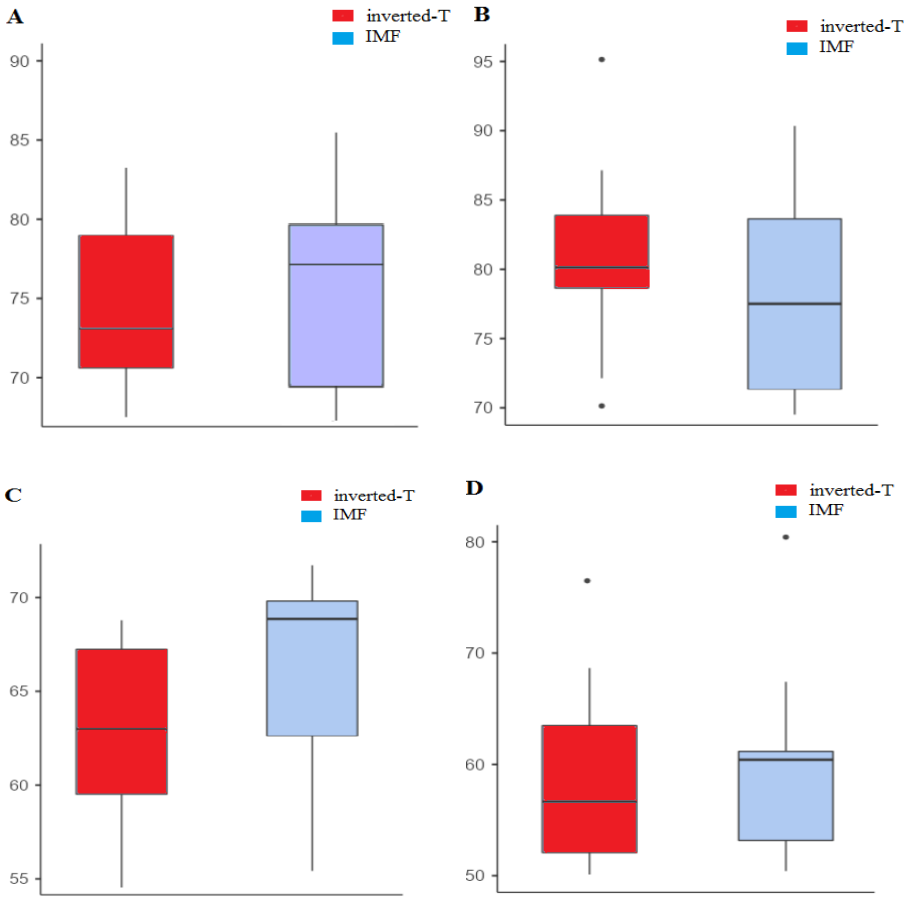

Fig 12. Boxplots of Beast-Q scores: (A) satisfaction with breast, (B) psychosocial well-being, (C) sexual well-being (D) physical well-being.

6. DISCUSSION

The main findings of our study are: (1) Systematic review and meta-analysis of 15 studies with 3,101 patients demonstrated that prepectoral IBBR has similar outcomes with significantly lower rates of capsular contracture (odds ratio [OR], 0.54; 95% CI, 0.32–0.92; p=0.02), prosthesis failure (OR, 0.58; 95% CI, 0.42–0.80; p=0.001), and animation deformity (OR, 0.02; 95% CI, 0.00–0.25; p=0.002) than subpectoral IBBR. (2) Patients in the RT group had a higher rate of capsular contracture (p=0.04) and implant loss (p=0.05) than those in the non-RT group independent on the surgical approaches. (3) Variations in surgical approaches did not affect oncologic outcomes (p=1.00) in NSM following immediate prepectoral IBBR for BC patients; The 3-year overall survival was 97.4% in inverted-T group and 98.5% in IMF group. (4) Both operation techniques showed similar complication rates and excellent overall quality of life. (5) The IMF technique is a preferable method for cup A-B sized breasts with ptosis grade 0-I in BC patients after immediate prepectoral IBBR. The inverted-T technique is a preferable method for cup C-D sized breasts with ptosis grade II-III in BC patients after immediate prepectoral IBBR.

Breast reconstruction rates have increased over the last decade in the world. Implant-based breast reconstruction (IBBR) remains the most common reconstructive approach with more than 137,000 procedures during 2020 in the USA.[8] One of the controversies associated with IBBR is whether to perform the reconstruction in 1 stage (direct to implant) or 2 stages (tissue expander/implant). One stage technique emphasize a low revision rate, fewer operations, and excellent patient outcomes. Two stage technique emphasize improved patient outcomes based on recontouring and selecting an ideal device for the second stage, reduced capsular contracture in the setting of post mastectomy radiation, a lower unplanned revision rate, and excellent patient outcomes.[238–241] In our study, almost in all cases (n=83) we used immediate prepectoral IBBR. We used two stage technique only in complicated cases (heavy smokers or etc.). We believe, that success with either technique is ultimately based on proper patient selection, surgical technique, and surgeon experience. Regarding the complication rates, both techniques have been reported to have higher complication rates in patients who are scheduled to undergo adjuvant radiotherapy or who have a history of local irradiation.[242,243]

The selection of the implant plane during breast reconstruction has recently become a subject of debate. Mostly, we perform prepectoral IBBR. We believe that with adequate preoperative planning, prepectoral IBBR can

be performed successfully in patients with ptotic and non ptotic breasts. Multiple studies have shown comparable results between prepectoral and subpectoral IBBR techniques.[244] However, one of the largest meta-analysis by Fitzal et al., which compared preectoral with subpectoral IBBR based on pooled analysis of 3,101 patients form 15 comparatives studies, showed that the mean number of complications, especially capsular contracture and implant loss were significantly higher in subpectoral IBBR.[221] Moreover, they found no differences in overall complications, seroma, and hematoma rates. They also suggested that prepectoral IBBR was associated with better Breast-Q scores and a lower rate of skin flap necrosis, which was not observed in our larger analysis.[221]

The use of acellular dermal matrices (ADMs) and synthetic meshes in IBBR is becoming more preferable every day, especially with promising opportunities for prepectoral single-stage placement. The use of ADM and meshes also allowed for larger pocket sizes to facilitate immediate IBBR. Early reports showed several benefits, including less skin flap necrosis, capsular contracture, less need for tissue expander, superior aesthetic results, and lower reoperations rates.[245,246] Surgeons have started the usage of ADMs and synthetic meshes in IBBR to avoid a theoretical increase in complication rates. However, the advantages of ADM and synthetic meshes have not been universally accepted and additional causes for doubt have been created by reports concerning harm, specifically higher rates of infection and implant loss.[247] Eventually, in a randomized clinical trial, Lohmander et al.[248] found that immediate IBBR with ADM did not yield fewer reoperations than conventional IBBR without ADM. Several prospective studies also found no difference in IBBR with or without biological or synthetic mesh.[249–251] In our study, the combination of prepectoral IBBR with synthetic meshes was in 13 (13.2%) patients, when the pocket was too large for the planned implant (TiLOOP Bra Pocket).

The incision type is a very important factor for the skin flap and NAC necrosis rate in NSM. Daar et al.[252] performed a systematic literature review and meta-analysis including 51 studies with 9975 NSM, and identified that inframammary incision (IMF) could be the preferred choice with fewer complication and better aesthetic outcome. IMF incision had a comparably low NAC necrosis rate of 4.62%. In our series, complications characterized by -partial or -full NAC necrosis were observed in 1.61% of the IMF and 8.3% of the inverted-T group, respectively (p=.139). The reason for this difference could be that more patients in the inverted-T group had the NAC harvested as a free graft and grafted to the new location at the time of NSM, followed by prepectoral IBBR (p=.002).

During NSM due to breast cancer the main aim is to achieve oncological safety. Surgeons are worried about the residual breast tissue (RBT) left behind within the subcutaneous tissue as well as behind the nipple, especially in ptotic breasts. In fact, in the SKINI trial, Tausch et al.[253] found that almost every second SSM or NSM had RBT in the subcutaneous tissue, with the most likelihood in NSM and behind the nipple. However, new evidence has shown that NSM is oncological safe as SSM. A recent study of 944 patients by Wu et al.[254] reported 39 cases (4.1%) of cancer recurrence at the NAC. The 5-year cumulative incidence rate of cancer recurrence at the NAC was 3.5%. Another study by Galimberti et al.[255] revealed that among 1989 patients, 36 (1.8%) had NAC recurrence. Overall survival at 5-year were 96.1% in women with invasive cancer and 99.2% in women with in situ disease. In our study, at a follow-up of 31 months, five (5.1%) local recurrences and two (2.04%) distant recurrences were observed. The three-year overall survivals were 97.4% and 98.5% in inverted-T and IMF groups.

PMRT is a well-known risk factor that increases the risk of complications and decreases aesthetic outcomes and quality of life following IBBR. In women with locally advanced breast cancer, adjuvant radiotherapy was shown to decrease local recurrence and improve survival in patients with node-positive disease. Despite its therapeutic advantages, adjuvant radiotherapy represents serious risk factors for major complications such as capsular contracture and reconstructive failure in IBBR. In our clinical study, the early BC was omitted and only 28 patients (28,5%) received PMRT after immediate IBBR. The main indications for PMRT were: larger than 5cm (≥T3) and/or skin invasion, spread to four or more lymph nodes, R1 or infiltration of the pectoralis muscle. Our findings showed that patients in the PMRT group had higher rates of implant loss (p=.07) and capsular contracture (p=.09), than non-irradiated patients. These results are consistent with previous studies.[12,232] It is important to note that the longer duration of follow-up can increase the rate of capsular contracture, as the degree of capsular contracture often increases after the first three years. However, the rates of capsular contracture in prepectoral IBBR are lower compared to subpectoral IBBR.[221]

In patients with IBBR, the contracture affect the skin, capsule, and muscle. It has been suggested that fibrosis of contractile muscle tissue could predispose patients after subpectoral reconstruction to breast contracture and implant deformation. Sinott et al.[232] revealed that adjuvant radiotherapy increases the rate of capsular contracture in both groups: subpectoral IBBR (from 2.9% to 52.2%) and prepectoral IBBR (from 3.5% to 16.1%). Sobti et al.[15] showed that prepectoral IBBR is associated with a lower rate of capsular contracture in an irradiated patient population when compared to subpectoral

breast reconstruction. Despite the advantages of prepectoral IBBR, we should be careful in patient selection especially with advanced BC who are candidates for PMRT.

