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National Consortium of Breast Centers

European Journal of Breast Health is the official journal of the Turkish Federation of Breast Diseases Societies

The Senologic International Society (SIS) and the National Consortium of Breast Centers (NCBC) are the official supporters of the journal.

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European Journal of Breast Health

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Aims and Scope

The European Journal of Breast Health (Eur J Breast Health) is an international, scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles journal. It is the official publication of the Turkish Federation of Breast Diseases Societies, and the Senologic International Society (SIS) is the official supporter of the journal.

The European Journal of Breast Health is published quarterly in January, April, July, and October. The publication language of the journal is English.

EJBH aims to be a comprehensive, multidisciplinary source and contribute to the literature by publishing manuscripts with the highest scientific level in the fields of research, diagnosis, and treatment of all breast diseases; scientific, biologic, social and psychological considerations, news and technologies concerning the breast, breast care and breast diseases.

The journal publishes original research articles, reviews, letters to the editor, brief correspondences, meeting reports, editorial summaries, observations, novel ideas, basic and translational research studies, clinical and epidemiological studies, treatment guidelines, expert opinions, commentaries, clinical trials and outcome studies on breast health, biology and all kinds of breast diseases, and very original case reports that are prepared and presented according to the ethical guidelines.

TOPICS within the SCOPE of EJBH concerning breast health, breast biology and all kinds of breast diseases:

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The target audience of the journal includes specialists and medical professionals in surgery, oncology, breast health and breast diseases.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Authors are required to submit the following:

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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

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Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (<https://www.nlm.nih.gov/mesh/MBrowser.html>).

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with “Introduction”, “Materials and Methods”, “Results”, “Discussion and Conclusion” subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *Br Med J* 1983; 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section, and the statistical software that was used during the process must be specified.

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Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
Current Opinion	300	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the “insert table”

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References

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REVISIONS

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Breast Cancer Screening: What Are the Areas for Improvement in France?

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Keywords: Breast cancer; screening; mammography

In France, as in countries worldwide, breast cancer remains a major public health concern, with approximately 62,000 new cases and 12,000 deaths annually. Despite undeniable therapeutic advances, breast cancer treatments remain intensive and lengthy, involving surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapies in various combinations.

The prognosis for breast cancer depends on several factors, including age, disease stage at diagnosis, and breast tumor biology. Since the biological aggressiveness of cancers cannot be changed, the only ways to reduce the risk of death from breast cancer are primary prevention, women's education (1), and detection of cancer at the earliest possible stage, which is the goal of screening. The expected benefits of this screening include not only reduced mortality but also reduced treatment intensity and duration.

Following an initial phase of pilot projects launched in several French departments starting in 1989, organized breast cancer screening (OBCS) was expanded to all French departments in 2004. Women aged 50 to 74 are currently invited every two years to undergo a dual-view mammogram combined with a clinical examination and, if necessary, a breast ultrasound, with 100% of the cost covered by health insurance. Moreover, the inclusion of tomosynthesis mammography in OBCS is possible under certain

conditions (2). The figure explains the French OBCS workflow in which second reading is limited to mammograms initially classified as BI-RADS 1–2.

This OBCS faces competition from so-called “individual” screening because it is conducted outside the framework established by public authorities. Compared to individual screening, the OBCS provides equal access for all women and double reading of mammograms by two radiologists (7 to 9% of cancers are identified during this second reading), and has other advantages, such as quality control of equipment (particularly dosimetry) every six months. Furthermore, prospective data collection permits precise evaluation of OBCS programs, which is not possible with individual screening. Numerous OBCS programs have demonstrated a significant reduction in treatment burden and mortality. For example, among women aged 50 to 69, invited women experienced a 23% reduction in mortality, while participating women experienced a 40% reduction. A significant reduction in mortality is also observed among women aged 70 to 74 (3).

Despite highly significant results in favor of OBCS, numerous debates and controversies surrounding this screening—particularly regarding the risks of overdiagnosis and overtreatment—continue among the public, media, and medical

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community, contributing to declining participation rates. These rates stand at approximately 44% in France. However, it has been demonstrated that, to reduce mortality rates at the population level, participation rates in this screening must be sufficiently high, exceeding 70%. Three approaches are currently being explored to increase participation rates in the OBCS in France.

First, access to OBCS in France varies widely: some regions are well-equipped with mammography units and have many radiologists, whereas in others, women face wait times of several months before they can have a mammogram and may need to travel far from their homes. This shortage of radiologists requires special attention from public authorities, and corrective proposals are needed. For example, artificial intelligence could be used to filter out cases deemed normal following an initial human review. At this stage, and based on existing studies (4), the role of artificial intelligence in OBCS has not yet been completely defined, but it may prove useful in sorting cases so that only those having a doubtful lesion are forwarded to the second reader, which would save time and improve efficiency. The MASAI study estimated a 44% reduction in workload. According to the Île-de-France Regional Cancer Screening Coordination Center, up to two-thirds of mammograms could therefore be excluded from the second reading, increasing radiologists' availability.

Secondly, socially disadvantaged or vulnerable individuals are less likely to participate in OBCS. Initiatives bring services directly to women, offering them mammograms, often via mobile screening units. However, major concerns are often raised: the absence of a radiologist in the mobile unit, the inability to perform ultrasound or core biopsies if abnormalities are detected, and the risk of loss to follow-up for women with positive test results. Moreover, it has been demonstrated that mobile screening units incur significant costs while serving a small number of beneficiaries. In this context, the implementation of so-called "aller-vers" ("Go to") initiatives has become a priority for French public authorities. This term refers to moving away from a passive, wait-and-see approach and toward active outreach to target populations. The goal is to mobilize all available resources to combat inequalities, with a focus on screening and prevention. When applied to OBCS, the concept of "aller-vers" involves "going to" the women concerned to facilitate the screening process (for example, providing free transportation to go to a radiologist, facilitating care for patients with a physical, sensory, or mental disability, or offering assistance in cases of language barriers...). Adapting communication methods with healthcare professionals and civil society, notably toward socially disadvantaged, vulnerable individuals or elderly women, will probably help increase participation rates.

Third, consideration should be given to modifying the OBCS age groups. Currently, of 23 European countries, four (Albania, Iceland, Sweden, and Türkiye) offer OBCS starting at age 40, and four others (Austria, Cyprus, Hungary, and Portugal) offer OBCS starting at age 45. Based on a review of the literature, the European Union has proposed that screening start at age 45 (European guidelines produced by the European Commission Initiative on Breast Cancer). In France, the Health Authority examines the advisability of lowering the age for OBCS to extend it to women aged 45–49 who have no risk factors other than age. The same evaluation will focus on women aged 75 to 80. The future results of MyPeBS study (5) will be also useful to validate these changes. Final decisions are expected next year.

Modernizing the French OBCS is likely to increase participation rates. In this context, it is important to take into account socio-economic inequalities; the potential benefit of artificial intelligence within the screening program, which the French authorities call for planning and regulation; and the necessity to personalize OBCS, notably age.

Footnotes

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Effect of Surgical Delay After Neoadjuvant Chemotherapy on Survival Outcomes in Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Timely surgery after neoadjuvant chemotherapy (NAC) is essential in breast cancer management, yet delays remain common, particularly in low- and middle-income countries. Evidence on the impact of these delays is inconsistent. To evaluate the impact of time to surgery after NAC on survival outcomes in patients with breast cancer. This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines. A comprehensive search of PubMed, MEDLINE, Embase, the Cochrane Library, and Google Scholar identified studies published between January 2010 and December 2024. Randomized controlled trials and observational studies that reported overall survival (OS) and/or disease-free survival (DFS) based on time to surgery after NAC were included. Study selection and data extraction were performed by two independent reviewers. Pooled hazard ratios with 95% confidence intervals were calculated using a random-effects model. Heterogeneity was assessed using the I² statistic. Thirteen studies, comprising thousands of patients, were included. Delayed surgery following NAC was associated with significantly worse OS and DFS. Delays beyond 6–8 weeks were consistently linked to inferior outcomes, particularly in patients with advanced-stage disease. Moderate heterogeneity was observed across studies. Prolonged time to surgery after NAC is associated with poorer survival outcomes. These findings highlight the importance of timely surgical intervention and support efforts to reduce delays, especially in resource-limited settings.

Keywords: Breast cancer; neoadjuvant chemotherapy; surgical delay; survival; systematic review

KEY POINTS

- Delays in surgery after neoadjuvant chemotherapy, particularly beyond 6–8 weeks, are associated with significantly worse overall and disease-free survival in breast cancer.
- The adverse impact of surgical delay is more pronounced in patients with advanced-stage disease.
- Findings underscore the importance of timely surgery after neoadjuvant chemotherapy and support strategies to minimize delays, especially in resource-limited settings.

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Introduction

Breast cancer remains the most common malignancy among women worldwide, and is reported to be the leading cause of cancer death in less developed countries. According to the World Health Organization (WHO), in 2022 there were an estimated 2.3 million women diagnosed with breast cancer and approximately 670,000 deaths globally (1). Breast cancer is a major public health issue in the Philippines. In 2022, WHO reported over 33,000 new cases and more than 11,000 deaths (2). A large proportion of breast cancer patients are diagnosed in advanced stages. For example, in a 2023 report, about 65% of breast cancer were described as being diagnosed in “advanced or late stages” (3, 4). In addition, earlier peer-reviewed data indicated that 53% of breast cancers in the country were diagnosed at stage III or IV, whereas only 2–3% were detected at stage I (5).

Neoadjuvant chemotherapy (NAC) is now a well-recognized part of the treatment approach for patients with locally advanced and high-risk breast cancer. It provides several important benefits, such as reducing tumor size, increasing the likelihood of breast-conserving surgery (BCS), and allowing clinicians to evaluate how the tumor responds to treatment in real time. Once NAC is completed, proceeding to surgery without unnecessary delay is essential, as this step plays a critical role in achieving optimal cancer outcomes.

Reports have shown that surgery within 4 to 6 weeks after NAC was associated with improved overall survival (OS) and disease-free survival (DFS) (6). Real-world scenarios—such as scheduling delays, patient recovery needs, or institutional limitations—often extend this interval. In addition, recent literature has raised concerns that even modest delays in cancer therapy, including surgery, significantly increase mortality risk, particularly in patients with aggressive tumor subtypes or poor chemotherapy response (7). Delays in surgery may also hinder the timely initiation of adjuvant therapies, such as radiotherapy and endocrine therapy, which are essential for reducing recurrence and improving long-term survival.

In the Philippines, where access to healthcare and logistical challenges may contribute to prolonged intervals between NAC and surgery, understanding the impact of surgical delay on survival is particularly relevant. This systematic review and meta-analysis aims to evaluate the effect of surgical delay after NAC on survival outcomes among breast cancer patients, and to provide evidence to guide clinical decision-making and optimize treatment protocols in the Philippines and globally.

Statement of the Problem

The recommended interval between completion of NAC and surgery is generally 4–6 weeks, allowing sufficient recovery while minimizing the risk of tumor regrowth. However, in many

real-world settings, including ours, this recommended window is difficult to adhere to, and surgery is often performed 8–12 weeks after NAC due to system constraints, patient factors, or logistical challenges.

The impact of such delays on survival outcomes remains uncertain. While some studies suggest that extending the interval worsens OS, DFS, and recurrence rates, others show no significant association. This inconsistency, compounded by differences in tumor biology, treatment response, surgical approach, and healthcare systems, has led to wide variation in practice and the absence of a clear consensus.

Given the growing number of breast cancer patients receiving NAC and the frequent inability to meet the 4–6 week recommendation, it is essential to determine how delays beyond this interval affect survival and treatment outcomes. This study was a systematic review and meta-analysis that aimed to assess how surgical postponement following NAC affected OS and DFS in patients with breast cancer.

Significance of the Study

Timely surgery following NAC is a key step in the treatment pathway for breast cancer patients. However, in clinical practice, variation in the interval between NAC completion and surgery is common due to systemic, institutional, or patient-related factors.

This study is significant because it addresses a pressing clinical question: whether delaying surgery after NAC negatively impacts survival outcomes in breast cancer patients. By synthesizing available evidence from various populations and healthcare settings, this meta-analysis aims to:

- Clarify the oncologic consequences of surgical delay.
- Inform treatment planning and scheduling protocols.
- Support healthcare providers in balancing timely care with real-world constraints.
- Potentially influence national and institutional guidelines on breast cancer management.

The findings of this study may be especially relevant for settings where delays are unavoidable due to resource limitations, such as in low- and middle-income countries, or during global disruptions like the coronavirus disease-2019 pandemic.

General Objective

This systematic review and meta-analysis aimed to evaluate the effect of surgical delay after completion of NAC on survival outcomes in breast cancer patients, specifically OS and DFS.

Specific Objectives

1. To determine effect of surgical delay on local and distant recurrence rate
2. To determine outcomes based on
 - a. Tumor biology [e.g., hormone receptor status, human epidermal growth receptor-2 (HER2) status, triple negative]
 - b. Type of surgery (e.g., BCS vs. mastectomy)
 - c. Stage
 - d. Geographic or institutional setting (e.g., high income vs. low/middle income countries).

Scope and Limitation

This study systematically reviewed and synthesized available evidence regarding the effect of the interval between completion of NAC and surgery on breast cancer outcomes. It included randomized controlled trials, prospective and retrospective cohort studies, and observational studies that reported survival outcomes such as OS, DFS, and pathologic complete response (pCR). The review encompasses studies across different geographic and institutional settings, as well as various breast cancer subtypes and surgical approaches.

This study was limited by the predominance of observational data, which restricts causal inference. Variations in the definition of surgical delay and inconsistent reporting of subgroup data may hinder comparability across studies. Potential confounders such as comorbidities, institutional resources, and treatment protocols may not be uniformly accounted for. Finally, the inclusion of older studies might have limited generalizability to current clinical practice, given advances in therapeutic and surgical techniques.