One of the main goals of implant-based breast reconstruction is to improve the quality of life of patients. Well-developed measurement tools such as the Breast-Q have made it possible to directly compare different breast reconstruction types. In the present study, we examined prospectively quality of life using the BREAST-Q subscales in women who underwent NSM following immediate prepectoral IBBR. Patients reported high Q-scores in all 4 categories of the post-reconstruction module of the BREAST-Q questionnaire (*Table 4*). We believe that preservation of the NAC increased the reported high Q-scores in both groups. However, we had few patients with minor animation deformity and implant malposition which are not reflected in the Q-scores. Despite minor complications, we found no significant differences in aesthetic outcomes between inverted-T and IMF incisions. This demonstrates that patients who are candidates for prepectoral IBBR and have ptotic breasts can achieve similarly high aesthetic outcomes with their reconstruction as patients with non ptotic breasts without compromising the oncological safety.

7. LIMITATIONS

The most serious limitations of the study was that it involved retrospective analysis, although from a prospectively maintained database, and may include bias. However, our study included one of the largest NSM following immediate prepectoral IBBR series for invasive breast cancer to date with long-term follow-up from a single institution. In this study, patients were not randomized to procedure types; consequently, our results may have been subject to confounding by unrecognized demographic or clinical covariates.

The limitations of the meta-analysis was the variation in the sample size among the included studies. Although we analyzed 3101, the sample size ranged widely among the studies from 63 to 642 patients. The included studies were observational in design with limited data on long-term oncological outcomes. The impact of adjuvant therapy on surgical outcomes following implant-based breast reconstruction was conducted by limited number of studies and introduces a risk for bias. Several other factors that were not considered also could affect the outcomes, including different follow-up durations between prepectoral and subpectoral IBBR.

Future research should include randomized, clinical trials or well-designed, prospective, matched studies with adequate follow-up to assess long-term outcomes between comparative groups.

8. CONCLUSIONS

1. The results of the systematic review and meta-analysis demonstrated that prepectoral IBBR has similar outcomes with significantly lower rates of capsular contracture, prosthesis failure, and animation deformity compared with subpectoral IBBR.
2. Performed scientific research confirm the thesis that variations in surgical approaches did not affect oncologic outcomes in immediate prepectoral IBBR.
3. The inverted-T technique for BC patients with ptotic breasts is a safe modality with similar complication rates and high aesthetic results compared with IMF technique for non ptotic breasts.
4. Patients in the PMRT group had statistically higher rates of implant loss and capsular contracture, than non-irradiated patients regardless of the surgical approach in immediate prepectoral IBBR.
5. Data revealed that the IMF technique is a preferable method for cup A-B sized breasts with ptosis grade 0-I in BC patients after immediate prepectoral IBBR. The inverted-T technique is a preferable method for cup C-D sized breasts with ptosis grade II-III in BC patients after immediate prepectoral IBBR.

9. RECOMMENDATION

1. Results suggest that prepectoral IBBR should be considered for any BC patient, who is candidate for immediate IBBR.
2. IMF technique is a preferable method for cup A-B sized breasts with ptosis grade 0-I in BC patients after immediate prepectoral IBBR.
3. Inverted-T technique is a preferable method for cup C-D sized breasts with ptosis grade II-III in BC patients after immediate prepectoral IBBR.
4. According to our data, adjuvant RT could be successfully omitted in patients with early BC.
5. This structured information presented as recommendations, is likely to be useful and relevant to breast surgeons in future studies and clinical practice for BC patients who are candidates for NSM following immediate prepectoral IBBR.

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11. SUPLEMENTARY CONTENT

SUPPLEMENTARY CONTENT 1

SEXUAL WELL-BEING

Thinking of your sexuality, how often do you generally feel:

	None ofthe time	A little ofthe time	Some ofthe time	Most ofthe time	All of the time
a. Sexually attractive in your clothes?	**1**	**2**	**3**	**4**	**5**
b. Comfortable/at ease during sexual activity?	**1**	**2**	**3**	**4**	**5**
c. Confident sexually?	**1**	**2**	**3**	**4**	**5**
d. Satisfied with your sex-life?	**1**	**2**	**3**	**4**	**5**
e. Confident sexually about how your breast area lookswhen unclothed?	**1**	**2**	**3**	**4**	**5**
f. Sexually attractive when unclothed?	**1**	**2**	**3**	**4**	**5**

Note to Investigators: This scale can be used independently of the other scales. This scale is exactly the same across the three Breast Cancer Preoperative and Postoperative Modules (i.e. Mastectomy, Reconstruction, and Breast Conserving Therapy). The following statement can be added to the stem to provide an opportunity for the patient todecline completing this scale. 'The following questions ask about your sexual well-being. If you are uncomfortable answering these questions or do not feel that they apply to you, please check the box and skip the questions that follow.

SEXUAL WELL-BEING CONVERSION TABLE

Instructions: If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
6	**0**
7	**14**
8	**20**

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
9	**24**
10	**27**
11	**31**
12	**34**
13	**36**
14	**39**
15	**41**
16	**43**
17	**46**
18	**48**
19	**50**
20	**53**
21	**56**
22	**59**
23	**62**
24	**66**
25	**70**
26	**74**
27	**79**
28	**84**
29	**91**
30	**100**

SUPPLEMENTARY CONTENT 2

SATISFACTION WITH BREASTS

With your breast area in mind, in the past week, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	**Somewhat Dissatisfied**	**Somewhat Satisfied**	**Very Satisfied**
a. How you look in the mirror clothed?	**1**	**2**	**3**	**4**
b. How comfortably your bras fit?	**1**	**2**	**3**	**4**
c. Being able to wear clothing that is more fitted?	**1**	**2**	**3**	**4**
d. How you look in the mirror unclothed?	**1**	**2**	**3**	**4**

Note to Investigators: This scale can be used independently of the other scales.

SATISFACTION WITH BREASTS CONVERSION TABLES

Instructions: If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
4	**0**
5	**23**
6	**29**
7	**34**
8	**39**
9	**44**
10	**48**
11	**53**
12	**58**
13	**64**
14	**71**
15	**82**
16	**100**

SUPPLEMENTARY CONTENT 3

PSYCHOSOCIAL WELL-BEING

With your breast area in mind, in the past week, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	**1**	**2**	**3**	**4**	**5**
b. Emotionally able to do the things that you want to do?	**1**	**2**	**3**	**4**	**5**
c. Emotionally healthy?	**1**	**2**	**3**	**4**	**5**
d. Of equal worth to other women?	**1**	**2**	**3**	**4**	**5**
e. Self-confident?	**1**	**2**	**3**	**4**	**5**
f. Feminine in your clothes?	**1**	**2**	**3**	**4**	**5**
g. Accepting of your body?	**1**	**2**	**3**	**4**	**5**
h. Normal?	**1**	**2**	**3**	**4**	**5**
i. Like other women?	**1**	**2**	**3**	**4**	**5**
j. Attractive?	**1**	**2**	**3**	**4**	**5**

Note to Investigators: This scale can be used independently of the other scales. This scale is exactly the same across the three Breast Cancer Preoperative and Postoperative Modules (i.e. Mastectomy, Reconstruction, and Breast Conserving Therapy).

PSYCHOSOCIAL WELL-BEING CONVERSION TABLE

Instructions: If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
10	**0**
11	**13**
12	**18**
13	**21**
14	**24**
15	**27**
16	**29**
17	**31**
18	**32**
19	**34**
20	**35**
21	**37**
22	**38**
23	**39**
24	**41**
25	**42**
26	**43**
27	**44**
28	**45**
29	**47**
30	**48**
31	**49**
32	**50**
33	**52**
34	**53**
35	**55**
36	**56**
37	**58**
38	**60**
39	**62**
40	**64**
41	**66**
42	**69**
43	**71**
44	**74**
45	**77**
46	**80**
47	**83**
48	**87**
49	**93**
50	**100**

SUPPLEMENTARY CONTENT 4

PHYSICAL WELL-BEING

In the past week, how often have you experienced:

	None of thetime	Some of thetime	All of the time
a. Pain in the muscles of your chest?	**1**	**2**	**3**
b. Difficulty lifting or moving your arms?	**1**	**2**	**3**
c. Difficulty sleeping because of discomfort in your breast area?	**1**	**2**	**3**
d. Tightness in your breast area?	**1**	**2**	**3**
e. Pulling in your breast area?	**1**	**2**	**3**
f. Nagging feeling in your breast area?	**1**	**2**	**3**
g. Tenderness in your breast area?	**1**	**2**	**3**
h. Sharp pains in your breast area?	**1**	**2**	**3**
i. Aching feeling in your breast area?	**1**	**2**	**3**
j. Throbbing feeling in your breast area?	**1**	**2**	**3**

Note to Investigators: This scale can be used independently of the other scales.

PHYSICAL WELL-BEING TABLE

Instructions: Item 'k' for postoperative patients is a stand-alone item that is not included in the scale score. Rescore items a, b, c, d, e, f, g, h, i, and j as follows: "None of the time" = 3; "Some of the time" = 2; "All of the time" = 1. If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw summed scale score into a score from 0 (worst) to 100 (best). Higher scores reflect a better outcome.

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
10	**0**
11	**8**

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
12	14
13	20
14	24
15	28
16	32
17	36
18	40
19	45
20	50
21	55
22	60
23	64
24	68
25	72
26	76
27	80
28	85
29	92
30	100

SUPPLEMENTARY CONTENT 5

Risk of Bias Assessment Based on ROBINS-I Tool

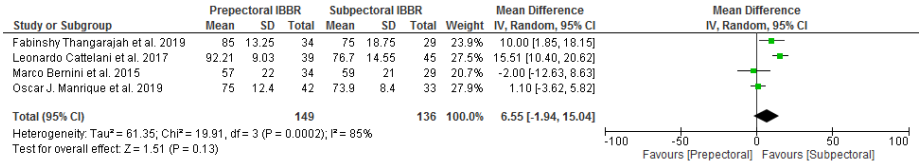
Author, year	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reporter results	Other source of bias
Nicholas J. Walker et al.[218] 2021	Low	Moderate	Low	Low	Low	Low	Low	n/a
Oscar J. Manrique et al.[219] 2018	Moderate	Moderate	Low	Low	Low	Low	Low	n/a
Diego Ribuffo et al.[2020] 2020	Low	Moderate	Low	Low	Low	Low	Moderate	n/a
Jun Young Yang et al.[221] 2019	Low	Serious	Low	Low	Low	Low	Moderate	n/a
Mihir N. Chandarana et al.[222] 2018, UK	Low	Serious	Low	Low	Low	Low	Low	n/a
Oscar J Manrique et al.[223] 2019	Low	Moderate	Low	Low	Low	Low	Low	n/a
Fabinshy Thangarajah et al.[224] 2019	Low	Moderate	Low	Low	Low	Low	Low	n/a

Author, year	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reporter results	Other source of bias
Caroline A. King et al.[225] 2021	Serious	Serious	Low	Low	Low	Moderate	Low	n/a
Sarah J. Plachinski et al.[226] 2021	Low	Moderate	Low	Low	Low	Low	Low	n/a
Gianluca Franceschini et al.[227] 2021	Serious	Moderate	Low	Low	Low	Moderate	Moderate	n/a
Catherine J. Sinnott et al.[228] 2018	Low	Moderate	Low	Low	Low	Low	Low	n/a
Kassandra P. Nealon et al.[229] 2020	Low	Moderate	Low	Low	Low	Low	Low	n/a
Shayda J. Mirhaidari et al.[230] 2019	Moderate	Moderate	Low	Low	Low	Low	Low	n/a
Leonardo Cattelani et al.[231] 2017	Moderate	Low	Low	Low	Low	Moderate	Low	n/a
Marco Bernini et al.[232] 2015	Low	Low	Low	Low	Low	Low	Low	n/a

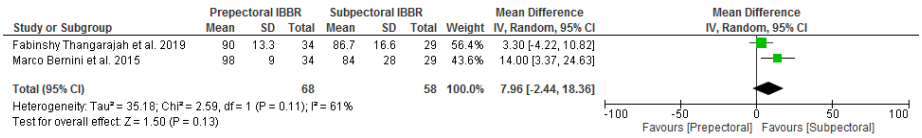
SUPPLEMENTARY CONTENT 6

Forest Plot of BREAST-Q

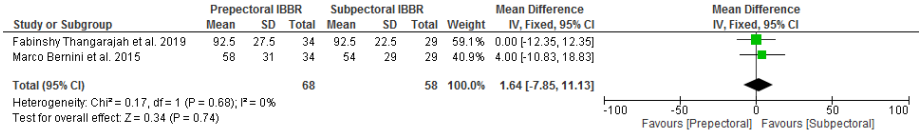
6A. Satisfaction with breast



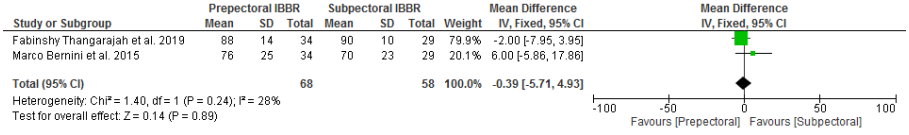
6B. Satisfaction with outcome



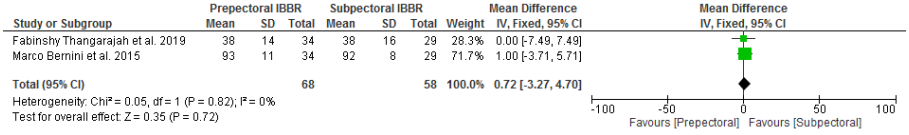
6C. Sexual well-being



6D. Psychosocial well-being



6E. Physical well-being



12. SUMMARY

SANTRUMPOS

BI – bendras išgyvenamumas
BRCA1, BRCA2 – vėžio genai
CDK – Clavien-Dindo klasifikacija
DCIS – duktalinė karcinoma in situ
HER2 – žmogaus epidermio augimo faktoriaus receptorius
IBL – išgyvenamumas be ligos atkryčio
IMR – inframamarinė raukšlė
Ki67 – prognostinis krūties vėžio žymuo
KM – konservatyvi mastektomija
KMI – kūno masės indeksas
KO-TM – krūties odą tausojanti mastektomija
KRI – krūtų rekonstrukcija implantais
KV – krūties vėžys
LA – lokalus atkrytis
LCIS – lobulinė karcinoma in situ
pCR – patologinis visiškas atsakas
PL – Pedžeto liga
PR – progestrogeno receptorius
PSO – Pasaulio sveikatos organizacija
RT – radioterapija
RTPM – radioterapija po mastektomijos
SAK – spenelio ir areolės kompleksas
SAK-TM – spenelio ir areolės kompleksą tausojanti mastektomija
SLB – sarginio limfmazgio biopsija
TNKV – trigubai neigiamas krūties vėžys

ĮVADAS

2020 m. pasaulyje diagnozuota daugiau kaip 2,3 mln. naujų krūties vėžio (KV) atvejų. KV yra labiausiai paplitęs moterų vėžys tiek išsivysčiusiose, tiek mažiau išsivysčiusiose pasaulio šalyse. KV – tai antra pagal dažnį piktybinė liga po plaučių vėžio ir dažniausia moterų piktybinė liga pasaulyje: 2020 m. registruota 7,8 mln. moterų, kurioms per pastaruosius 5 metus buvo diagnozuotas KV.[1] Lietuvoje, kaip ir visame pasaulyje, KV yra dažniausia piktybinė moterų liga, kurios sergamumo rodikliai sparčiai didėja. Paskutiniais Lietuvos vėžio registro duomenimis, 2020 m. Lietuvoje nustatyti 1 769 KV atvejai (21,7% visų vėžio atvejų) ir 490 mirties atvejų.[2]

Sergamumas KV yra didesnis ekonomiškai stipriose šalyse bei aukštesnio socialinio ir ekonominio statuso moterų, o mirtingumas dėl KV yra didesnis tarp moterų iš skurdesnių šalių, taip pat iš žemesnių socialinių ir ekonominių sluoksnių.[3] Tai iš dalies gali būti susiję su didesniu ekonomiškai stiprių šalių gyventojų informuotumu, pažangesniais diagnostikos metodais ir aktyvesniu dalyvavimu atrankinės patikros programose.

Per pastaruosius 50 metų buvo atliktas didelis įdirbis tobulinant chirurginio gydymo metodus, siekiant ne tik prailginti gyvenimą, bet ir užtikrinti geresnę to gyvenimo kokybę. Halstedo mastektomiją pakeitė kvadrantektomija ir konservatyvioji mastektomija (KM), kuri pirmiausia apėmė krūties odą tausojančią mastektomiją (KO-TM), o dabar – spenelio ir areolės kompleksą tausojančią mastektomiją (SAK-TM) krūties vėžiu sergantiems pacientams.[4] Skirtingai nuo įprastinės mastektomijos, kai pašalinama visa krūtis, KO-TM būdingas krūties audinio pašalinimas per nedidelį, bet gerai suplanuotą odos pjūvį. Operuojant taip pat kartu pašalinamas spenelio ir areolės kompleksas (SAK). Tobulinant chirurginio gydymo metodus ir gerinant pacientų, sergančių KV, gyvenimo kokybės rezultatus buvo sukurtas naujas metodas, būtent SAK-TM, kurios tikslas – pašalinti visą krūties liaukinį audinį visiškai išsaugant odą ir SAK.[5] Pastarąjį dešimtmetį SAK-TM skaičiai didėja.[6] Tai lemia daug faktorių, įskaitant išaugusį vienmomentės krūtų rekonstrukcijos implantais (KRI) dažnį, genetinius tyrimus dėl didelės rizikos genetinių mutacijų, tokių kaip BRCA1 ir BRCA2, taip pat padidėjusį informuotumą apie KV ir patobulintus KV diagnostikos metodus.[7]

Kasmet pasaulyje daugėjant KV atvejų, gerėja diagnostikos bei gydymo galimybės ir pacientų bendras išgyvenamumas (BI), todėl gyvenimo kokybė tampa vis svarbesnė. Per paskutinįjį dešimtmetį pasaulyje padaugėjo krūtų rekonstrukcijos atvejų.[8] KRI tebėra labiausiai paplitęs rekonstrukcinis metodas – 2020 m. JAV atlikta daugiau kaip 137 000 tokių procedūrų[8]. Šiuo metu KRI

skirstomos į vieno arba dviejų etapų rekonstrukciją. Atliekant vienmomentę KRI, po SAK-TM tos pačios operacijos metu įdedamas nuolatinis implantas.[9] Krūties rekonstrukciją atliekant dviem etapais, per pirmąjį etapą įdedamas audinių plėtiklis – ekspanderis, o per antrąjį etapą ekspanderis pakeičiamas numatyto tūrio nuolatiniu implantu.[10]