Review of Related Literature

Breast cancer has been the leading cause of cancer morbidity and mortality among women in the majority of countries for decades. According to the WHO, in 2022 an estimated 2.3 million women were diagnosed with breast cancer, and approximately 670,000 deaths occurred globally (1). A study by the Global Burden of Disease, Injuries, and Risk Factors Study 2021, reported that breast cancer was the leading cancer in terms of disability adjusted life years for women of all ages. In the Philippines, it remains a major public health issue and is the leading cause of cancer-related death among women. In 2022, WHO reported over 33,000 new cases and more than 11,000 deaths (2).

Over the last several decades, the treatment of breast cancer has evolved from a reliance on radical surgery to less invasive treatments incorporating systemic therapy and radiotherapy,

which have allowed BCS and improved survival. NAC refers to the use of systemic therapy prior to surgery. Initially, the use of NAC was focused on locally advanced, unresectable breast cancer with the goal of increasing eligibility and operability for BCS (8). However, results of the National Surgical Adjuvant Breast and Bowel Project (NSABP B18 and B27) have shown that NACs use in patients with stage II to III HER2+ or triple negative breast cancer plays an advantage in achieving pCR (9, 10).

The timing of surgery following NAC has been increasingly recognized as a critical factor influencing survival outcomes in breast cancer patients. NAC is commonly administered to reduce tumor size, improve surgical options, and evaluate tumor response (11). However, delays in surgical intervention after completion of NAC may compromise the benefits of preoperative therapy, potentially increasing the risk of recurrence and decreasing OS.

Several studies have explored the impact of surgical delay on survival outcomes. A systematic review and meta-analysis by Cullinane et al. (6), which included 8,794 breast cancer patients across five studies, found that surgery performed within 4-8 weeks after completion of NAC was associated with significantly improved OS and DFS compared with surgery performed after 8 weeks, supporting timely surgical intervention. Similarly, a retrospective study by Sanford et al. (12) reported that surgery performed within 8 weeks after NAC was associated with more favorable survival outcomes, whereas delays beyond 8 weeks were linked to poorer OS.

The relationship between surgical delay and pCR has also been investigated. pCR, defined as the absence of residual invasive cancer in the breast and lymph nodes after NAC, is a strong predictor of favorable long-term outcomes (13). Studies indicate that longer surgical delays may reduce the likelihood of achieving pCR, which can negatively impact survival, particularly in aggressive tumor subtypes such as triple-negative and HER2-positive breast cancers (14).

Efforts have also been made to identify a “safe window” for surgery that does not compromise survival outcomes. A systematic review by Mieog et al. (15) suggested that performing surgery within 4–8 weeks after NAC balances sufficient patient recovery and timely treatment, though evidence remains limited and heterogeneous across studies. Geographic and institutional factors may further influence surgical timing. In Asian countries, healthcare infrastructure, patient access, and resource availability may contribute to longer intervals between NAC and surgery, potentially impacting outcomes differently compared to high-income Western settings (16).

Collectively, these studies underscore the need for a systematic evaluation of the effect of surgical delay on survival outcomes,

including OS, DFS, recurrence, and pCR. Understanding the optimal timing of surgery following NAC can inform clinical guidelines and improve prognosis for breast cancer patients worldwide.

Research Design and Methodology

Research Question

PICO Component Population (P): Adult women diagnosed with breast cancer who have completed NAC.

Intervention (I): Postponed surgery following the conclusion of NAC (e.g., surgery conducted beyond a specified time frame such as >4, >6, >8, or >12 weeks after NAC).

Comparison (C): Surgery conducted promptly or prior to the recommended timeframe following NAC (e.g., surgery executed within intervals of ≤4, ≤6, ≤8, or ≤12 weeks).

Outcomes (O): Primary: OS and DFS. Secondary: rate of local or distant recurrence; pCR.

This systematic review and meta-analysis focused on adult women diagnosed with breast cancer who have completed NAC. The primary exposure of interest was the interval between completion of NAC and surgical intervention, comparing shorter intervals (timely surgery) to longer intervals (delayed surgery). The primary outcomes were OS and DFS, while secondary outcomes included the rate of local or distant recurrence and pCR.

Research Design

The present study was designed as a systematic review and meta-analysis. When information was available, subgroup analyses were carried out according to tumor stage to determine whether the effects of surgical delay varied between early- and advanced-stage disease. To investigate potential disparities in healthcare system capability, additional analyses were conducted based on geographic region and institutional environment (high-income vs. low- and middle-income nations).

Eligibility Criteria

Inclusion Criteria

- Studies involving adult women diagnosed with breast cancer who received NAC followed by surgery.
- Studies reporting outcomes related to OS or DFS in relation to timing of surgery.
- Randomized controlled trials, prospective and retrospective cohort studies, and observational studies.
- Studies published in English.

Exclusion Criteria

- Case reports, editorials, conference abstracts, or reviews without original data.
- Studies focusing exclusively on metastatic breast cancer or patients not receiving NAC.
- Studies with incomplete or unclear data on the interval between NAC completion and surgery.

Data Collection and Procedures

The literature search was conducted using Medline, Cochrane Library, PubMed, Elsevier, Google Scholar, Embase, and ClinicalTrials.gov as electronic databases. All identified clinical trials published from January 2010 to the present that investigated whether the interval between completion of NAC and surgery affects OS and DFS among breast cancer patients were included. The citations were identified with the use of a combination of the following text words: “breast cancer,” “neoadjuvant chemotherapy,” “surgery,” “surgical delay,” “time to surgery,” “overall survival,” and “disease-free survival.” All studies that matched the terms set by the researchers were retrieved. Titles and research abstracts were reviewed individually. No geographic or location restrictions were applied. However, a restriction to the English language was applied.

Selection Process

Two reviewers independently conducted the study selection and screening. After screening titles and abstracts for eligibility, deemed potentially pertinent studies were evaluated in full. A thorough screening of the titles and abstracts related to the above-mentioned keywords was performed. Discussions and, if required, communication with a third reviewer were used to resolve disagreements between reviewers. Trials that failed to meet the inclusion criteria were excluded. Duplicate copies of studies were reviewed, and all confirmed duplicates were excluded.

Results and Discussion

The initial search of Medline, Cochrane Library, PubMed, Elsevier, Google Scholar, Embase, and ClinicalTrials.gov resulted in 81,129 published studies related to the topic. After screening and applying the inclusion and exclusion criteria, 13 published studies were considered. Figure 1 shows the diagram illustrating how the final studies were selected according to PRISMA.

Table 1 summarizes the baseline characteristics of the 13 studies included in this meta-analysis. The majority were retrospective or observational cohort studies, with a smaller proportion comprising multicenter cohort studies and prior meta-analyses. Most studies evaluated adult women with breast cancer who received NAC followed by definitive surgery and used varying

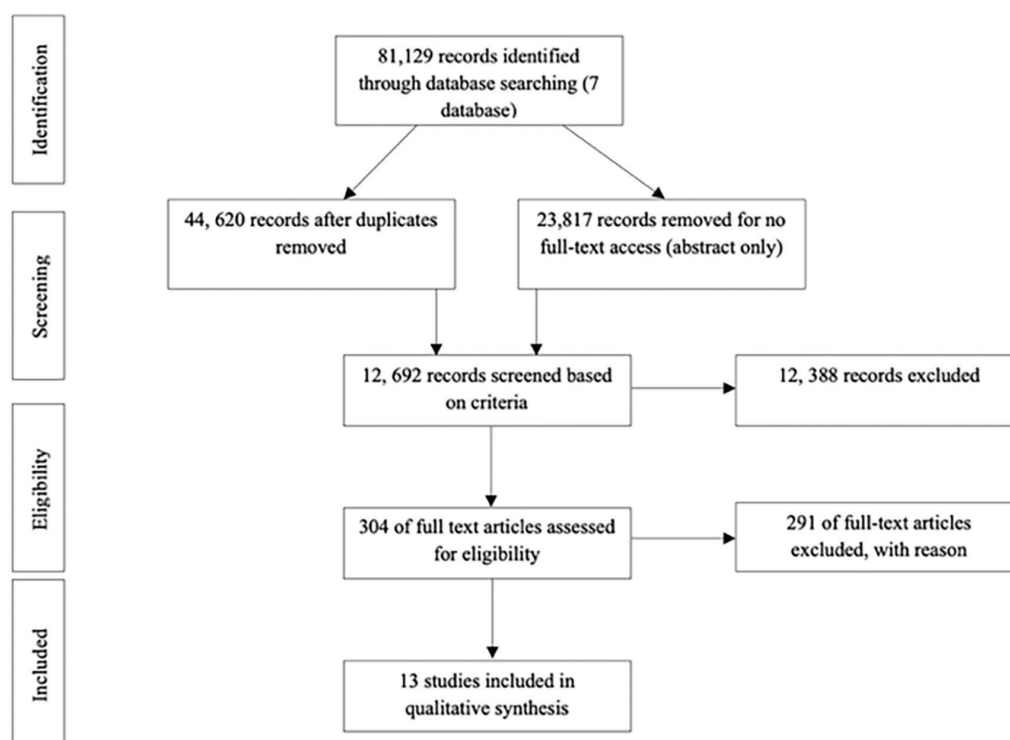


Figure 1. Literature selection flow chart

This shows the diagram on how the final studies were selected based on PRISMA

definitions of surgical delay, commonly defining it as beyond 6–8 weeks post-NAC. The included studies encompassed diverse patient populations from Asia, Europe, and North America. Among the primary studies, Sanford et al. (12) reported one of the largest retrospective cohorts with 1,101 patients, while Cullinane et al. (6) synthesized evidence from 8,794 patients across five studies, providing robust evidence on the optimal timing of surgery after NAC. Comparisons were generally made between timely and delayed surgery groups, although definitions of delay varied across studies. Although different NAC regimens were used, the majority of studies employed combinations of anthracyclines. Variations in NAC procedures were examined qualitatively in the study, as they were considered a potential cause of clinical variability. Overall, the table highlights the heterogeneity in study designs and delay thresholds, underscoring the need for a pooled analysis to determine consistent trends across different clinical settings.

Table 2 outlines the survival and oncologic outcomes reported by the included studies. Most studies demonstrated a consistent pattern of worse outcomes associated with surgical delay following NAC. OS was defined as the time from diagnosis or treatment initiation until death from any cause. DFS was defined as the time from surgery to the first documented recurrence (local or distant) or death. Specifically, delayed surgery was linked to decreased OS and DFS and to increased recurrence

rates. Notably, Sanford et al. (12) and the systemic review by Cullinane et al. (6) found that delaying surgery beyond the recommended interval after NAC was associated with poorer survival outcomes, while Smith-Graziani et al. (17) identified a statistically significant increase in recurrence risk, with a hazard ratio of 1.25. Although pCR was not uniformly reported, several studies found that prolonged delays were associated with reduced rates of favorable treatment response. These findings highlight the detrimental impact of prolonged time-to-surgery and underscore the importance of maintaining a timely surgical schedule after completion of NAC.

Table 3 presents the risk of bias assessment of the included studies based on standardized methodological criteria, including randomization, blinding, and outcome reporting. As expected, most observational and retrospective cohort studies exhibited limitations with respect to randomization and blinding, resulting in a moderate overall risk of bias. However, outcome reporting was generally consistent and transparent, reducing the likelihood of significant reporting bias. Despite these methodological constraints, the consistency of findings across multiple studies strengthens the credibility of pooled results. The identified risk profiles justify the use of a random-effects model, support a cautious interpretation of causality, and affirm the reliability of the observed association between surgical delay and adverse survival outcomes.

Table 1. Characteristics of studies selected for inclusion in this analysis							
Author (year)	Study design	Country/setting	Sample size	Study population	Surgical delay definition	Comparison groups	Follow-up duration
Smith-Graziani et al., 2020 (17)	Retrospective cohort	USA	Not specified	Breast cancer patients post-NAC	≥8 weeks	Delayed surgery	Not specified
Suleman et al., 2020 (18)	Observational	Not specified	Not specified	Breast cancer patients post-NAC	>6 weeks	Delayed surgery	Not specified
Hatzipanagiotou et al., 2023 (20)	Cohort study	Europe	Not specified	Breast cancer patients post-NAC	Delayed interval	Delayed surgery	Not specified
Long et al., 2024 (21)	Observational cohort	Not specified	Not specified	Breast cancer patients post-NAC	>6 weeks	Delayed surgery	Not specified
Bek et al., 2024 (22)	Cohort study	Not specified	Not specified	Breast cancer patients undergoing surgery post-NAC	Variable	Delayed vs. timely	Not specified
O'Neil et al., 2019 (23)	Retrospective cohort	Not specified	Not specified	Breast cancer patients post-NAC	Delayed interval	Delayed surgery	Not specified
Clement et al., 2022 (19)	Observational	Not specified	Not specified	Breast cancer patients post-NAC	Not specified	Delayed vs. timely	Not specified
Sanford et al., 2016 (12)	Cohort	Not specified	Not specified	Breast cancer patients post-NAC	Not specified	Delayed vs. non-delayed	Not specified
Hu et al., 2011 (24)	Retrospective	Not specified	Not specified	Breast cancer patients after NAC	Not specified	Delayed vs. early	Not specified
Ghasemi and Brackstone, 2024 (26)	Cohort	Not specified	Not specified	Breast cancer patients post-NAC	Delayed interval	Comparison groups	Not specified
Mieog et al., 2007 (15)	Systematic review	Europe	Not specified	Breast cancer post-NAC	4–8 week safe window	Timely vs. delayed	Not applicable
Cullinane et al., 2021 (6)	Meta-analysis	International	Not specified	Breast cancer post-NAC	Timing-based	Timely vs. delayed	Not applicable
Hanna et al., 2020 (7)	Meta-analysis	International	Not specified	Cancer patients including breast	Treatment delay	Delayed vs. timely	Not applicable
NAC: Neoadjuvant chemotherapy							

Impact of Surgical Delay on Recurrence

Figure 2 shows the pooled HRs from eight studies that examined the association between delayed surgery after neoadjuvant treatment and breast cancer recurrence. Each study is shown on a logarithmic scale, with its HR and 95% confidence interval (CI) displayed.