Prepektoralinė (virš krūtinės raumens) KRI – implanto įdėjimas tarp didžiojo krūtinės raumens ir odos, o subpektoralinė (po krūtinės raumeniu) KRI – implanto įdėjimas tarp didžiojo krūtinės raumens ir krūtinės ląstos – dažniausiai atliekamas metodas.[11] Prepektoralinės KRI metodas leidžia išvengti krūtinės raumens, gretimų raumenų ir fascijos pakėlimo bei pažeidimo, todėl išsaugoma krūtinės raumens anatominė padėtis, krūtys atrodo natūraliau ir po atliktos operacijos jas mažiau skauda.[12] Pirmą kartą aprašyta XX a. septintajame dešimtmetyje, prepektoralinė KRI buvo susijusi su dideliu komplikacijų skaičiumi, įskaitant infekciją, implanto atsidengimą, kapsulės kontraktūrą ir kt. Siekiant sumažinti komplikacijų riziką, procedūra buvo modifikuota ir implantas dedamas subpektoraliai.[13] Subpektoralinė KRI buvo patikima ir saugi alternatyva. Paskutiniaisiais metais prepektoralinė KRI pradėta naudoti vis dažniau dėl keleto priežasčių, tokių kaip geresnis klinikinis mastektomijos perfuzijos supratimas, nauji rekonstrukcijos metodai, naujos kartos kokybiški implantai, kurie siejami su mažesniu kapsulės kontraktūrų kiekiu, ir leidžia saugiai bei efektyviai įdėti implantą.[13-16] Tačiau prepektoralinės ir subpektoralinės KRI lyginamųjų tyrimų yra nedaug, o jų rezultatai skiriasi. Bet to, pacientai, kuriems bus atliekama SAK-TM ir kurių krūtys didelės bei ptotiškos, yra techninis iššūkis chirurgams dėl onkologinio saugumo ir gyvenimo kokybės rezultatų, ypač kai atliekama vienmomentė prepektoralinė KRI.[17,18] Kitas iššūkis, susijęs su šio gydymo metodu, yra bendras komplikacijų dažnis po adjuvantinės radioterapijos (RT). Be to, nepaisant teigiamo SAK išsaugojimo poveikio psichosocialinei gerovei, kūno įvaizdžiui ir estetiniam pasitenkinimui, nėra įtikinamų įrodymų, patvirtinančių SAK-TM onkologinį saugumą po vienmomentės prepektoralinės KRI.[19,20]

Tyrimo hipotezė

Prepektoralinė KRI yra saugus ir priimtinas metodas, rekomenduotinas KV sergantiems pacientams.

Tyrimo tikslas

Pagrindinis šio tyrimo tikslas – pateikti mokslu pagrįstus įrodymus dėl prepektoralinės KRI onkologinio saugumo; įvertinti kombinuoto gydymo

rezultatus bei gyvenimo kokybę ir optimizuoti SAK-TM chirurginius metodus po vienmomentės prepektoralinės KRI pacientams, sergantiems KV.

Tyrimo uždaviniai

1. Atlikti sisteminę apžvalgą ir metaanalizę, siekiant nustatyti prepektoralinės ir subpektoralinės KRI kombinuoto gydymo rezultatus pacientams, sergantiems KV.
2. Įvertinti ir palyginti onkologinį saugumą (lokalius ir atokius atkryčius), atsižvelgiant į taikomą chirurginį metodą po vienmomentės prepektoralinės KRI.
3. Įvertinti ir palyginti gyvenimo kokybę, naudojant BREAST-Q klausimyną ir atsižvelgiant į taikomą chirurginį metodą po vienmomentės prepektoralinės KRI.
4. Įvertinti ir palyginti RT veiksmingumą, atsižvelgiant į chirurginį gydymo metodą po vienmomentės prepektoralinės KRI.
5. Nustatyti SAK-TM chirurginių gydymo metodų indikacijas KV sergantiems pacientams po vienmomentės prepektoralinės KRI.

Tyrimo naujumas

Mūsų žiniomis, tai pirmasis Europos Sąjungoje atliktas klinikinis tyrimas, kuriame lyginamas onkologinis saugumas, gyvenimo kokybė ir kombinuoti rezultatai, atsižvelgiant į chirurginį SAK-TM gydymo metodą pacientams, sergantiems KV, po vienmomentės prepektoralinės KRI.
Mūsų atlikta prepektoralinės KRI ir subpektoralinės KRI sisteminė apžvalga ir metaanalizė apėmė 15 tyrimų, kuriuose dalyvavo 3 101 pacientas. Šiuo metu tai yra didžiausia šios srities metaanalizė pasaulyje.

METODAI

Prepektoralinės ir subpektoralinės KRI sisteminė apžvalga ir metaanalizė

Ši sisteminė apžvalga ir metaanalizė atlikta pagal PRISMA (*angl. preferred reporting items for systematic reviews and meta-analyses*) standartus[210]. Pagrindinis protokolas užregistruotas PROSPERO duomenų bazėje (CRD42022312094).

Literatūros paieška ir paieškos kriterijai

Sisteminė apžvalga atlikta naudojantis *PubMed* ir *Cochrane Library*, ieškant tyrimų, paskelbtų nuo 2011 m. sausio 1 d. iki 2021 m. gruodžio 31 d. Buvo taikomi šie įtraukimo kriterijai: (1) ataskaitose nurodomas bent 1 metų stebėjimas; (2) straipsnyje aprašoma KRI, kai implantas dedamas prepektoraliai arba subpektoraliai; (3) publikacijos paskelbtos nuo 2011 m. sausio 1 d. iki 2021 m. gruodžio 31 d.; (4) prieinamas visas tekstas; (5) nurodomi svarbūs rezultatai, t. y. pooperacinės komplikacijos; (6) tyrimai paskelbti anglų kalba.

Pacientų neįtraukimo į tyrimą kriterijai buvo šie: (1) tyrimai, kuriuose vertinta < 60 pacientų; (2) santraukos; (3) pacientai, kuriems atliktos kitos krūtų rekonstrukcijos operacijos; (4) nepakanka duomenų arba jie neatitinka mūsų įtraukimo kriterijų.

Duomenų rinkimas

Duomenis, skirtus prepektoralinės KRI ir subpektorinės KRI analizei, nepriklausomai vienas nuo kito rinko du recenzentai (E.O. ir F.F.); nesutarimai buvo sprendžiami diskusijose. Kiekvieno tyrimo duomenys, įskaitant publikavimo metus, kilmės šalį, pacientų demografinius duomenis (pvz.: lytį, vidutinį amžių, stebėjimo laiką, krūtų rekonstrukcijos tipą ir pagrindinius rezultatus), buvo apibendrinti naudojant standartizuotą formą. Siekiant išsiaiškinti trūkstamus bet kurio iš įtrauktų tyrimų duomenis, buvo bandoma susisiekti su atitinkamu autoriumi.

Šališkumo rizikos ir publikavimo šališkumo vertinimas

Šališkumo riziką vertinome naudodami „Cochrane risk of bias in nonrandomized studies of interventions“ (ROBINS-I) įrankį[11]. Įvertinimas buvo įrašytas kaip „maža“, „vidutinė“, „rimta“, „kritinė“ šališkumo rizika arba „be informacijos“. Šališkumo laipsnis buvo vertinamas naudojant Eggerio šališkumo testą.

Prepektoralinės KRI operaciniai metodai

Etika

Šiam tyrimui pritarė Vienos medicinos universiteto etikos komitetas (Nr. 1597/2021). Visos su tyrimu susijusios procedūros buvo atliekamos pagal Helsinkio deklaraciją.

Pacientai ir tyrimo dizainas

Į šį retrospektyvaus dizaino tyrimą įtraukti visi pacientai, kurie dėl KV gydyti Vienos medicinos universiteto Bendrosios chirurgijos skyriuje nuo 2017 m. kovo mėn. iki 2021 m. lapkričio mėn. ir kuriems buvo atlikta prepektoralinė KRI po SAK-TM. Įtraukimo į tyrimą kriterijai: 1) >18 metų amžiaus arba vyresni; 2) pacientams buvo taikytos tik apverstos T arba IMR operacijos metodai. Į tyrimą neįtraukti pacientai, kuriems buvo atliktos kitos mastektomijos arba taikyti kiti krūties rekonstrukcijos metodai. Taikant įtraukimo ir neįtraukimo į tyrimą kriterijus, atrinkti 98 pacientai, kurie pagal operacinį metodą (apverstos T ir IMR) buvo suskirstyti į dvi grupes. Apverstos T operacinis metodas buvo tinkamiausias esant ptotiškoms krūtims (II, III laipsnio), o IMR operacinis metodas – ne ptotiškoms. Buvo palyginti abiejų grupių rezultatai.

Apverstos T grupė

Į šią grupę buvo įtraukti KV sergantys pacientai, kuriems nuo 2017 m. kovo mėn. iki 2021 m. lapkričio mėn. buvo atlikta prepektoralinė KRI po SAK-TM. Į šią grupę buvo įtraukti 36 pacientai. Po operacijos buvo išanalizuoti 33 „BREAST-Q“ klausimynai (atsakymų dažnis 91%). Pacientų amžiaus vidurkis: 46,14 ± 11,15 metų (nuo 34 iki 68 metų). Įtraukimo kriterijai: pacientai buvo 18 metų ar vyresni, pacientams buvo taikomas tik apverstos T gydymo metodas. Į tyrimą neįtraukti pacientai, kuriems buvo atliktos kitos mastektomijos ar taikyti kiti KRI gydymo metodai.

IMR grupė

Į šią grupę buvo įtraukti KV sergantys pacientai, kuriems nuo 2017 m. rugsėjo mėn. iki 2021 m. gegužės mėn. buvo atlikta prepektoralinė KRI po SAK-TM. Į galutinę analizę buvo įtraukti 62 pacientai. Po operacijos išanalizuoti 53 „BREAST-Q“ klausimynai (atsakymų dažnis 85%), iš kurių 51 (atsakymų dažnis 82%) buvo visiškai užpildytas. Pacientų amžiaus vidurkis 45,17 ± 10,30 metų

(nuo 41 iki 78 metų). Įtraukimo kriterijai: pacientai buvo 18 metų ar vyresni, pacientams buvo taikomas tik IMR gydymo metodas. Į tyrimą neįtraukti pacientai, kuriems buvo atliktos kitos mastektomijos ar taikyti kiti KRI gydymo metodai.

Pacientų savybės ir klinikiniai duomenys

Visų pacientų duomenys buvo surinkti iš ligoninėje esančių duomenų bazių, kuriose sukaupta medicininė dokumentacija, bei iš perspektyviai surinktos duomenų bazės, kurioje registruojami KV atvejai. Įvardijant KV ligos stadiją, naudota 8-oji AJCC/UICC TNM sistemos klasifikacija. Vertinti klinikiniai ir demografiniai duomenys: gretutiniai susirgimai, radioterapijos bei chemoterapijos poveikis ir onkologinės charakteristikos (naviko patologija, BRCA nešiotojo statusas, naviko stadija, pažasties mazgų stadija, metastazių stadija, estrogenų receptorių statusas, progesterono receptorių statusas ir žmogaus epidermio augimo faktoriaus 2 receptoriaus statusas).

Atliekant tyrimą, vertintas operacijos pobūdis (įskaitant vieno ar dviejų etapų metodą bei implanto vietą), SAK-TM metodai (apverstos T ar IMR), pažasties operacija (pažasties limfmazgių disekcija ar sarginio mazgo biopsija), krūties ptozės laipsnis (vertinama pagal Regnault klasifikaciją)[123] ir pacientų stebėsena. Be to, vertintas pooperacinių komplikacijų dažnis, įskaitant infekciją, seromą, hematomą, odos ir SAK nekrozę, kapsulinę kontraktūrą (vertinama pagal Bakerio skalę[210]; tyrime atsižvelgta tik į II, III ir IV laipsnio Bakerio skalę), implanto pašalinimą, lokalius ir atokius atkryčius. Pooperacinės komplikacijos buvo apibrėžtos kaip bet kokie nukrypimai nuo normalios pooperacinės eigos hospitalizacijos metu. Siekiant įvertinti pooperacinės RT įtaką komplikacijų dažniui, pacientus suskirsčius į dvi grupes pagal adjuvantinės RT, t. y. RT ir ne RT grupes, buvo atlikta analizė.

Pacientų stebėsena

Pacientams, kuriems buvo atlikta vienmomentė prepektoralinė KRI, kasmet buvo numatyti vizitai. Minimalus stebėsenos laikotarpis svyravo nuo 12 iki 60 mėnesių. Abiejų grupių pacientams kasmet buvo atliekamos krūtų mamogramos, krūtinės ląstos ir pilvo kompiuterinė tomografija bei kaulų tankio tyrimai. Jei pacientų stebėsena buvo atliekama tyrime nedalyvaujančiose gydymo įstaigose, duomenys apie sekimo metu atliktų tyrimų rezultatus buvo renkami susiekus su pacientu ar jo šeimos gydytoju. Nuotraukos taip pat buvo daromos prieš operaciją ir atliekant stebėseną: praėjus 6, 12, 24, 36, 48 ir 60 mėnesių po operacijos.

Gyvenimo kokybės vertinimas

Siekiant įvertinti pacientų gyvenimo kokybę, buvo prašoma perspektyviai užpildyti BREAST-Q klausimyną po KRI[211]. BREAST-Q balai buvo renkami praėjus vidutiniškai dvejiems metams po KRI. Pagrindinį BREAST-Q klausimyną sudarė: (1) seksualinės gerovės klausimų grupė (*1 priedas*); (2) pasitenkinimo krūtine klausimų grupė (*2 priedas*); (3) psichosocialinės gerovės klausimų grupė (*3 priedas*); bei (4) fizinės savijautos klausimų grupė (*4 priedas*).

Šie keturios stambesnės klausimų grupės buvo vertinamos balais nuo 0 iki 100, kai didesnis skaičius reiškia didesnį pasitenkinimą arba geresnę gyvenimo kokybę. Be to, klausimų grupės buvo vertinamos nepriklausomai viena nuo kitos, neužpildytos klausimų grupės nebuvo įvertintos balais ir į analizę neįtrauktos.

Clavien-Dindo klasifikacija

Pooperacinės komplikacijos klasifikuotos pagal Clavien-Dindo klasifikaciją (CDK)[212]. Taikant CDK šiame tyrime komplikacijos buvo klasifikuojamos į I stadijos – pacientai, kurie pooperaciniu laikotarpiu nepatyrė komplikacijų; II stadijos – pacientai, kuriems pasireiškė nežymios pooperacinės komplikacijos ir kuriems užteko medikamentinio gydymo; III stadijos – pacientai, kuriems pasireiškė pooperacinės komplikacijos ir kuriems prireikė intervencijos arba operacijos.

Chirurginiai metodai

Spenelio areolės kompleksą tausojanti mastektomija (SAK-TM)

IMR metodas

Tinkamiausias metodas A–B dydžio krūtinei, esant 0–I laipsnio krūtų ptozei. Prieš operacinį pjūvį į poodinio audinį infiltruojama 1% ksilokarino (25 ml 500 cm^3 0,9 % fiziologinio tirpalo), kad sumažėtų odos kraujavimas. Paprastai pjūviui naudojama IMR, atliekant 5 cm pjūvį nuo medialinės linijos į lateralinę pusę. Po pjūvio ieškoma *fascia scarpa*. Ši fascija skyla į dvi atskiras dalis: priekinę, kuri tampa paviršine fascija tarp poodinio audinio ir krūties parenchimos, ir užpakalinę, kuri perauga į krūtininę fasciją. Abiejų fascijų atsiskyrimo vietoje yra IMR, kurios nereikėtų pažeisti, nes gali įvykti implanto dislokacija. Toliau, sekant fasciją, pjaunama tarp odos ir paviršinės plokštelės. Preparavimas sustabdomas maždaug 2 cm spenelio link, išpjaunama fascija ties krašto pabaiga

ir ji vėl sekama vidinėje dalyje iki IMR. Galiausiai gautas fascijos lopas uždengia implantą.

Po šio veiksmo pjūvis tęsiamas tiesiai prie užpakalinės fascijos plokštelės ties krūtininiu raumeniu. Taip mažinamas kraujavimas antroje pjūvio dalyje tarp odos ir krūties.

Krūties parenchima pašalinama nuo krūtinės raumens. Vėliau krūties audinys atskiriamas nuo odos. Šiai disekcijai tarp poodžio ir krūties parenchimos naudojamos žirklės (šalta disekcija), kad būtų išvengta terminio sužalojimo. Krūtis sekama dviem Kocherio spaustukais, tada pradedama aštri disekcija. Baigus disekciją tarp odos lopo ir krūties parenchimos, paimamas retroareolinio audinio mėginys, kuris yra ištiriamas skubos tvarka. Jei nėra netipinių ląstelių arba vėžinių ląstelių, spenelį galima išsaugoti. Galiausiai išpjaunamas likęs krūties audinys.

Apverstos T metodas

Tinkamiausias metodas C–D dydžio krūtinei, esant II–III laipsnio krūtų ptozei. Pacientams prieš operaciją pažymėti SAK-TM operaciniai pjūviai su iš anksto suplanuota nauja SAK padėtimi. Po deepitelizacijos oda atsargiai pakeliama nuo krūties parenchimos. Paimamas laisvas SAK lopas ir fiksuojamas naujoje padėtyje, atsižvelgiant į prieš operaciją buvusį atstumą tarp krūtinkaulio ir krūtinės ląstos bei intraoperacinius duomenis.

Vienmomentė prepektoralinė KRI

Pabaigus SAK-TM etapą, atliekama vienmomentė prepektoralinė KRI. SAK-TM turi būti atlikta teisingai, tarp paviršinės dermos fascijos ir Cooperio raiščių. Kišenė turi atitikti naudojamo implanto dydį, kuris pirmiausia išmatuojamas liniuote, po to – specialiu implanto matuokliu. Jei nenaudojamas sintetinis tinklelis, implantas įdedamas į paruoštą prepektoralinę kišenę. Jei naudojamas sintetinis tinklelis (*TiLOOP Bra Pocket*), jis prisiuvamas prie viršutinio ir šoninio poliaus. Operaciniam pjūviui naudojamas 4/0 tirpus monofilamentas (Monocryl® arba V-Lock®).

Statistinė analizė

Visi statistiniai skaičiavimai atlikti naudojantis *IBM SPSS 24* versija (*IMB Corp., Armonk, NY, JAV*) ir *STATA programos 16.0* versija (*Stata Corporation, College Station*, Teksasas).