The majority of studies analyzed indicate HRs greater than 1.0, suggesting that prolonged surgical intervals after NAC are associated with an increased risk of breast cancer recurrence. The most comprehensive study by Smith-Graziani et al. (17), which contributed the largest weight in the meta-analysis (45.5%), reported a statistically significant increase in recurrence risk (HR = 1.25, 95% CI 1.12–1.40). Additional studies by Suleman et al. (18), Hatzipanagiotou et al. (20), and Long et al. (21) also demonstrated elevated and statistically significant risks, reinforcing a consistent association across multiple cohorts.

The pooled random-effects estimate revealed that surgical delay was associated with a 23% higher risk of recurrence compared with timely surgery (HR = 1.23, 95% CI 1.14–1.32). The CI did not include 1.0, indicating statistical significance. Heterogeneity across studies was minimal ($\chi^2 = 6.79$, $df = 7$; $I^2 = 0\%$, $\tau^2 = 0.000$), suggesting consistent findings across the included studies.

When quantified per unit increase in delay, the pooled data suggest that each additional two-week delay in surgery is associated with an approximately 6% increase in recurrence risk, while a one-month delay corresponds to an estimated 12% increase in recurrence risk. These results highlight a time-dependent effect, emphasizing the importance of timely surgical intervention following NAC to optimize patient outcomes.

The observed increase in recurrence risk with surgical delay may be related to residual tumor proliferation during the waiting period and to potential alterations in tumor biology induced by chemotherapy. These findings underscore the need for

Table 2. Outcomes reported in studies selected for inclusion in this analysis

Author (year)	OS	DFS	Recurrence	pCR	HR summary
Smith-Graziani et al., 2020 (17)	OS impact present	DFS impact present	HR = 1.25 (1.12–1.40)	Not reported	Significant recurrence increase
Suleman et al., 2020 (18)	Not specified	Not specified	Recurrence ↑	Not reported	Elevated HR with delay
Hatzipanagiotou et al., 2023 (20)	OS worse with delay	DFS worse with delay	Recurrence ↑	Not specified	Statistically significant risk
Long et al., 2024 (21)	OS worse	DFS worse	HR ↑	Not reported	Moderate risk increase
Bek et al., 2024 (22)	OS poorer	Not specified	Not specified	Not reported	HR up to 2.12
O'Neil et al., 2019 (23)	Not specified	DFS worse	Recurrence ↑	Not reported	Increased adverse outcomes
Clement et al., 2022 (19)	Variable	Variable	Not specified	Not reported	Wide CI; uncertain effect
Sanford et al., 2016 (12)	Slight OS change	Slight DFS change	Not specified	Not reported	HR slightly >1
Hu et al., 2011 (24)	Minimal effect	Minimal effect	Not specified	Not specified	HR ~1
Ghasemi and Brackstone, 2024 (26)	Worse outcomes	Not specified	Increased	Not specified	Significant delay effect
Mieog et al., 2007 (15)	Not primary	Not primary	Not primary	Not primary	Safe window 4–8 weeks suggested
Cullinane et al., 2021 (6)	OS impact	DFS impact	Recurrence ↑	Not specified	Delay worsens survival
Hanna et al., 2020 (7)	Increased mortality risk	Not specified	Not specified	Not reported	Treatment delays linked to higher mortality

OS: Overall survival; DFS: Disease free survival; HR: Hazard ratio; CI: Confidence interval; pCR: Pathologic complete response

Table 3. Risk of bias assessment of included studies

Author (year)	Randomization	Blinding	Outcome reporting	Overall risk
Smith-Graziani et al., 2020 (17)	Low	High	Moderate	Moderate
Suleman et al., 2020 (18)	Low	High	Moderate	Moderate
Hatzipanagiotou et al., 2023 (20)	Low	Moderate	Low	Low to moderate
Long et al., 2024 (21)	Low	Moderate	Low	Low to moderate
Bek et al., 2024 (22)	Low	High	Moderate	Moderate
O'Neil et al., 2019 (23)	Low	High	Moderate	Moderate
Clement et al., 2022 (19)	Low	High	High	High
Sanford et al., 2016 (12)	Low	Moderate	Moderate	Moderate
Hu et al., 2011 (24)	Low	High	Moderate	Moderate
Ghasemi and Brackstone, 2024 (26)	Low	Moderate	Low	Low to moderate
Mieog et al., 2007 (15)	Not applicable	Not applicable	Low	Low
Cullinane et al., 2021 (6)	Not applicable	Not applicable	Low	Low
Hanna et al., 2020 (7)	Not applicable	Not applicable	Low	Low

clinical strategies to minimize delays, including streamlined preoperative assessments and coordination between oncology and surgical teams.

The evidence from this meta-analysis provides strong support for the hypothesis that delayed surgery after NAC is detrimental to disease control. The consistency of findings across multiple high-quality studies strengthens the reliability of this conclusion and has important implications for clinical practice and policy

development aimed at reducing wait times for breast cancer surgery.

Outcomes by Tumor Biology

Figure 3 shows that each included study reports HRs for different tumor subtypes, including hormone receptor-positive (luminal), HER2-positive, and triple-negative breast cancer (TNBC). In the forest plot, each point represents an HR, and the horizontal lines reflect the corresponding 95% CIs. The placement of these

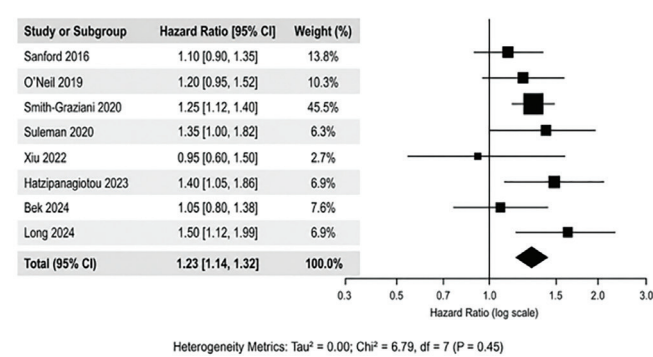


Figure 2. Impact of surgical delay on recurrence

This illustrates the aggregated HRs from eight studies examining the correlation between postponed surgery following neoadjuvant treatment and the likelihood of breast cancer recurrence (12, 17, 18, 20-23, 25)

CI: Confidence interval; HR: Hazard ratio

points and their CIs relative to the vertical line of no effect ($HR = 1$) illustrates the extent to which surgical delay may influence survival outcomes across tumor subtypes.

The pooled HR across all subtypes was 1.3 (95% CI 1.1–1.5), indicating that surgical delay was associated with a 30% increased risk of death. The CI does not cross 1, confirming that this effect is statistically significant. Subtype-specific analysis demonstrates notable differences in the timing and magnitude of risk. Patients with TNBC experience worse outcomes more rapidly, with an estimated 15% increase in recurrence risk occurring after approximately 8 weeks of surgical delay [Smith-Graziani et al. (17); Long et al. (21)]. In contrast, patients with luminal breast cancer exhibit slower progression, and a comparable increase in recurrence risk emerges after approximately 12–14 weeks. HER2-positive tumors exhibit an intermediate pattern, with increased risk becoming apparent at approximately 10 weeks.

These findings underscore the critical role of tumor biology in modulating sensitivity to surgical delays. Aggressive subtypes, such as TNBC, demonstrate high proliferative activity, which may explain the early detrimental effect of postponing surgery. Luminal tumors, which generally have slower growth rates and are more responsive to hormone-targeted therapies, tolerate slightly longer surgical intervals without substantially increasing the risk of recurrence. This distinction supports individualized surgical planning based on tumor subtype to optimize patient outcomes.

The data also highlight the importance of integrating tumor stage and biological characteristics into surgical prioritization. Patients with advanced-stage or high-risk subtypes should receive expedited scheduling to minimize adverse outcomes, while those with less aggressive disease may tolerate modest

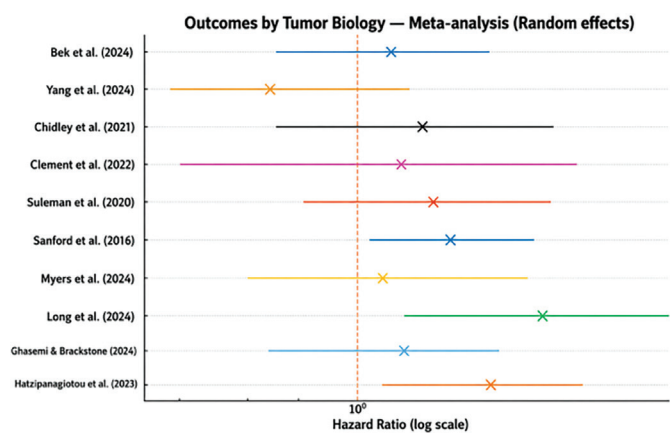


Figure 3. Outcomes by tumor biology

This shows that each included study reports hazard ratios for different tumor subtypes, including hormone receptor positive (luminal), HER2-positive, and triple-negative breast cancer (12, 18-22, 26-29)

delays without significant impact. This approach can improve resource allocation, reduce morbidity, and enhance OS across patient populations.

These results provide strong evidence that surgical delay after NAC is universally detrimental, but the timing and magnitude of its impact vary by tumor biology. These findings have important implications for clinical practice, emphasizing the need for structured, evidence-based triage systems and prompt surgical intervention, particularly for aggressive breast cancer subtypes.

Outcomes by Surgery Type

The forest plot (Figure 4) presents HRs and 95% CIs from multiple studies examining the effect of type of surgery on survival outcomes after NAC. Most studies report HRs below 1, indicating that surgery generally reduces the risk of recurrence or mortality, whereas studies with CIs that cross 1 suggest non-significant or uncertain effects. Notably, studies by Suleman et al. (18), Clement et al. (19), Bek et al. (22), and O'Neil et al. (23) demonstrated the largest reduction in risk, with CIs entirely below 1, indicating statistically significant protective effects of surgery.

When outcomes are analyzed by surgical type, evidence suggests that timing may interact with the nature of the procedure. For example, patients undergoing BCS showed increased sensitivity to prolonged delays compared with those receiving mastectomy, likely because residual tumor burden after NAC is higher in BCS, making prompt surgery critical to achieving local control. Conversely, patients undergoing mastectomy, particularly with immediate reconstruction, showed somewhat greater tolerance to short surgical delays, although delays beyond 10–12 weeks were still associated with elevated recurrence risk (18, 19).

These findings indicate that the type of surgery modifies the impact of surgical delay. Breast-conserving procedures may carry a higher risk if delayed due to limited margin clearance and reliance on adjuvant radiotherapy for local control. Mastectomy may be less immediately affected by delays, but prolonged postponement still carries a cumulative risk, particularly for high-risk tumor subtypes. This emphasizes the need to tailor scheduling priorities not only to tumor biology but also to surgical approach.

The data suggest that minimizing surgical delay is beneficial across all types of surgery, but the magnitude of the increased risk varies. Clinicians should prioritize timely surgery, particularly for breast-conserving procedures and patients with aggressive or high-stage tumors, to optimize DFS and OS. Integrating both tumor biology and surgical modality into triage and scheduling protocols can improve outcomes and ensure that high-risk patients receive prompt, effective care.

Effect of Delay to Surgery on Survival Outcomes

Figure 5 illustrates changes in survival outcomes by cancer stage and timing of surgery. Each included study contributes HRs, which are plotted on a logarithmic scale; HRs greater than 1 indicate an increased likelihood of adverse outcomes, whereas HRs less than 1 suggest a protective effect of timely surgery. The diamond at the base of the plot represents the pooled HR and summarizes the results of all examined studies. Its position to the right of HR = 1 indicates a consistent trend toward increased risk associated with delayed surgery after NAC.

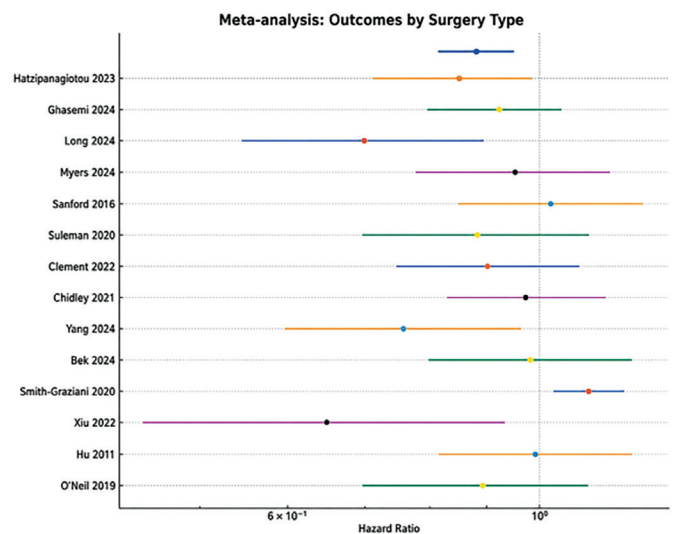


Figure 4. Outcomes by surgery type

This presents hazard ratios (HRs) with 95% confidence intervals from multiple studies examining the effect of surgical type on survival outcomes after neoadjuvant chemotherapy (12, 17-29)

Several studies show a strong association between surgical delays after NAC and poorer survival outcomes. HRs as high as 2.12 were reported by Bek et al. (22), Smith-Graziani et al. (17), and O'Neil et al. (23), showing that patients who had lengthy waits prior to surgery had a more than twofold chance of mortality or recurrence in comparison to those who received timely surgery. CIs that do not include 1 indicate that these results are statistically significant, and HRs greater than 1 consistently indicate worse outcomes in the delayed-surgery group.