Kiekybiniai kintamieji pateikiami kaip vidurkis su standartiniu nuokrypiu

arba kaip mediana su intervalu. Dviejų grupių klinikinės charakteristikos palygintos siekiant parodyti tinkamą atitikimą ir naudojant aprašomąją statistiką. Nustatytas galimybių (šansų) santykis (ŠS) ir su juo susijęs 95 proc. pasikliautinasis intervalas (PI). Statistinis heterogeniškumas tikrintas naudojant *Chi* kvadrato ir neatitikimo (I2) statistiką. I2 vertė, svyruojanti nuo 0%. iki 100%, naudota kiekybiniam heterogeniškumo poveikiui įvertinti. I2 reikšmė, didesnė arba lygi 40%, reiškė reikšmingą heterogeniškumą, o jungtiniai galimybių (šansų) santykiai (ŠS) buvo apskaičiuoti taikant atsitiktinio efekto modelį (DerSimonian ir Laird metodą). Kai statistinio heterogeniškumo nepastebėta (I2 reikšmė mažesnė nei 40 %), taikytas fiksuoto efekto modelis (Mantelio-Haenšelio metodas). Publikacijų šališkumas įvertintas naudojant Eggerio regresijos testus.

Ryšiams tarp kategorinių reikšmių ir komplikacijų dažnio įvertinti naudotas $\chi 2$/Fisherio testas. Grupių kintamieji analizuoti ir lyginti naudojant nepriklausomų imčių t testą arba Mann-Whitney U testą (atsižvelgiant į nenormalųjį skirstinį). Siekiant nustatyti nepriklausomą rekonstrukcijos metodų (apverstos T ir IMR) įtaką kapsulinės kontraktūros atsiradimo tikimybei pacientams, kuriems buvo atlikta RTPM, sudarytas daugialypės loginės regresijos modelis. BI vertintas nuo operacijos datos iki mirties, ištikusios dėl bet kokios priežasties. BI ir IBL vertinti taikant Kaplano-Mejerio metodą ir palyginti naudojant Long-rank testą. Apskaičiuoti kiekvieno rezultato galimybių (šansų) santykiai, 95 proc. pasikliautinieji intervalai ir p reikšmės. Visuose skaičiavimuose reikšmė $p < 0.05$ laikyta statiškai reikšminga.

REZULTATAI

Prepektoralinės ir subpektoralinės KRI sisteminė apžvalga ir metaanalizė

Tyrimų atranka

Tyrimo eigos schema pavaizduota *8 pav.* Iš viso atrinkta 440 tyrimų. Pašalinus pasikartojančius, peržiūrėti 428 tyrimai ir santraukos. Iš jų 400 tyrimų atmesti, o visa išsami likusių 28 tyrimų informacija gauta tolesniam vertinimui. 13 tyrimų atmesta dėl įvairių priežasčių, įskaitant neteisingus palyginimus, trumpą stebėsenos laikotarpį ir netinkamus statistinei analizei reikalingus duomenis. Galiausiai į šią metaanalizę įtraukta 15 tyrimų[15-29].

Tyrimų charakteristikos

Tyrimų charakteristikos, įskaitant imties dydį, operacijos metodą ir rezultatus, pateiktos *3 lentelėje*. Aštuoni tyrimai atlikti Jungtinėse Amerikos Valstijose[15,16,20,22,23,25-27]; keturi tyrimai – Italijoje[17,24,28,29]; vienas tyrimas –Pietų Korėjoje[18]; vienas tyrimas – Jungtinėje Karalystėje[19] ir vienas tyrimas – Vokietijoje[21]. Imties dydis svyravo nuo 63 iki 642 pacientų. Penkiolikoje tyrimų dalyvavo 3 101 pacientas, iš kurių 1 642 (52,9%) buvo atlikta subpektoralinė KRI. Stebėjimo trukmė svyravo nuo 12 iki 60 mėnesių. Vidutinis stebėjimo intervalas – 19,12 mėnesio. Vidutinis KMI reikšmingai didesnis atliekant prepektoralinę KRI, palyginti su subpektoraline KRI (25,6, palyginti su 23,4; p=.01) (*3 lentelė*).

Šališkumo rizikos ir publikavimo šališkumo vertinimas

Nenustatyta nė vieno iš metaanalizėje tirtų rezultatų lyginant prepektoralinę ir subpektoralinę KRI publikavimo šališkumo. Dėl nepakankamo tyrimų skaičiaus nebuvo atlikta krūtų deformacijos ir pasikartojimo dažnio rezultatų publikacijos šališkumo analizė. Šališkumas atrenkant dalyvius, šališkumas klasifikuojant intervencijas, šališkumas dėl nukrypimo nuo numatytų intervencijų ir šališkumas atrenkant galutinį rezultatą buvo nedidelis (*5 priedas*).

Bendras komplikacijų skaičius

Į metaanalizę buvo įtraukti visi penkiolika tyrimų[15-29], kuriuose aprašytas bendras komplikacijų skaičius. Bendras prepektoralinės KRI komplikacijų skaičius buvo 25,08% (366 iš 1 459), o subpektoralinės KRI – 29,65% (487 iš 1 642). Kaip parodyta *9A pav*., statistiškai reikšmingo skirtumo tarp

prepektoralinės ir subpektoralinės KRI nenustatyta; jungtinis ŠS 0,83; 95% PI, 0,64-1,09; P=.19. Jungtinė analizė atlikta taikant atsitiktinio efekto modelį, nes nustatytas vidutinis tyrimų heterogeniškumas (P=.02, I2=49%).

Seroma

Dvylikoje metaanalizės tyrimų[15-21,23,25-27,29] buvo pateikti seromos rodikliai. Kaip parodyta *9B pav*., statistiškai reikšmingo skirtumo tarp prepektoralinės ir subpektoralinės KRI nenustatyta; bendras seromos ŠS 1,21; 95% PI, 0,59-2,51; P=.60. Analizė atlikta taikant atsitiktinio efekto modelį, nes nustatytas didelis tyrimų heterogeniškumas (P=.0007, I2=71%).

Hematoma

Į metaanalizę įtraukta trylika tyrimų[15-23,25-27,29], kuriuose pateikti duomenys apie hematomų dažnį. Kaip parodyta *9C pav*., statistiškai reikšmingo skirtumo tarp prepektoralinės ir subpektoralinės KRI nenustatyta; jungtinis ŠS 0,76; 95% PI, 0,49-1,18; P=.22. Analizė atlikta taikant fiksuoto efekto modelį, nes nustatytas minimalus tyrimų heterogeniškumas (P=.25, I2=20%).

Kapsulinė kontraktūra

Į metaanalizę įtraukta dešimt tyrimų[17-23,25,26,29], kuriuose pateikti duomenys apie kapsulinės kontraktūros dažnį. Kaip parodyta *10A pav*., mūsų atlikta jungtinė analizė parodė, kad esant subpektoralinei KRI kapsulinės kontraktūros dažnis buvo statistiškai reikšmingai didesnis, palyginti su prepektoraline KRI (ŠS 0,54; 95% PI, 0,32-0,92; P=.02). Analizė atlikta taikant atsitiktinio efekto modelį, nes nustatytas didelis tyrimų heterogeniškumas (P=.02, I2=53%).

Implanto netekimas

Į metaanalizę įtraukti visi penkiolika tyrimų[15-29], kuriuose aprašytas implanto netekimas. Kaip parodyta *10B pav*., mūsų apibendrinta analizė atskleidė, kad atlikus subpektoralinę KRI implantų netekimo dažnis buvo gerokai didesnis, palyginti su prepektoralinės KRI (ŠS 0,61; 95% PI, 0,44-0,84; P=.002). Jungtinė analizė atlikta taikant fiksuoto efekto modelį, nes reikšmingo tyrimų heterogeniškumo nenustatyta (P=.77, I2=0%).

Infekcija

Į metaanalizę įtraukta trylika tyrimų[15-21,23-27,29], kuriuose pateikti duomenys apie infekcijų dažnį. Kaip parodyta 10C pav., reikšmingo infekcijų dažnio

skirtumo tarp prepektoralinės ir subpektoralinės KRI nenustatyta (ŠS 0,87; 95 % CI, 0,63-1,20; P=.39). Jungtinė analizė atlikta taikant fiksuoto efekto modelį, nes reikšmingo tyrimų heterogeniškumo nenustatyta (P=.79, I2=0%).

Odos nekrozė

Į metaanalizę įtraukta dvylika tyrimų[15,16,18-20,21,23-27,29], kuriuose pateikti duomenys apie odos nekrozę. Kaip parodyta 11A pav., reikšmingo odos nekrozės dažnio skirtumo tarp prepektoralinės ir subpektoralinės KRI nenustatyta (ŠS 0,70; 95% PI, 0,45-1,08; P=.11). Jungtinė analizė atlikta taikant fiksuotų efektų modelį, nes reikšmingo tyrimų heterogeniškumo nenustatyta (P=.61, I2=0%).

Krūtų deformacija

Į metaanalizę įtraukti keturi tyrimai[17,18,22,23], kuriuose aprašyta krūtų deformacija. Kaip matyti *11B pav*., mūsų apibendrinta analizė parodė, kad subpektoralinės KRI krūtų deformacijos dažnis buvo statistiškai reikšmingai didesnis, palyginti su prepektoralinės KRI krūtų deformacijos dažniu (ŠS 0,02; 95% PI, 0,00-0,25; P=.002). Analizė atlikta taikant atsitiktinio efekto modelį, nes nustatytas didelis tyrimų heterogeniškumas (P=.01, I2=73%).

Onkologiniai rezultatai

Į metaanalizę buvo įtraukti keturi tyrimai[24,25,26,29], kuriuos atliekant buvo pranešta apie atkryčius. LA dažnis pacientams, kuriems buvo atlikta prepektoralinė KRI – 2,77% (14 iš 504), o kuriems buvo atlikta subpektoralinė KRI – 1,91% (7 iš 366). Kaip parodyta *11C pav*., statistiškai reikšmingo LA dažnio skirtumo tarp prepektoralinės ir subpektoralinės KRI nenustatyta (ŠS 1,31; 95% PI, 0,52-3,39; P=.55). Jungtinė analizė atlikta taikant fiksuoto efekto modelį, nes reikšmingo tyrimų heterogeniškumo nenustatyta (P=.67, I2=0%). Vis dėlto abiejų grupių vidutinė stebėjimo trukmė labai skyrėsi (prepektoralinės KRI – 20,4 [16–25] mėnesiai; subpektoralinės KRI – 27,6 [20–35,4] mėnesiai)[16,19,21,23].

Gyvenimo kokybė

Į metaanalizę įtraukti šeši tyrimai[15,20,21,24,28,29], kuriuose buvo pateikta informacija apie pacientų gyvenimo kokybę. Dviejuose[15,24] iš šių tyrimų naudotas pooperacinės gyvenimo kokybės (GK) matavimas: (1) estetinis pasitenkinimas; (2) odos jautrumas; (3) sutrikę seksualiniai santykiai; (4) sportas prieš operaciją; (5) sportas po operacijos; (6) lėtinis krūtinės srities skausmas ir (7) sutrikęs

rankos judrumas. Franceschini ir kt.[24] pastebėjo reikšmingą estetinio pasitenkinimo (p=.001), odos jautrumo (p=.025) ir lėtinio skausmo krūtinės srityje (p=.001) skirtumą – rodikliai buvo geresni atlikus prepektoralinę KRI. Keturiuose[20,21,28,29] iš šių tyrimų gyvenimo kokybė buvo vertinama naudojant BREAST-Q klausimyną, pagal kurį pasitenkinimas po KRI vertinamas penkiais aspektais: 1) seksualinės gerovės; 2) pasitenkinimo krūtimis; 3) psichosocialinės gerovės; 4) fizinės gerovės; 5) pasitenkinimo rezultatu. Kiekvienas klausimyno atsakymas buvo susumuotas ir paverstas balais nuo 0 iki 100. Iš keturių tyrimų, kuriuose buvo pateikti lyginamieji BREAST-Q klausimynai, tik dviejuose buvo vertinamos visos penkios klausimynų pozicijos. Keturi iš įtrauktų tyrimų pateikė duomenis apie pasitenkinimo krūtimis aspektą. Bendro abiejų KRI metodų pasitenkinimo krūtimis balai buvo geri: 77,3% prepektoralinės KRI grupėje ir 71,1% subpektoralinės KRI grupėje. Kaip matoma 6A priede, remiantis apibendrintais klausimyno balais (vidutinis skirtumas (MD) 6,55; 95 % PI, -1,94-15,04; P=,13), reikšmingo skirtumo tarp prepektoralinės ir subpektoralinės KRI grupių pasitenkinimo krūtimis nebuvo nustatyta. Jungtinė analizė atlikta taikant atsitiktinio efekto modelį, nes nustatytas didelis tyrimų heterogeniškumas (P=.0002, I2= 85%). Panašiai reikšmingų skirtumų nenustatyta ir šiais aspektais: pasitenkinimo rezultatais (6B priedas), seksualinės gerovės (6C priedas) psichosocialinės gerovės (6D priedas) ir fizinės gerovės (6E priedas).

Prepektoralinės KRI operaciniai metodai

Pacientai, jų pagrindinės klinikinės ir patologinės savybės

Taikant įtraukimo ir neįtraukimo į tyrimą kriterijus, atrinkti 98 pacientai, kuriems nuo 2017 m. kovo mėn. iki 2021 m. lapkričio mėn. atlikta SAK-TM ir prepektoralinė KRI. SAK-TM dažniausiai buvo atliekama gydant invazinį KV, neįtariant invazijos į SAK, todėl profilaktinių operacijų dėl genų mutacijų skaičius buvo mažas. Pacientų demografinės ir klinikinės charakteristikos apibendrintos 4 lentelėje. IMR operacinis metodas buvo taikytas 62 (63,3%) pacientams, o likusiems 36 (36,7%) pacientams buvo taikytas apverstos T operacinis metodas. Abiejų grupių pacientų amžius operacijos metu buvo panašus (46,14 ± 11,15, palyginti su 45,17 ± 10,30; p=.766). Apverstos T grupės pacientų vidutinis stebėsenos laikotarpis buvo ilgesnis, tačiau skirtumas nebuvo statistiškai reikšmingas (31,24 ± 14,11, palyginti su 30,84 ± 12,13; p=.912). Beveik visos prepektoralinės KRI abiejose grupėse buvo atliktos taikant vieno etapo, t. y. vienmomentės rekonstrukcijos metodą (91,7%, palyginti su 80,6%; p=.243). Sintetinis tinklelis KRI buvo naudojamas 13 (13,2%) pacientų (11,1%, palyginti su 14,5%, p=.763). Neoadjuvantinės chemoterapijos (47,2%, palyginti

su 38,7%; p=.524), adjuvantinės radioterapijos (36,1%, palygintis su 25,4%; p=.359), sarginio limfmazgio biopsijos (63,9%, palyginti su 71%; p=.504) ir pažasties limfmazgių disekcijos (33,3%, palyginti su 22,6%; p=.342) dažnis abiejose grupėse reikšmingai nesiskyrė.

Komplikacijos

Procedūrų komplikacijos apibendrintos 5 lentelėje. Iš 98 pacientų 25 (25,5%) patyrė bent vieną komplikaciją. Viena dažniausių pooperacinių komplikacijų buvo SAK nekrozė, pasireiškusi iš viso 4 pacientams (8,3%, palyginti su 1,61%; p=.139). Apverstos T grupės trims (8,3%) pacientams pasireiškė SAK nekrozė, iš jų dviems pacientams – dalinė SAK nekrozė ir vienam pacientui – visiška SAK nekrozė. IMR grupėje buvo 1 (1,61%) – dalinė SAK nekrozė. Bendras infekcijos dažnis dviejose grupėse buvo 5,1% (5,5% ir 4,84%, p=1.00), seromos dažnis dviejose grupėse buvo 3,06% (5,5% ir 1,61%, p=.552). Statistiškai reikšmingo skirtumo tarp šių grupių nebuvo. Hematomų (2,7%, palyginti su 0%; p=.367) ir odos nekrozės (2,7%, palyginti su 4,84%; p=1.00) dažnis tarp abiejų grupių taip pat buvo panašus. Implanto pašalinimas buvo atliktas 4 pacientams, iš kurių 3 pacientai priklausė apverstos T grupei (8,3%, palyginti su 1,61%; p=.139). Du implanto pašalinimai įvyko po infekcijos ir visiškos SAK nekrozės (po adjuvantinės RT). Dar vienam pacientui implantas buvo pašalintas po vietinio LA. IMR grupėje 1 pacientui (1,61%) implantas buvo pašalintas dėl visiškos odos nekrozės virš buvusio pjūvio srities. Kapsulinė kontraktūra nebuvo reikšmingai susijusi su amžiumi ir chemoterapija.

Radioterapija po mastektomijos

Atlikus pogrupių analizę, RT grupėje, palyginti su ne RT grupe, buvo akivaizdžiai matomas didesnis komplikacijų dažnis. Po adjuvantinės radioterapijos kapsulinė kontraktūra pasireiškė 17,9% RT grupės pacientų ir 4,29% ne RT grupės pacientų – skirtumas buvo statistiškai reikšmingas (p=.04). Be to, visos 5 kapsulinės kontraktūros atvejai RT grupėje buvo 3 arba 4 Bakerio laipsnio, o ne RT grupėje buvo vienas iš trijų atvejų (p=.06). Implanto netekimo dėl komplikacijų po galutinės prepektoralinės KRI dažnis RT grupėje buvo 10.7%, o ne RT grupėje – 1.42%, rezultatai buvo statistiškai reikšmingi (p=.05). RT grupėje du implantai buvo pašalinti po infekcijos ir visiškos SAK nekrozės, o vienam pacientui ne RT grupėje implantas pašalintas po lokalaus atkryčio. Hematomų (1.42%, palyginti su 0%; p=1.00), odos nekrozės (2,9%, palyginti su 7.14%; p=.321), seromos (2.9%, palyginti su 3.6%; p=1.00) ir infekcijos (4.3%, palyginti su 7.14%; p=.622) dažnis abiejose grupėse statistiškai reikšmingai nesiskyrė (*6 lentelė*).

Onkologiniai rezultatai

Vidutinis stebėsenos laikotarpis buvo 31,24 ± 14,11 mėnesio apverstos T grupėje ir 30,84 ± 12,13 mėnesio IMR grupėje. Nepastebėjome reikšmingų skirtumų tarp abiejų grupių (apverstos T ir IMR), LA (5,5% ir 4,84%; P = 1.00) ar atokaus atkryčio (2,7% ir 1,61%, p=0.1) rodiklių. LA buvo apibrėžiamas kaip biopsijos metu įrodytas vėžio atkrytis ipsilateralinėje krūtinės sienelėje, krūties odoje arba SAK. Bet kuri kita atkryčio vieta buvo laikoma atokiu atkryčiu. Pacientai, kuriems iš pradžių buvo nustatytas atokus atkrytis, į LA grupę nebuvo įtraukti. Iš 62 pacientų IMR grupėje 3 pacientams (4,84%) pasireiškė LA, iš 36 pacientų apverstos T grupėje 2 pacientams (5,5%) pasireiškė LA. Šiame populiacijos pogrupyje taip pat nebuvo reikšmingų skirtumų tarp abiejų grupių pagal amžių diagnozės nustatymo metu, klinikines ir patologines stadijas bei potipį. Nenustatyta ryšio tarp operacijos metodo ir LA.