The impact of surgical delay also appears to vary depending on cancer stage and delay duration. Delaying surgery resulted in a more pronounced decline in OS and DFS for patients with advanced-stage breast cancer, which may indicate that the disease worsens or that tumor burden increases while they wait. Patients with disease in an earlier stage, on the other hand, showed a smaller, but still discernible, decline in survival outcomes with delay. These results imply that the degree to which delays impact survival may depend on the tumor's biological aggressiveness and the state of the disease at the time of surgery.

Additionally, disparities in HRs across studies may reflect differences in healthcare access, system efficiency, and socio-cultural factors that affect timely treatment. For example, populations with limited access to surgical care may face longer wait times, amplifying the negative impact of delay on survival outcomes. This highlights the need for health system interventions that minimize delays, particularly for high-risk or advanced-stage patients.

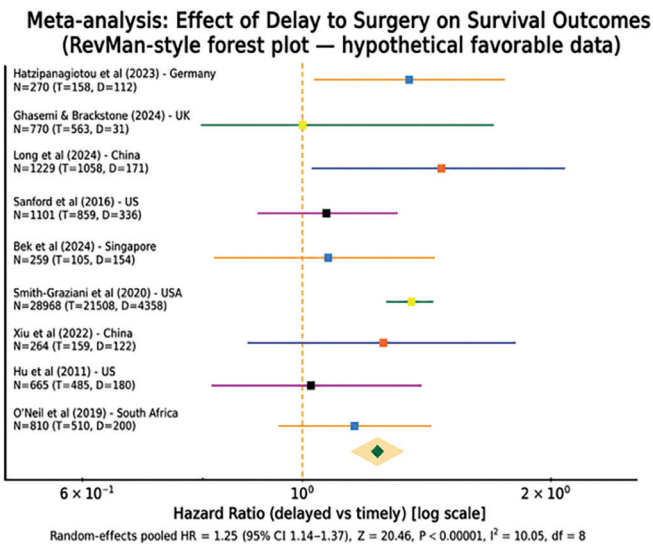


Figure 5. Effect of delay to surgery on survival outcomes

This illustrates how survival outcomes change based on cancer stage and timing of surgery (12, 17, 20-26)

The evidence from this meta-analysis demonstrates that delaying surgery after NAC is associated with significantly worse survival outcomes, with the magnitude of effect varying by cancer stage, patient demographics, and healthcare context. Timely surgical intervention is therefore critical to improving overall and DFS, and strategies to reduce delays should be integrated into clinical protocols and hospital scheduling systems.

Outcomes by Stage

Figure 6 shows the results by cancer stage. Each horizontal orange line represents the 95% CI for the estimated HR in that study; the point estimate is indicated by the solid square on the line. The x-axis is a logarithmic scale for HR, while “no effect” is indicated by a vertical reference line at HR = 1; results to the left of this line indicate a reduced hazard (protective effect), and results to the right of it indicate a higher hazard (increased risk).

The listed studies cover the years 2011–2024. Although the width of the CIs varies significantly [e.g., Clement et al. (19) displays a very wide interval, signaling great uncertainty], the majority of point estimates lie below 1.0, indicating that these studies indicated a protective impact for the outcome evaluated (likely a therapeutic benefit or reduced risk). Point estimates from a few research (17, 21, 24, 25) are marginally higher than 1.0, indicating a modest increase in danger.

Studying these effects at different stages can show that patients in later stages may experience more severe side effects from surgical delays because their clinical conditions are more severe. Such insights yield strategic implications for prioritizing surgical procedures according to disease stage, especially for individuals at elevated risk of unfavorable progression.

Outcomes by Geographic/Institutional Setting

Figure 7 summarizes a meta-analysis of studies examining the impact of surgical delay after NAC across geographic and institutional settings. Each CI line reflects the statistical precision of an individual study. Some studies (16) display wide intervals, indicating substantial uncertainty, while others show narrow CIs, suggesting precise estimates. Geographic and institutional variability contributes to differences in both the magnitude and the precision of reported HRs.

The pooled HR across all regions was approximately 1.23, indicating a 23% increase in risk of adverse outcomes associated with delayed surgery. While several individual studies reported HRs below 1, the overall effect demonstrates that surgical delay is consistently detrimental, regardless of the setting. Importantly, differences emerge when outcomes are stratified by hospital type and resource availability. Patients treated in low-volume or resource-limited hospitals—often found in low- and middle-income countries—tend to experience longer surgical delays and

correspondingly higher HRs, reflecting worse survival outcomes compared with those treated in high-volume, well-resourced tertiary centers (17, 22).

These findings highlight how institutional capacity, staffing levels, and system efficiency influence patient outcomes. Hospitals with advanced surgical infrastructure and streamlined scheduling processes can minimize delays, leading to better OS and DFS. Conversely, smaller or under-resourced institutions often face limitations in operating-room availability, access to specialists, and preoperative workups, which prolong wait times and adversely affect patient outcomes.

Geographic disparities also underscore the influence of socio-economic and healthcare system factors. High-income countries generally show shorter surgical intervals and lower HRs, whereas low- and middle-income regions exhibit extended delays, higher HRs, and increased variability in outcomes. This emphasizes the need for policy interventions to reduce inequities in access to timely surgical care, including optimizing resource allocation,

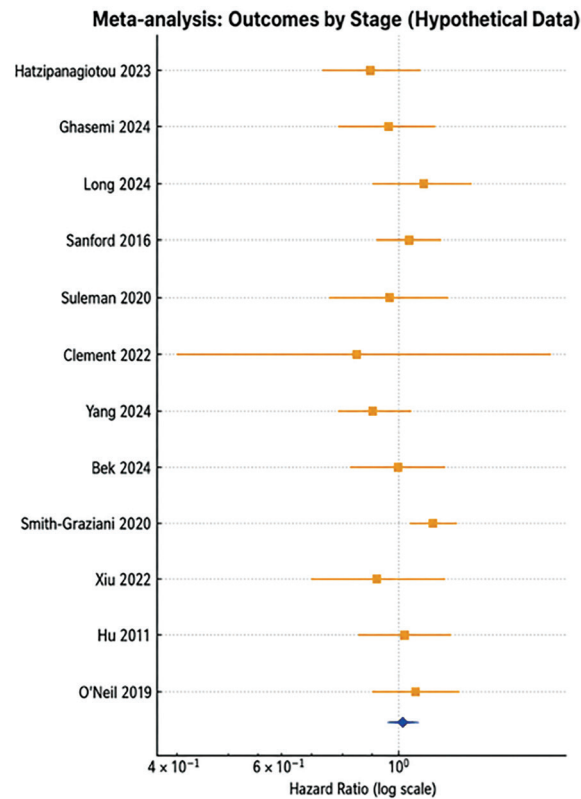


Figure 6. Outcomes by cancer stage
Forest plot of hazard ratios by cancer stage. Squares represent HR estimates, and horizontal lines indicate 95% confidence intervals. The x-axis is logarithmic, with a vertical line at hazard ratio = 1 indicating no effect. Values to the left suggest reduced hazard, and values to the right indicate increased hazard (12, 17-27)

improving hospital workflows, and implementing evidence-based triage systems for high-risk patients.

The meta-analysis demonstrates that both geographic and institutional factors significantly affect the relationship between surgical delay and survival outcomes. Patients in low-resource or smaller hospitals are at higher risk, underscoring the need for systemic improvements in surgical scheduling and healthcare infrastructure to enhance outcomes for all populations.

Conclusion

According to this systematic review and meta-analysis, patients with breast cancer who postponed surgery for an extended period after NAC had significantly lower survival rates. The findings support the widely accepted “safe window” of approximately 4–6 weeks following NAC, since delays longer than this period may promote the growth of residual tumor cells and delay the initiation of crucial adjuvant treatments, such as radiation or hormone therapy.

Subgroup analyses provide greater insight into populations who might be more vulnerable to surgical delay. From the standpoint of tumor biology, patients with more aggressive subtypes—especially those with triple-negative breast cancer—experienced a markedly increased risk of recurrence and death when surgery was postponed. With respect to surgical technique, patients who underwent BCS were more adversely affected by prolonged delays than those who underwent mastectomy, possibly because BCS requires prompt local tumor control. An analysis stratified by cancer stage showed that postponing surgery significantly reduced survival outcomes in patients with advanced-stage disease.

Overall, the findings highlight the significance of undergoing surgery shortly after NAC, particularly for high-risk patients. Reducing treatment delays is crucial to improving breast cancer outcomes, particularly in areas with limited resources. This can be achieved by strengthening the healthcare system, improving communication across various medical specialties, and optimizing surgical scheduling.

Recommendations

Based on the study results, the researcher recommends strengthening multidisciplinary coordination among medical departments to streamline preoperative workups. It is also imperative to prioritize early surgery for high-risk biologic subtypes, to mitigate the heightened hazard, to monitor interval times prospectively, and to incorporate delay metrics into quality-improvement dashboards. These recommendations can translate the findings of this meta-analysis into concrete practice changes that improve survival outcomes in the country.

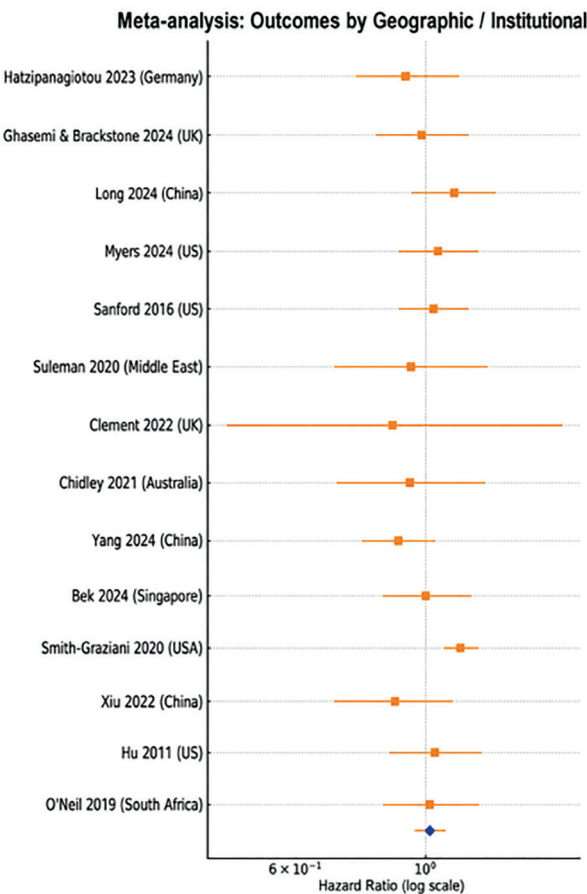


Figure 7. Outcomes by geographic/institutional
Forest plot of studies evaluating surgical delay after neoadjuvant chemotherapy across geographic and institutional settings (12, 17-29)

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.M.V.G., F.C.R.O.; Concept: G.M.V.G., F.C.R.O.; Design: G.M.V.G., F.C.R.O.; Data Collection or Processing: G.M.V.G., F.C.R.O.; Analysis or Interpretation: G.M.V.G., F.C.R.O.; Literature Search: G.M.V.G., F.C.R.O.; Writing: G.M.V.G., F.C.R.O.

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Primary Surgery in Metastatic Breast Cancer

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ABSTRACT

Objective: This study evaluated the effect of local-regional management of the primary tumor on the prognosis of patients with metastatic breast cancer. The primary outcome measure was overall survival, while progression-free survival was assessed as a secondary end-point.

Materials and Methods: We retrospectively analyzed metastatic breast cancer patients who underwent local-regional treatment over a 10-year period (May 2013 to May 2023). Sociodemographic and clinicopathological data were extracted from medical records and automated hospital systems. Statistical analyses were performed using SPSS.

Results: The study cohort consisted of 76 patients, with a mean age of 50 years and a median follow-up period of 58 months. The progression-free survival rate was 58%, while overall survival reached 75%, and the 5-year survival rate was 80%. Importantly, no deaths were observed among patients who achieved a pathological complete response during follow-up. Analysis of survival outcomes revealed that overall survival was significantly reduced in patients with axillary lymph node metastasis compared to those without ($p = 0.02$), in individuals with triple-negative breast cancer compared to those with hormone receptor-positive tumors ($p = 0.03$), in patients with T4 tumors compared to those with other T stages ($p = 0.04$), and in patients who experienced recurrence or distant metastasis during follow-up relative to those who did not ($p < 0.01$).

Conclusion: In metastatic breast cancer, surgical resection of the primary tumor was associated with improved overall survival and progression-free survival. While a response to systemic chemotherapy was a favorable prognostic factor, increased tumor size, axillary lymph node positivity, triple-negative status, and the development of new metastasis and/or recurrence during follow-up were associated with poorer outcomes.

Keywords: Breast cancer; metastasis; surgery; survival

KEY POINTS

- Primary tumor resection in metastatic breast cancer was associated with favorable overall survival and progression-free survival outcomes.
- Patients who achieved a pathological complete response after systemic chemotherapy demonstrated excellent prognosis, with no mortality observed during follow-up.
- Triple-negative breast cancer, T4 tumors, and axillary lymph node involvement were associated with significantly poorer overall survival.
- The development of recurrence and/or new metastasis during follow-up was identified as a strong negative prognostic factor.
- Careful multidisciplinary patient selection may optimize the potential benefit of locoregional surgical treatment in metastatic breast cancer.