Vidutinis laikas nuo operacijos iki LA buvo 14 mėnesių. Šių pacientų, kuriems išsivystė LA, amžiaus mediana buvo 37 metai (26–44 metai). Pirminio naviko dydžio mediana buvo 2,2 cm (0,7 – 3cm). Pirminio naviko histologinis požymis 4 atvejais buvo invazinė duktalinė karcinoma, o 1 pacientui – DCIS. Kiekvienoje grupėje buvo po vieną pacientą, kuriam buvo nustatytas atokus atkrytis (2,7%, palyginti su 1,61%, p=0.1). Pirminis naviko histologinis požymis abiem atvejais buvo invazinė duktalinė karcinoma, Apverstos T grupės pacientų grupėje naviko molekulinis potipis buvo luminalinis B, HER2 teigiamas, o IMR grupės – TN. Luminalinio B HER2 teigiamo atveju metastazės buvo smegenyse, o TN – plaučiuose. Vidutinis laikas nuo operacijos iki metastazavimo apverstos T grupėje buvo 14 mėnesių, o IMR grupėje – 17 mėnesių. Trejų metų BI apverstos T grupėje buvo 97,4%, o IMR grupėje – 98,5%.

Gyvenimo kokybė

BREAST-Q klausimynai po KRI buvo pildomi praėjus vidutiniškai dvejiems metams nuo galutinės rekonstrukcijos, įskaitant papildomas operacijas arba intervencijas. Tarp 98 moterų abiejų grupių visų *BREAST-Q* klausimynų rezultatai buvo geri. *7 lentelėje* pateikti abiejų grupių po galutinės KRI pasitenkinimo krūtimis, psichosocialinės gerovės, fizinės gerovės ir seksualinės gerovės aspektų rezultatai. Apverstos T grupės pacientų pasitenkinimo krūtimis aspekto vidutinis pokyčio balas buvo didesnis, palyginti su IMR metodo grupės, tačiau skirtumas nebuvo statistiškai reikšmingas. IMR grupės pacientai buvo labiau patenkinti savo krūtine negu apverstos T grupės, tačiau balai taip pat reikšmingai nesiskyrė (p=.364).

TYRIMO APRIBOJIMAI

Pagrindinis šio tyrimo apribojimas buvo tas, kad tai retrospektyvinis tyrimas, nors ir iš perspektyviai renkamos duomenų bazės. Šiame tyrime pacientai nebuvo atsitiktinės atrankos būdu suskirstyti pagal procedūrų tipus, todėl mūsų rezultatus galėjo suklaidinti neatpažinti demografiniai ar klinikiniai kovariaciniai veiksniai. Tačiau mūsų tyrimas apėmė vieną didžiausių iki šiol atliktų SAK-TM po vienmomentės prepektoralinės KRI serijų dėl invazinio krūties vėžio su ilgalaike stebėsena.

Atliekant metaanalizę didžiausia trūkumas buvo į tyrimą įtrauktų imčių dydžio skirtumai. Nors analizavome 3101, imties dydis tarp tyrimų svyravo – nuo 63 iki 642 pacientų. Taipogi RTPM poveikis chirurginiams rezultatams po KRI buvo atliktas ribotame skaičiuje tyrimų ir kelia šališkumo riziką. Keletas kitų veiksnių, į kuriuos nebuvo atsižvelgta, taip pat galėjo turėti įtakos rezultatams, įskaitant skirtingą stebėjimo trukmę tarp prepektorinės ir subpektorinės KRI.

Nepaisant visų čia įvardytų trūkumų, mes sugebėjome parodyti vienmomentės prepektoralinės KRI saugumą ir atokius rezultatus. Gautiems rezultatams patikrinti būtini tolesni aukštos kokybės daugiacentriniai perspektyviniai tyrimai su didesniu pacientų skaičiumi ir ilgesniu stebėsenos laikotarpiu.

IŠVADOS

1. Atliktos sisteminės apžvalgos ir metaanalizės rezultatai parodė, kad prepektoralinės KRI rezultatai yra lygiagretūs, o kapsulinės kontraktūros, implantų netekimo ir krūtų deformacijos dažnis yra statistiškai reikšmingai mažesnis, palyginti su tais atvejais, kai taikomas subpektoralinės KRI metodas.
2. Mūsų rezultatai ir atlikti moksliniai tyrimai patvirtina tezę, kad taikomi chirurginiai gydymo metodai neturėjo įtakos onkologiniams rezultatams po vienmomentės prepektoralinės KRI.
3. Apverstos T chirurginio metodo taikymas KV pacientams yra saugus būdas, pasižymintis panašių komplikacijų skaičiumi ir optimaliais gyvenimo kokybės rodikliais, palyginti su IMR chirurginiu metodu.
4. RTPM grupės pacientai dažniau patyrė implanto praradimą ir kapsulinę kontraktūrą, palyginti su pacientais, kuriems spindulinis gydymas nebuvo taikytas, nepriklausomai nuo chirurginio gydymo metodo po vienmomentės prepektoralinės KRI.
5. Atliekant vienmomentę prepektoralinę KRI pacientams, sergantiems KV ir turintiems A–B krūtinę, kuriai būdinga 0–I laipsnio ptozė, rekomenduotinas IMR chirurginio gydymo metodas. Apverstos T chirurginio gydymo metodas yra taikytinas KV sergantiems pacientams, turintiems C–D dydžio krūtinę, kuriai būdinga II–III laipsnio ptozė.

REKOMENDACIJOS

1. Prepektoralinė KRI yra saugus ir priimtinas metodas, kuris yra rekomenduotinas KV sergantiems pacientams nepaisant krūties dydžio ir ptozės laipsnio.
2. Atliekant vienmomentę prepektoralinę KRI pacientams, sergantiems KV ir turintiems A–B krūtinę, kuriai būdinga 0–I laipsnio ptozė, rekomenduotinas IMR chirurginio gydymo metodas.
3. Atliekant vienmomentę prepektoralinę KRI apverstos T chirurginio gydymo metodas yra taikytinas KV sergantiems pacientams, turintiems C–D dydžio krūtinę, kuriai būdinga II–III laipsnio ptozė.
4. Atlikto tyrimo rezultatai rodo, kad pacientai, sergantys ankstyvu KV, gali sėkmingai išvengti RT.
5. Tikėtina, kad ši susisteminta informacija, pateikta kaip rekomendacijos, bus naudinga ir aktuali krūtų onkochirurgams tolesniuose tyrimuose ir klinikiniame darbe atliekant SAK-TM kartu su vienmomente prepektoraline KRI pacientams, sergantiems KV.

CURRICULUM VITAE

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International Fellowships:

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2022 09–2022 12 Clinical Fellowship in European Institute of Oncology, Division of Breast Surgery, Milan, Italy

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13. LIST OF PUBLICATIONS

Publications on the subject of the doctoral dissertation

1. **Ostapenko E**, Nixdorf L, Devyatko Y, Exner R, Math P, Wimmer K, Haeusler T, Fitzal F. Ptotic versus Nonptotic Breasts in Nipple-sparing Mastectomy and Immediate Prepectoral Breast Reconstruction. Plast Reconstr Surg Glob Open. 2023 May 26;11(5):e5032. doi: 10.1097/GOX.0000000000005032.
2. **Ostapenko E**, Nixdorf L, Devyatko Y, Exner R, Wimmer K, Fitzal F. Prepectoral Versus Subpectoral Implant-Based Breast Reconstruction: A Systemic Review and Meta-analysis. Ann Surg Oncol (2022) doi:10.1245/s10434-022-12567-0.
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Presentations on the subject of the doctoral dissertation

1. Prepectoral versus subpectoral implant-based breast reconstruction: a systemic review and meta-analysis. Ostapenko, E., Nixdorf, L., Devyatko, Y., Exner R., Wimmer K., Fitzal F. 2022 San Antonio Breast Cancer Symposium, 2022.12.06-10, San Antonio, Texas.
2. Prepectoral versus subpectoral implant-based breast reconstruction. Ostapenko, E., Nixdorf, L., Devyatko, Y., Exner R., Wimmer K., Fitzal F. 36. Jahrestagung der Österreichschen Gesellscchaft fűr Senologie gemeinsam mit der Schweizerischen Gesellschaft fűr Senologie in Innsbruck, 22. Bis 24. September 2022
3. Ptotic versus non ptotic breasts in nipple-sparing mastectomy and immediate prepectoral breast reconstruction. Ostapenko, E., Nixdorf, L., Devyatko, Y., Exner R., Wimmer K., Fitzal F. The 18th St. Gallen international breast cancer conference, 2023.03.15-18, Vienna Austria
4. Prepectoral versus subpectoral implant-based breast reconstruction: a systemic review and meta-analysis. Ostapenko, E., Nixdorf, L., Devyatko, Y., Exner R., Wimmer K., Fitzal F. The 18th St. Gallen international breast cancer conference, 2023.03.15-18, Vienna Austria
5. Immediate prepectoral breast reconstruction: techniques, complications, limitations. Ostapenko, E. Annual International Meeting of the Lithuanian

Senological Society, 2023.05.12, Vilnius, Lithuania.

6. Ptotic versus non ptotic breasts in nipple-sparing mastectomy and immediate prepectoral breast reconstruction. Ostapenko, E., Nixdorf, L., Devyatko, Y., Exner R., Wimmer K., Fitzal F. Annual International Meeting of the Lithuanian Senological Society, 2023.05.12, Vilnius, Lithuania.
7. A retrospective comparison between large ptotic versus small non ptotic breasts in nipple-sparing mastectomy and immediate prepectoral breast reconstruction. Ostapenko, E., Nixdorf, L., Devyatko, Y., Exner R., Wimmer K., Fitzal F. 42nd Congress of the European Society of Surgical Oncology, 25-27 October, 2023, Florence, Italy.

NOTES

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