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Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide, accounting for approximately 11.6% of all cancer cases. In 2022, an estimated 2.3 million new cases were reported, ranking breast cancer the second most common cancer globally after lung cancer. Despite major advances in screening and treatment, breast cancer remains the fourth leading cause of cancer-related mortality, responsible for approximately 666,000 deaths annually, which represents 6.9% of all cancer-related deaths (1). In newly diagnosed breast cancer patients, synchronous distant metastasis is observed in 3.5% to 10% of cases (2-4).

The most common sites of distant metastasis in breast cancer are the bone, lung, liver, and brain. According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system, lymph node metastases other than those involving the ipsilateral axillary, internal mammary, and supraclavicular nodes are classified as distant organ metastases. Ipsilateral supraclavicular lymph node involvement is staged as N3c disease. Distant (non-regional) lymph nodes include the cervical, contralateral axillary, contralateral supraclavicular, and contralateral internal mammary nodes. Metastatic spread to these distant lymph nodes is categorized as M1 (stage IV) disease (5).

Survival outcomes strongly depend on the stage at diagnosis. In patients with non-metastatic localized breast cancer, the 5-year survival rate approaches 99%, whereas in locally advanced disease, it decreases to about 86%. However, in metastatic breast cancer (MBC) patients, this rate drops significantly to 27% (6, 7). Given the substantial reduction in survival rates, the importance of effective MBC treatment is increasingly recognized. Current guidelines recommend primary tumor resection in MBC primarily for symptomatic relief and as a palliative measure (8).

In a pivotal trial conducted by the South Western Oncology Group, patients with stage IV renal cell carcinoma were randomized to receive interleukin-based therapy alone or in combination with cytoreductive nephrectomy. The addition of surgery improved median overall survival (OS) from 8 months in the non-surgical group to 11 months among those who underwent nephrectomy (9). These findings have sparked interest in whether similar survival benefits could be achieved through aggressive local treatment in other metastatic cancers, including breast cancer.

Evidence from several studies has indicated that surgical intervention may confer a survival advantage in carefully selected patients with MBC (10-16). Improved OS has been most frequently observed in those with hormone receptor-positive disease, limited metastatic involvement, favorable response to systemic therapy (ST), and achievement of negative surgical margins. Nevertheless, the role of surgery in this setting remains

controversial. While some investigations have demonstrated an association with improved OS, others report minimal or no survival advantage, supporting the use of surgery mainly for palliative purposes (17-20).

This study was designed to address the ongoing uncertainty regarding the survival impact of primary tumor resection in MBC. The main objective was to determine whether locoregional treatment of the primary lesion improved OS in patients with stage IV disease. OS serves as the primary endpoint, with progression-free survival (PFS) defined as the secondary outcome.

Materials and Methods

This retrospective analysis included patients who underwent surgical treatment over a 10-year period, from May 2013 to May 2023. Patient data were collected from the records of cases managed by a single academic breast surgeon. Inclusion criteria comprised patients whose treatment plans were discussed and approved by the breast council, and who consistently attended routine follow-up visits.

Data on patient demographics, clinicopathological characteristics, and treatment outcomes were extracted from automated hospital systems and manually maintained patient files. The study focused on patients with MBC, including those with oligometastatic or multiple metastases, who received adjuvant chemotherapy (CT) and were deemed by the breast council to gain benefit from primary tumor resection.

This study evaluated the prognostic impact of primary tumor resection in patients with MBC by analyzing OS and PFS as its primary and secondary end-points, respectively.

For each patient, demographic information including age and gender was recorded. Tumor characteristics were documented, including tumor size, laterality, histological type, grade, and hormone receptor status, as well as regional lymph node involvement and sites of distant metastasis. The diagnosis of distant organ metastases was established based on imaging findings and histopathological confirmation. Disease stage was determined according to the 8th edition of the AJCC staging system. Recurrence data, including the date and type of recurrence, were also collected. Information on treatment modalities, such as surgical procedures, radiotherapy, CT, and hormonal therapy, was obtained. Finally, follow-up data, including the date of the last visit, recurrence, metastasis, and mortality during the follow-up period, were recorded. In this study, PFS was evaluated by analyzing dates of recurrence and metastasis dates, while OS was assessed using recorded death.

Patients were excluded from the study if their medical records were missing or incomplete, if they failed to attend routine follow-up visits, or if there was no documented breast cancer

multidisciplinary council decision regarding their treatment plan.

Ethical Approval: This study received ethical approval from the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Scientific Research Ethics Committee (decision no: 19/20) on 03.11.2023. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was conducted using SPSS (IBM Inc., Armonk, NY, USA). Categorical variables were summarized using frequency and percentage values. For numerical variables, the arithmetic mean $\pm$ standard deviation was reported if the data followed a normal distribution; otherwise, the median (minimum-maximum) values were provided.

Comparisons between groups for categorical data were evaluated using the chi-square test, with Fisher's exact test applied in cases where the assumptions for the chi-square test were not fulfilled.

For comparisons between two groups, of continuous data normally distributed variables were analyzed using the independent samples t-test, whereas non-normally distributed variables were assessed with the Mann-Whitney U test.

Survival outcomes were evaluated with Kaplan-Meier analysis, and differences between groups were compared using the log-rank test. A two-sided p -value <0.05 was considered statistically significant.

Results

This study included patients who underwent surgical treatment between May 2013 and May 2023. A total of 1,404 patients who underwent breast cancer surgery by a single faculty member were reviewed. Among these, 76 (5.4%) diagnosed with stage 4 breast cancer (characterized by distant organ metastasis) were included in the study (Table 1).

The OS rate was 64.3% in patients aged 55 years and older, compared to 81.3% in those younger than 55 years.

During the follow-up period, no mortality was observed among patients who attained a pathological complete response (pCR). Patients with T4 tumors had significantly lower OS rates compared to those with other T stages ($p = 0.04$) (Table 2).

Axillary nodal involvement was a significant negative prognostic factor for both OS ($p = 0.02$) and PFS ($p = 0.001$). A higher number of involved lymph nodes was associated with poorer survival outcomes, achieving statistical significance for PFS ($p = 0.001$) and showing a significant trend for OS ($p = 0.03$) (Table 3).

Table 2. Pathological data

Tumor size, T score, n (%)	
Pathological complete response	11 (14)
T1	32 (42)
T2	22 (29)
T3	2 (3)
T4	9 (12)
Histologic grade, n (%)	
Grade I	8 (11)
Grade II	42 (55)
Grade III	26 (34)
Tumor type, n (%)	
Invasive ductal	52 (68)
Invasive lobular	5 (7)
Invasive	17 (22)
Mucinous	2 (3)
ER/PR (+), n (%)	60 (79)
HER2/neu (+), n (%)	23 (30)
Triple negative, n (%)	6 (8)
Ki-67% mean $\pm$ SD	26.2 $\pm$ 2.3
Axillary lymph node, n (%)	
N0	27 (35)
N1	25 (33)
N2	19 (25)
N3	5 (7)
SD: Standard deviation; PR: Progesterone receptor; ER: Estrogen receptor	

Table 1. Sociodemographic characteristics

Number of patients (n)	76
Age	
Age, years, mean $\pm$ SD	49.9 $\pm$ 12.5
<55 (n)	48
$\geq$ 55 (n)	28
Follow-up, months, mean $\pm$ SD	58.1 $\pm$ 30.6
SD: Standard deviation	

Table 3. Survival according to axillary lymph node status

Axillary lymph node	Overall survival (%)	Progression-free survival (%)
N0	92.6	88.9
N1	76.0	56.0
N2	57.9	31.6
N3	40.0	0

The OS rate was 50% in patients with triple-negative breast cancer (TNBC), compared to 77.1% in other patients. TNBC was significantly associated with reduced OS ($p = 0.03$).

Lung, liver, and brain metastases are classified as visceral organ metastases. The presence of visceral organ metastasis did not significantly affect the OS rate ($p = 0.6$) (Table 4).

In terms of distant organ metastasis, there was no difference between single and multiple metastases for the OS rate ($p = 0.1$).

The surgical procedure performed on the patients was mostly mastectomy. All of the patients received adjuvant CT (Table 5).

Progression (including recurrence, metastasis, or death) occurred in 32 (42.1%) patients during the follow-up period. Of these, 19 patients (25%) had died. Among the deceased, 12 (15.8%) developed metastasis, while three (3.95%) experienced both recurrence and metastasis (Table 6).

In the cohort of 57 patients who did not die, metastasis developed in 11 (14.5%), and recurrence occurred in two (2.6%).

Table 4. Metastasis status	
Solitary/multiple metastasis, <i>n</i> (%)	
Solitary	55 (72)
Multiple	21 (28)
Metastasis site, <i>n</i> (%)*	
Lung	13 (17)
Liver	8 (11)
Bone	35 (46)
Distant lymph node	46 (61)
Solid organ metastasis, <i>n</i> (%)	21 (28)
*Some patients had multiple metastatic sites	

Table 5. Treatment	
Preoperative chemotherapy, <i>n</i> (%)	60 (79)
Adjuvant chemotherapy, <i>n</i> (%)	76 (100)
Adjuvant radiotherapy, <i>n</i> (%)	66 (87)
Hormone therapy, <i>n</i> (%)	59 (78)
Trastuzumab	23 (30)
Surgical procedure, <i>n</i> (%)	
BCS + SLNB	3 (4)
BCS + ALND	4 (5)
Mastectomy + SLNB	5 (7)
Mastectomy + ALND	64 (84)
BCS: Breast-conserving surgery; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection	

Patients who died were followed for an average of 52.3 months, while those who survived were followed for an average of 61.5 months. The PFS rate was $57.9\% \pm 6.2\%$ (Figure 1). OS rate was $75\% \pm 5.9\%$. The 5-year survival rate was $80.3\% \pm 1.28\%$ (Figure 2).

A total of 28 (36.8%) patients developed recurrence and/or metastasis during follow-up. The OS rate in these patients was 46.4%, compared to 91.7% in those without recurrence or metastasis. The development of recurrence and/or metastasis during follow-up significantly decreased the OS rate ($p < 0.01$).

Table 6. Follow-up	
Progression (recurrence, metastasis, and death), <i>n</i> (%)	32 (42)
Metastasis on follow-up, <i>n</i> (%)	26 (34)
Metastasis site, <i>n</i> (%)	
Lung	11 (14)
Liver	5 (7)
Brain	1 (1)
Bone	8 (11)
Adnexa	1 (1)
Recurrence on follow-up, <i>n</i> (%)	5 (7)
Recurrence site, <i>n</i> (%)	
Same breast	2 (3)
Contralateral breast	2 (3)
Bilateral breasts	1 (1)
Death, <i>n</i> (%)	19 (25)

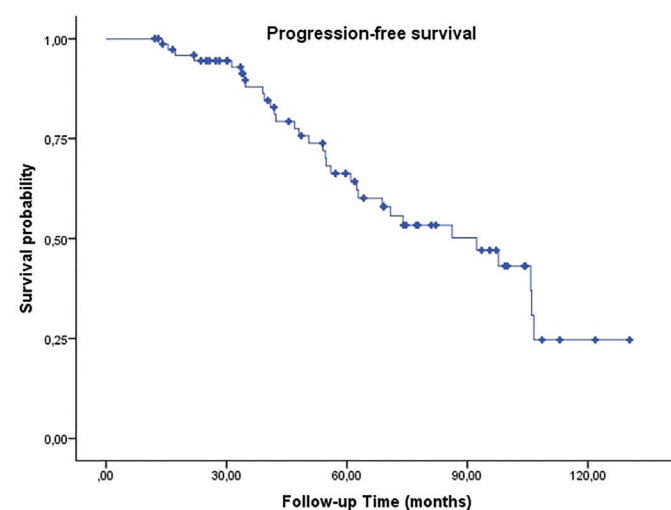


Figure 1. Progression-free survival

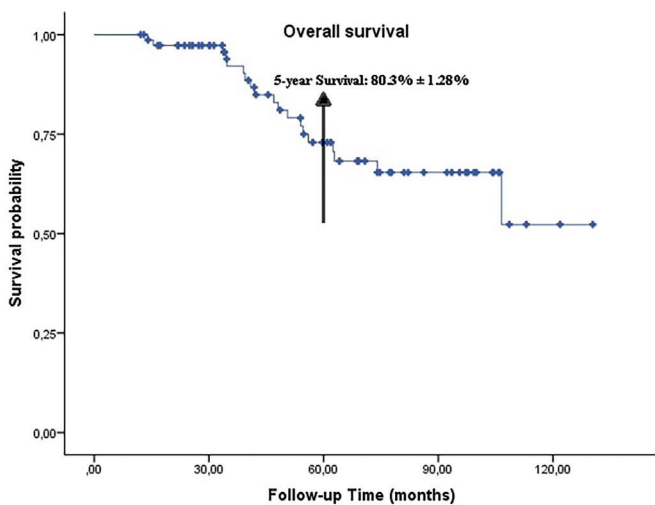


Figure 2. Overall survival

Discussion and Conclusion

MBC is generally considered an incurable disease, and systemic therapies remain the cornerstone of treatment (21). Current guidelines recommend primary tumor resection in MBC primarily for symptomatic relief and as a palliative measure (8). The role of locoregional therapy (LRT) in MBC treatment remains controversial, with no clear consensus in the literature regarding its impact on OS. However, the National Comprehensive Cancer Network guidelines suggest that LRT may be considered for selected patients (22).

In the randomized controlled MF07-01 trial conducted in 2021, a 10-year follow-up revealed that the OS rate in the LRT group was 14% higher compared to the group receiving ST alone (23). Similarly, a review of 24,150 cases from the National Cancer Data Base demonstrated significantly higher 5-year and 10-year OS rates in patients who underwent surgery compared to those treated with ST alone (11). However, conflicting evidence exists. A study conducted in India found no significant difference in OS rates between the LRT and ST groups (24). In addition, the ECOG-ACRIN 2108 multicenter trial reported no significant difference in OS rates between LRT and ST over a 3-year follow-up period (25).

The literature reports a 5-year survival rate of 27% for MBC (6, 7). In this study, the 5-year OS rate for MBC patients who underwent surgery was 80%, significantly higher than the reported average. Patients undergoing surgery may represent a selected group with better performance status and lower metastatic burden. These findings suggest that LRT may have a substantial impact on OS in MBC patients, though further research is needed to reconcile these disparities and establish definitive guidelines.

In the ECOG-ACRIN 2108 multicenter trial, during the 3-year follow-up period, locoregional progression or recurrence was significantly higher in the ST arm compared to the LRT arm (25.6% vs. 10.2%; $p = 0.003$) (25). In the present study, the PFS rate in MBC patients who underwent surgery was 58%, significantly higher than the PFS rates reported in the literature for patients receiving ST alone, again this may have been in part due to the selected nature of the study cohort.

In a study conducted in Türkiye in 2019, the average age at diagnosis for breast cancer was 51 years (range: 14–97) (26). Similarly, Soran et al. (23) reported a significant OS benefit in MBC patients under the age of 55 years who underwent primary surgery. Consistent with previous reports, the mean age at diagnosis in our cohort was 50 years. Although patients younger than 55 years showed a trend toward improved OS, this difference did not reach statistical significance. Studies with larger cohorts are warranted to confirm and further investigate this potential association.

In a meta-analysis, patients who received neoadjuvant CT and achieved a pCR demonstrated significantly higher OS rates (27). Consistent with these findings, there was no mortality during follow-up among patients who achieved pCR following preoperative CT in the cohort of the present study. These results suggest that MBC patients who respond favorably to CT have an improved prognosis. However, more comprehensive analyses involving longer follow-up periods and larger patient cohorts are necessary to validate these findings.

TNBC is characterized by rapid growth, aggressive clinical behavior, early metastasis, and poor prognosis, accompanied by greater proliferation (28). Consistent with previous literature, the present study found that TNBC patients who underwent surgical resection had a worse prognosis compared to those with hormone receptor-positive tumors. Moreover, a previous cohort study reported that LRT did not significantly impact OS in TNBC patients (14). Further research involving larger patient cohorts is necessary to explore the potential OS benefits of LRT in the TNBC population.

In another study, a significant OS benefit was observed with LRT in estrogen receptor (ER)/progesterone receptor (PR)-positive, HER2/neu-negative patients during a 10-year follow-up period. The only variable that demonstrated a statistically significant favorable prognostic effect was a positive ER status (23). In the present study, ER-positive and HER2/neu-negative status did not impact the prognosis. The prognosis was only poor for patients with TNBC.

Multivariate analyses revealed that the presence of visceral metastasis was an unfavorable prognostic factor (29-31). Among

patients with MBC, including those presenting with visceral metastases at initial diagnosis, receipt of LRT was associated with a significant improvement in OS compared with patients who did not undergo such treatment (14). In another study, surgery reduced OS in patients with multiple visceral organ metastases, while surgical treatment increased OS in those with bone metastasis (32). Contrary to some publications, our study did not identify a significant association between visceral involvement and OS outcomes. Larger studies with multivariate analyses are needed to further investigate this relationship.

According to aggregated study results, the greatest OS benefit from LRT was observed in subgroups with lower-volume metastatic disease, particularly in cases where metastasis was isolated to a single site or restricted to the skeletal system (10, 33). Another study found that MBC patients with a single bone metastasis had significantly higher OS rates (23). However, in this study, factors such as single organ metastasis, multiple organ metastasis, bone metastasis alone, and bone metastasis without visceral organ involvement did not affect OS, possibly due to the relatively small study cohort in the present study. Further studies with larger sample sizes are recommended.

Local progression within a study was characterized as 'local progression/symptom recurrence' (LPRS). The analysis indicated that surgical intervention for the primary tumor was associated with a reduced incidence of LPRS in MBC patients. Furthermore, the absence of LPRS constituted a significant prognostic factor, as evidenced by a markedly superior median OS of 45 months compared to 2.9 months in patients with LPRS ($p = 0.001$) (34). In the present study and, consistent with the literature, the development of recurrence and/or metastasis during follow-up was identified as a negative prognostic factor. In MBC, primary tumor resection was associated with a positive prognostic impact on OS and PFS. Response to systemic CT was also considered a favorable prognostic factor. Conversely, factors such as increased tumor size, axillary lymph node positivity, triple-negative status, and the development of new metastases or recurrence during follow-up were negative prognostic indicators. The treatment of MBC should be tailored to each patient. In multidisciplinary tumor boards, surgical treatment should be considered for suitable patients, with prognostic factors taken into account. Ongoing research will help clarify the role of primary surgery in this setting.

Ethics

Ethics Committee Approval: This study received ethical approval from the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Scientific Research Ethics Committee (decision no: 19/20) on 03.11.2023.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.E.; Concept: E.B., M.A.E.; Design: E.B., A.S.M.; Data Collection and/or Processing: A.S.M.; Analysis and/or Interpretation: E.B.; Literature Search: E.B.; Writing: E.B., M.A.E.

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Role of Chest Wall Perforator Flaps in Breast Surgery: Military Cancer Centre Experience

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ABSTRACT

Objective: Chest wall perforator flaps (CWPFs) are a muscle-sparing alternative in oncoplastic breast surgery (OPBS). CWPFs offer favourable cosmetic and surgical outcomes while minimising donor-site morbidity. Despite their increasing global adoption, there is a paucity of data from the Middle East and North Africa (MENA) region. This retrospective, descriptive case series aimed to assess our institutional experience with CWPFs, emphasising their feasibility, versatility, and surgical and cosmetic results in breast surgery.

Materials and Methods: This retrospective case series included all patients who underwent CWPF-based OPBS at the Military Cancer Centre between December 2017 and January 2025. Data on patient demographics, tumour characteristics, surgical indications, flap types and techniques, complications, and patient satisfaction were collected.

Results: CWPF procedures were performed on 69 patients. The most popular flap type (78.3%) was the lateral intercostal artery flap. Indications included volume replacement (84.1%), implant coverage (4.3%), implant salvage (2.9%), wound closure (7.2%), and deformity correction (1.4%). Most flaps were intended to be turnover flaps (75.4%) rather than propeller flaps (24.6%). No flap loss was noted; the complication rates were low, and the re-excision rate was 0%. Over 85% of patients reported good-to-excellent satisfaction with cosmetic outcomes.

Conclusion: CWPFs are reliable and versatile techniques in breast-conserving surgery and OPBS, serving as a surgical solution for various reconstructive indications. The findings from this study emphasise the need for broader adoption of CWPFs in Jordan and the MENA region and demonstrate the effective use of CWPFs at a national centre in Jordan.

Keywords: Chest wall perforator flaps; oncoplastic surgery; breast reconstruction; breast cancer; retrospective observational study

KEY POINTS

- This manuscript presents a single-center experience with chest wall perforator flaps (CWPFs) in oncoplastic breast surgery over a seven-year period.
- It represents one of the largest reported series from the Middle East and North Africa region, addressing a significant gap in the current literature.
- The study demonstrates the versatility of CWPFs beyond traditional volume replacement, including implant coverage, implant salvage, wound closure, and deformity correction.
- Excellent oncological safety was observed, with zero flap loss and no re-excision for positive margins.

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- Surgical morbidity was minimal, and patient-reported cosmetic satisfaction was high, with more than 85% rating outcomes as good or excellent.
- The findings support CWPFs as a reliable, muscle-sparing alternative to myocutaneous flaps with favorable functional and aesthetic outcomes.
- This work encourages wider adoption of CWPF techniques in similar healthcare settings and contributes valuable regional data to the global literature.

Introduction

Breast-conserving surgery (BCS), also known as lumpectomy, partial mastectomy, or wide local excision, involves removing the tumour with clear margins. BCS is regarded as a safer, less invasive and less morbid alternative to mastectomy for patients with breast cancer (BC), which is also linked to better survival outcomes (1). Nevertheless, BCS per se might not be the ideal option in terms of aesthetic outcomes, sexual wellbeing or overall quality of life in certain patient subgroups, particularly those with multicentric tumours or large tumour-to-breast size ratios (2).

As a result, oncoplastic breast surgery (OPBS) has become the standard of care in the management of patients with BC. OPBS combines tumour resection and plastic surgery techniques to enable immediate reconstruction of defects resulting from BCS. OPBS permits the removal of large tumours while maintaining breast shape and symmetry, thus being associated with better aesthetic outcomes, higher patient satisfaction and improved quality of life (3). This integrated approach has been shown to enhance surgical and cosmetic results without compromising the oncological outcome (4). Furthermore, it has been demonstrated to lower the re-excision rate of BCS (4).

OPBS techniques can be categorised into volume-displacement and volume-replacement procedures. Volume displacement involves advancing, rotating, or transposing a large portion of breast tissue to fill the defect caused by a partial mastectomy. This technique is more appropriate for small- to medium-sized defects. Common examples of volume-displacement procedures include reduction mammoplasty and mastopexy. Conversely, for larger defects, higher tumour-to-breast ratios or women with insufficient residual breast tissue for rearrangement, volume replacement techniques are preferred (5). A common example is the use of the latissimus dorsi (LD) myocutaneous flap. The LD flap has long been a fundamental method for both complete and partial (mini-LD flap) breast reconstruction. However, LD volume replacement can cause functional donor-site morbidity, such as functional impairment of corresponding shoulders, and an increased rate of wound complications such as seroma (6).

These limitations of myocutaneous flaps, combined with increased understanding of chest wall perforator anatomy, have led to the rising use of chest wall perforator flaps (CWPFs) in partial reconstruction procedures (7).

CWPFs are muscle-sparing flaps that use skin and subcutaneous fat from the chest wall and are supplied by perforating vessels arising from underlying arteries, such as the lateral thoracic, thoracodorsal, and intercostal arteries. CWPF is proven to be an excellent choice for improving aesthetic outcomes, reducing mastectomy rates and lowering donor-site morbidity associated with conventional myocutaneous flaps (8).

Despite the well-known benefits and widely recognised value of CWPFs for breast reconstruction, they remain relatively new and are not yet broadly adopted. Furthermore, data concerning their use and clinical outcomes, particularly in the Middle East and North Africa (MENA) region and Jordan, are limited. This gap emphasises the need to implement CWPFs and evaluate their effectiveness across diverse clinical settings. Consequently, this retrospective descriptive single-centre case series aimed to examine the functional, cosmetic, and surgical outcomes of CWPF reconstruction at the Military Cancer Centre (MCAC) in Jordan and to highlight the versatile roles of CWPFs beyond conventional volume replacement. To our knowledge, this is the first single-centre case series from Jordan and the MENA region to illustrate both conventional and emerging indications for CWPFs, including implant salvage, wound closure, and deformity correction.

Materials and Methods

Ethical Considerations

This study was approved by the Ethics Review Board of Military Cancer Center Royal Medical Services, Amman, Jordan (approval number: 8/2025, date: 17.06.2025). Informed consent was obtained from all participants, and written informed consent for the publication of clinical photographs was acquired from all patients.

Study Design and Setting

This retrospective, descriptive case series included all patients who underwent OPBS using CWPFs between December 2017 and January 2025 at the MCAC of the Jordanian Royal Medical Services. The study aimed to describe institutional experience with CWPF across reconstructive indications, rather than to compare outcomes with alternative reconstructive techniques.

Inclusion Criteria

All patients who underwent BCS with immediate or delayed CWPF reconstruction at the MCAC during the predefined period were

included in the study. Moreover, patients with all reconstructive indications were considered: volume replacement, implant coverage or salvage, wound closure, and correction of deformities. No exclusion criteria were applied, as all patients undergoing CWPF at MCAC were included.

In routine practice, candidates for CWPF reconstruction are selected based on defect characteristics and reconstruction requirements. Therefore, a comprehensive pre-operative assessment is vital and should include clinical evaluation of breast size, ptosis grade, tumour location and size, as well as Doppler mapping of the perforators.

Preferred factors for using CWPF include small-to-moderate breast size, no or mild ptosis, tumour location suitable for perforator coverage, a small tumour-to-breast ratio, and defect volumes not exceeding one-quarter of the breast parenchyma.

Patient-related factors, such as comorbidities, especially smoking, diabetes, and obesity, are also carefully evaluated. However, selected patients with these risk factors may still be considered suitable candidates if a preoperative Doppler assessment confirms reliable, well-perfused perforators.

Data Collection

Data were collected from the hospital's electronic records, multidisciplinary team meeting reports, and physicians' notes. The data were then entered into Microsoft Excel spreadsheets.

The collected data were categorised into four sections. The first section included patients' demographics and medical history. The second section covered tumour characteristics: laterality, location, focality, histological type and grade, receptor status, Breast Imaging Reporting & Data System category, and the Nottingham prognostic index. The third section contained operative details, including the type of oncologic procedure (wide local excision, simple mastectomy, nipple-sparing mastectomy, and axillary surgery), flap type, size, technique, specimen weight, and the size of the invasive component. The fourth section collected data on post-operative complications, length of hospitalisation, adjuvant treatments, re-excision rate, and cosmetic satisfaction scores.

Operative Technique

Pre-operative Preparation

Breast and flap markings were performed for all patients during preoperative preparation. The inframammary fold, lateral mammary fold, and anterior axillary line were marked. Surgical markings were tailored to each case based on the anatomical and reconstructive requirements.

For example, Figure 1 illustrates the markings performed for a patient with an upper outer quadrant tumour. The figure depicts the midline and sternal notch markings, the planned tumour location, expected resection zone and the flap-specific markings, which included perforator mapping along the mid-axillary line between the 5th and 8th intercostal spaces as well as markings of the lateral breast border and projected flap skin paddle. Other possible markings needed in some cases included the breast meridian from the midpoint of the clavicle through the nipple, the boundaries of the nipple-areolar complex, the degree of nipple ptosis based on the Regnault classification, the skin excision markings if the oncologic resection was expected to include the skin, and the areas requiring skin replacement if a skin island was planned (some of which are shown in the figures presented in the results section).

A handheld Doppler was used to identify the perforators. The flap was shaped to include the identified perforator. The flap size was determined based on the expected defect size, while ensuring primary closure of the donor site.

Tumour factors (location, multifocality/multicentricity, histology, estimated defect size and nipple ptosis grade), treatment pathway (surgery upfront versus after neoadjuvant systemic therapy), and patient-related variables [body mass index (BMI), smoking status, breast size, diabetes mellitus and comorbidities] were considered in the decision to proceed with CWPF reconstruction and in the choice of flap.

Oncologic Resection and Flap Harvest and Inset

The oncologic breast resection/BCS procedures were performed by specialised breast surgeons, following institutional guidelines. Preoperative imaging and intraoperative observations guided both the extent of resection and the resulting defect size. The defect size was initially estimated preoperatively based on imaging and physical examination, and then precisely determined during surgery, after tumour removal.

Flaps were designed based on the perforator location and reconstructive needs. Various types of flaps were utilised in this study, each serving a specific purpose.

- Intercostal artery perforator flap: this category included the lateral intercostal artery flap (LICAP), the anterior intercostal artery flap (AICAP), and the medial intercostal artery flap (MICAP).
- The thoracodorsal artery perforator flap (TDAP) was harvested as a turnover or propeller flap and utilised for volume restoration, implant coverage, implant salvage, wound closure, or deformity correction.



Figure 1. Pre-operative marking for LICAP flap partial breast reconstruction. Frontal and lateral views demonstrate key anatomical landmarks, including the midline, inframammary fold, anterior axillary line, and tumour location. The planned LICAP flap design is illustrated, with perforators identified preoperatively using handheld Doppler and marked accordingly

LICAP: Lateral intercostal artery flap

Flap Selection

LICAP flaps are commonly used for reconstructing defects in the outer quadrant of the breast. When additional volume is required, they can be combined with lateral thoracic artery perforator (LTAP) flaps to increase the bulk of the transferred tissue. Although used less frequently, LICAP flaps can be employed for inner-quadrant defects in selected cases involving small-to-moderate breasts, especially when adequate perforator length and reach are available. LICAP flaps are highly versatile and can be customised to meet individual reconstructive needs, whether the aim is volume replacement alone or with the inclusion of a skin island.

In comparison, MICAP and AICAP flaps have similar features but are less versatile and generally provide a smaller tissue volume. These flaps are mainly used for medial and lower quadrant defects. The flaps are especially useful for restoring volume and soft-tissue coverage in the medial and inferior parts of the breast, which are often challenging to address with LICAP or TDAP flaps.

The TDAP flap is particularly useful for addressing lateral breast defects. However, it is larger and its perforators reach farther, making it highly valuable in various settings. In addition to volume replacement, it can serve multiple functions, including covering implants, aiding wound closure, assisting in salvage procedures, and correcting contour deformities. Overall, TDAP flaps are beneficial when increased tissue volume, greater reach, or reliable wound closure are required, particularly when LICAP flaps are unsuitable.

Outcome Measures

All patients were followed up regularly at 1 week, 2 weeks, 1 month, 3 months, and 1 year.

Surgical Outcomes

Surgical outcomes included flap viability, short- and long-term complications (such as hematoma, necrosis, infection, and atrophy), re-operation, and oncological safety (margin status).

Oncological outcomes, re-excision rates, and mastectomy rates were also reported.

Cosmetic Outcomes

Patient satisfaction with the cosmetic result was evaluated using a five-category scale (very poor, poor, fair, good, and excellent). Patients were asked to rate their overall postoperative satisfaction with breast volume, shape, and symmetry.

Statistical Analysis

Data were analysed using SPSS (version 27; IBM, Armonk, NY, USA). Given the descriptive nature of the study and the absence of a comparison group, analyses were primarily descriptive and were reported as frequencies, percentages and means $\pm$ standard deviations. In addition, 95% confidence intervals (CIs) were calculated for key outcome proportions, including overall complication and flap loss rates.

Results

Patient Demographics and Clinical Features

A total of 69 patients underwent oncoplastic surgery with CWPF during the study period, with a median follow-up of 12 months. The mean age was 42.87±7.29 years. The average BMI was 25.56±3.92 kg/m². Most patients had no significant medical comorbidities, and the prevalence of smoking was 11.6%. Patient characteristics are summarised in Table 1.

Tumour Characteristics

Tumour laterality was balanced, with 56.5% occurring in the right breast and 43.5% in the left breast. Most tumours were located in the upper outer quadrant (63.8%), followed by the lower inner (10.1%), the upper inner (5.8%), the lower outer (4.4%) quadrants. Only one patient had a centrally located tumour. Approximately seven tumours were multicentric, involving multiple quadrants.

Most patients (69.6%) had unifocal disease, whereas multifocal and multicentric disease accounted for 17.4% and 10.1%, respectively. Two patients had previously undergone a mastectomy and therefore were excluded from location and nipple ptosis assessments.

Evaluation of nipple ptosis indicated that grade II was the most common category (59.4%), followed by grade I (27.6%) and grade III (10.1%).

Invasive ductal carcinoma was the most common histological diagnosis (85.5%). The other cases included ductal carcinoma

in situ, invasive lobular carcinoma, lobular carcinoma *in situ*, phyllodes tumour, and one case of squamous cell carcinoma with lung metastasis. The other metastatic case also involved a fungating mass. Although metastasis is a contraindication to surgery, the procedure was performed as a palliative measure to control ulceration and bleeding. Other tumour characteristics are summarised in Table 2.

Surgical and Perioperative Parameters

Wide local excision was performed in 85.5% of cases. Simple mastectomy and nipple-sparing mastectomy were performed in 3 (4.3%) and 2 (2.9%) cases, respectively. Five patients had previously undergone their primary oncological surgery and had received CWPF reconstruction for other indications, as described in the following section. Sentinel lymph node biopsy was performed in 42.0% of cases, and axillary lymph node clearance was performed in 49.3%. Only one patient (1.4%) underwent axillary lymph node sampling.

The average post-operative hospital stay was 3.26±7.35 days, and none of the patients required margin re-excision. Table 3 presents additional therapeutic details.

Utilisation and Roles of CWPF

Within our cohort, CWFs demonstrated significant versatility across various reconstructive applications (Table 4). Flap sizes ranged from 7 cm to 14 cm; most (75.4%) were performed using a turnover technique, and the remaining 24.6% were performed as propeller flaps, mainly when a skin island was necessary.

LICAP flaps constituted the majority of reconstructions (78.3%) and were primarily used for volume replacement in outer-quadrant tumours; they were occasionally used in other cases, such as implant salvage and corrective surgery (see Table 4 for details). One combined LICAP-LTAP flap was utilised in a patient with a large defect in the upper outer quadrant. For implant coverage and wound closure, TDAP flaps were employed, representing 11.6% of cases. MICAP (7.3%) and AICAP (1.4%) were utilised for inner-quadrant reconstructions where the reach of LICAP is limited.

All procedures were performed as single-stage operations.

Volume Replacement (n = 58, 84.1%)

Volume replacement was the most common reason for CWPF in this cohort (84.1%). Tumours located in the outer quadrants were the predominant type, occurring in 47 patients, and these were reconstructed using LICAP flaps. Both unifocal and multifocal tumours were observed among these patients. An example of such a case is shown in Figure 2. One case involved using LTAP in addition to LICAP, owing to a larger defect.

Table 1. Patient demographics and clinical characteristics	
Variable	n = 69 (%)
Age (years)	42.87±7.29
BMI (kg/m²)	25.56±3.92
Smoking status	
Smoker	8 (11.6)
Non-smoker	61 (88.4)
Comorbidity	
None	58 (85.6)
DM ± HTN	6 (8.7)
Hypothyroidism	2 (2.9)
Osteoporosis	1 (1.4)
Heart failure	1 (1.4)
Method of diagnosis	
Screening	2 (2.9)
Symptomatic	67 (97.1)
Data are presented as n (%) for categorical variables and mean ± standard for continuous variables. BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension	

Table 2. Tumour characteristics

Variable	n = 69 (%)
Site	
Left	30 (43.5)
Right	39 (56.5)
Tumour location	
Central	1 (1.4)
Lower inner	7 (10.1)
Lower outer	4 (5.8)
Upper inner	4 (5.8)
Upper outer	44 (63.8)
Multiple quadrants	7 (10.4)
NA (post mastectomy)	2 (2.9)
Disease extent	
Unifocal	48 (69.6)
Multifocal	12 (17.4)
Multicentric	7 (10.1)
Not applicable (post mastectomy)	2 (2.9)
Nipple ptosis grade	
I	19 (27.6)
II	41 (59.4)
III	7 (10.1)
Post mastectomy	2 (2.9)
BIRADS	
2	1 (1.4)
3	2 (2.9)
4	12 (17.4)
5	30 (43.5)
6	24 (34.8)
Distant metastasis	2 (2.9)
Histologic type	
DCIS	5 (7.2)
IDC	59 (85.5)
ILC	2 (2.9)
LCIS	1 (1.4)
Phyllode tumour	1 (1.4)
Skin SCC	1 (1.4)
Grade	
1	5 (7.2)
2	25 (36.2)
3	31 (45.0)
NA (not invasive carcinoma)	8 (11.6)
NPI	4.2±1.8
Tumour receptor status	

Table 2. Continued

Variable	n = 69 (%)
HR +ve HER2 –ve	33 (47.9)
HR +ve HER2 +ve	11 (15.9)
HR –ve HER2 +ve	5 (7.2)
HR –ve HER2 –ve	12 (17.4)
NA (Histologic type - not invasive carcinoma)	8 (11.6)
Data are presented as n (%) for categorical variables and mean ± standard for continuous variables. BIRADS: Breast Imaging Reporting & Data System; DCIS: Ductal carcinoma <i>in situ</i> ; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; LCIS: Lobular carcinoma <i>in situ</i> ; NA: Not applicable; phyllodes tumour, fibroepithelial tumour of the breast; SCC: Squamous cell carcinoma	

Table 3. Surgical and treatment characteristics of the study cohort

Variable	n = 69 (%)
Oncologic surgery	
WLE	59 (85.5)
Simple mastectomy	3 (4.3)
NSM	2 (2.9)
None	5 (7.2)
Surgery on the axilla	
ANC	34 (49.3)
ANS	1 (1.4)
SNLBx	29 (42.0)
No axillary surgery	5 (7.2)
Specimen weight (g) (WLE specimen)	160±95.151
Size of invasive component (cm)	2.62±3.61
Post-operative hospital stay	3.26±7.35
Neoadjuvant chemotherapy	36 (52.2)
Adjuvant chemotherapy	38 (55.1)
Adjuvant radiotherapy	67 (97.1)
Adjuvant hormonal therapy	49 (71.0)
Adjuvant biologic treatment	16 (23.2)
Data are presented as n (%) for categorical variables and mean ± standard deviation for continuous variables. ANC: Axillary lymph clearance; ANS: Axillary lymph node sampling; NSM: Nipple-sparing mastectomy; SLNBx: Sentinel lymph node biopsy; WLE: Wide local excision	

Conversely, tumours in the inner quadrants were managed using MICAP ($n = 5$), LICAP ($n = 4$), and AICAP ($n = 1$) flaps; one case with tumour skin invasion required a skin island to replace the involved skin defect. Figure 3 illustrates the MICAP flap used for an inner-quadrant tumour.

In one instance, CWPF was utilised for a centrally located tumour. A LICAP flap was employed for this case, with a skin island used alongside the flap to cover the central defect and the involved nipple-areolar complex. Figure 4 shows preoperative,

intraoperative, and postoperative photographs of this case. The outcomes were satisfactory at follow-up.

Implant Coverage (n = 3, 4.3%)

TDAPs were utilised in three patients as an alternative to mesh for providing soft-tissue coverage of the breast implant. Two of these cases involved immediate reconstruction following a nipple-sparing mastectomy, while the third case involved delayed reconstruction after a previous mastectomy for a phyllodes tumour. Figure 5 illustrates the use of the TDAP flap for breast implant coverage, whereas Figure 6 demonstrates its application for nipple-sparing mastectomy.

All of them reported a satisfactory aesthetic outcome, according to the patient. No complications were reported on follow-up.

Implant Salvage (n = 2, 2.9%)

LICAP flaps with skin islands were utilised were utilised for breast implant salvage in cases of implant extrusion post radiotherapy and wound dehiscence (shown in Figure 7) to prevent implant loss and restore soft tissue coverage.

Correction Surgery (n = 1, 1.4%)

A LICAP flap was used to correct a bird-beak deformity in a patient who had previously undergone a wide local excision of the left breast with involved margins and later presented with deformity

Table 4. Indications and characteristics of CWPF				
Flap type	n (%)	Indication	n	Technique Turned over: 52 (75.4%) Propeller: 17 (24.6%)
LICAP	54 (78.3)	Volume replacement/outer quadrants	46	3 propeller, 45 turned over
		Volume replacement/inner quadrants	4	Turned over
		Volume replacement/central defect	1	Propeller
		Implant salvage	2	Propeller
		Deformity correction	1	Propeller
LICAP + LTAP	1 (1.4)	Volume replacement (large outer-quadrant defect)	1	Turned over
TDAP	8 (11.6)	Implant coverage	3	Propeller
		Wound closure	5	Propeller
MICAP	5 (7.3)	Volume replacement/inner quadrant	5	2 propeller, 3 turned over
AICAP	1 (1.4)	Volume replacement/inner quadrant	1	Turned over

Data are presented as n (%) for categorical variables and mean ± standard for continuous variables. AICAP: Anterior intercostal artery perforator; LICAP: Lateral intercostal artery perforator; LTAP: Lateral thoracic artery perforator; MICAP: Medial intercostal artery perforator; TDAP: Thoracodorsal artery perforator



Figure 2. Use of the LICAP flap for volume replacement following resection of the outer quadrant tumour. (A) Pre-operative marking for LICAP flap (B) Intra-operative preparation of the de-epithelized LICAP flap, and (C) Post-operative outcome at 2-week follow-up

LICAP: Lateral intercostal artery flap

at the 6 o'clock position (as shown in Figure 8). Therefore, she underwent an oncological wide local excision combined with correction of the deformity.

Wound Closure ($n = 5$, 7.2%)

TDAP flaps were also utilised in five cases for wound closure, allowing immediate closure of extensive defects, including four cases following toilet mastectomy for large fungating tumours (example shown in Figure 9), and one case following excision of a recurrent right chest wall tumour, in which lesions were removed and a TDAP flap was employed for wound closure (shown in Figure 10).

Post-operative Complications

Post-operative complications were minimal in this cohort, occurring in 4 of 69 patients (5.8%, 95% CI: 2.3–14.1). One patient experienced a post-operative haematoma a few days after surgery and underwent haematoma evacuation. Another patient presented with significant atrophy and was managed conservatively. Partial necrosis was observed in two cases; both were treated conservatively and did not require further intervention. No flap loss was observed in any of the cases (0%; 95% CI: 0–5.2).

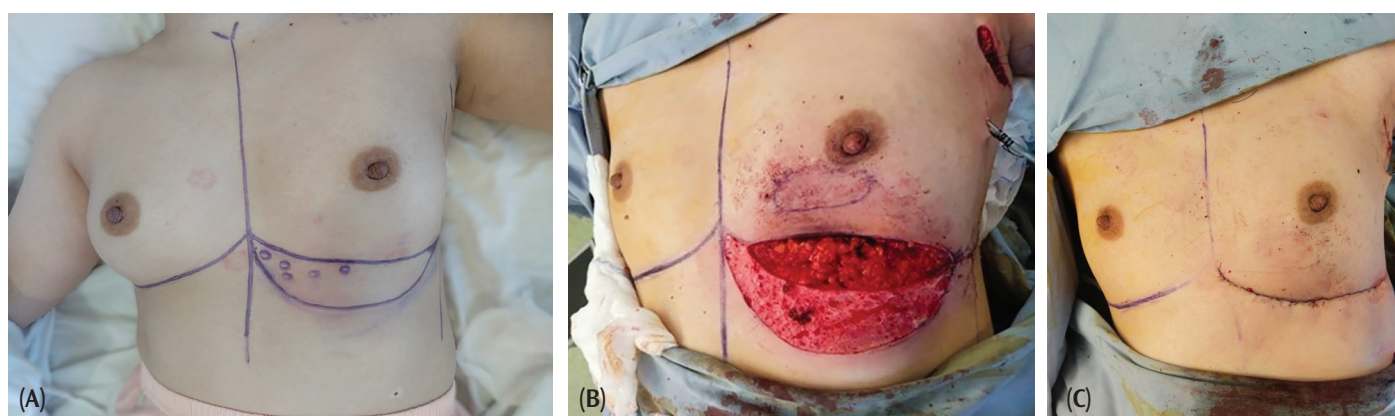


Figure 3. Use of the MICAP flap for volume replacement following resection of lower inner quadrant tumour. (A) Pre-operative marking outlining MICAP flap design with perforators identified and marked using hand-held Doppler, (B) Intra-operative view demonstrating the preparation of the MICAP flap, and (C) Immediate post-operative outcome showing satisfactory contour restoration

MICAP: Medial intercostal artery flap

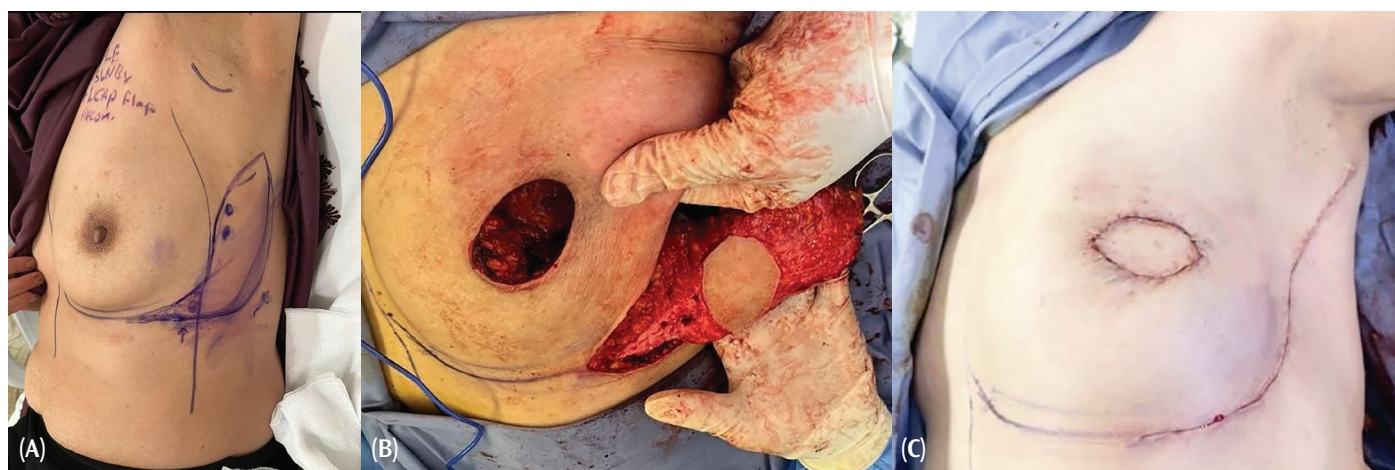


Figure 4. Use of the LICAP flap for volume replacement for a centrally located tumour. (A) Pre-operative marking for LICAP flap along with key anatomic landmarks. (B) Intraoperative preparation of LICAP flap with skin island designed to replace the nipple-areola complex. (C) Immediate post-operative outcome

LICAP: Lateral intercostal artery flap

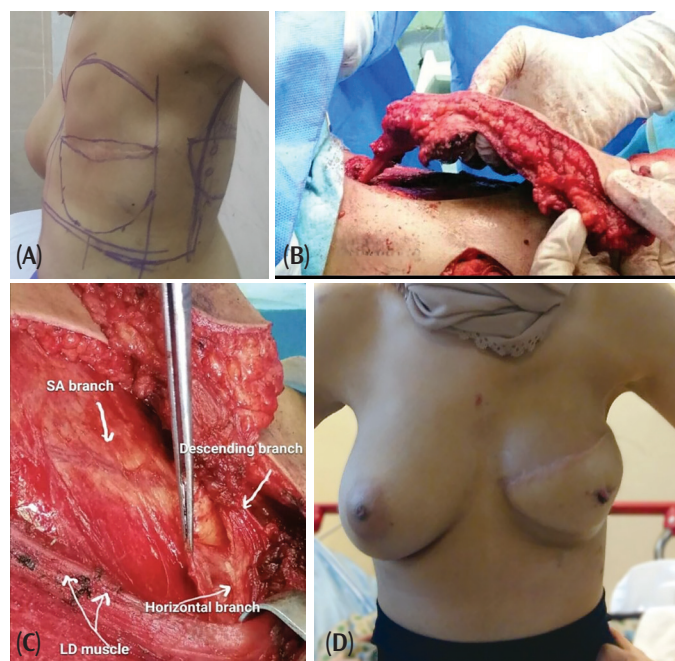


Figure 5. Using the TDAP flap with a skin island in a delayed reconstructive procedure to cover the implant. (A) Pre-op marking for TDAP flap and key anatomic landmarks and perforators, (B) Intraoperative illustration of TDAP flap with its skin island. (C) Intraoperative view demonstrating the thoracodorsal vascular pedicle and its branching pattern. The descending and horizontal branches of the thoracodorsal artery are clearly visualized, along with a serratus anterior branch. The latissimus dorsi muscle is exposed, serving as an anatomical landmark. These structures guide perforator selection and dissection during TDAP flap elevation. (D) Appearance at 1-year follow-up

TDAP: Thoracodorsal artery perforator flap

Cosmetic and Functional Results

The perceived satisfaction with the cosmetic outcome was assessed using a simple patient satisfaction score. Approximately 42% reported excellent satisfaction, while 44.9% reported good cosmetic results. Fair outcomes were reported by 13% of patients, and no patients reported poor outcomes.

Discussion and Conclusion

This retrospective, single-centre study is the first large series to report the use of CWPF in breast reconstruction surgery in the region. Among the 69 patients who underwent CWPF reconstruction, the LICAP flap was used most frequently (78.3%), primarily for outer-quadrant volume replacement. All procedures were performed in a single stage, and no cases required margin re-excision, indicating a high level of oncological safety. Notably, CWPFs were also employed for novel indications such as implant salvage and wound closure, which are less commonly reported in the literature. Furthermore, a low overall complication rate and

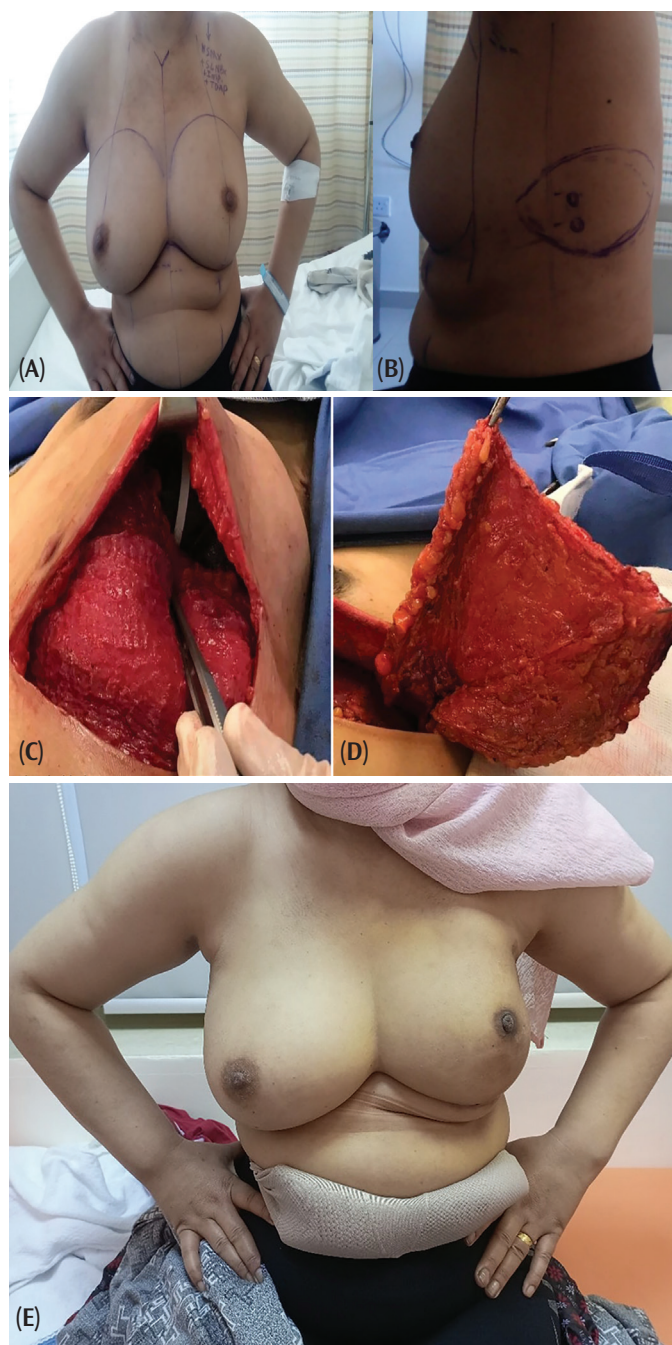


Figure 6. Use of the TDAP with nipple-sparing mastectomy in an immediate reconstructive procedure to cover the implant. (A-B) Pre-operative marking, (C-D) Intraoperative view of TDAP flap providing soft tissue coverage over the implant, (E) Clinical outcome at 1-year follow-up, demonstrating satisfactory contour and symmetry

TDAP: Thoracodorsal artery perforator flap

high patient satisfaction were observed. As expected for a case series, this study did not include a comparison group and aimed to reflect institutional experience with CWPF reconstruction rather than to establish comparative effectiveness against other reconstructive methods.

The reported use of CWPFs in our cohort aligns with global trends and supports their muscle-sparing and aesthetic benefits, as well as minimal donor-site morbidity. The anatomical reliability and reconstructive value of CWPFs in breast surgery have previously been emphasised by McCulley et al. (9) and Hamdi et al. (10). Nevertheless, our study broadens the application of CWPFs to reconstructive procedures following mastectomy and implant salvage scenarios, whereas most of the literature discusses their use for volume replacement in BCS.

The reliable vascular supply and muscle-sparing nature of CWPFs make them suitable for breast reconstruction. CWPFs are tissues supplied by perforator vessels. Harvesting these flaps

focuses on preserving the muscle and nerves, making them a good alternative to muscular flaps, which can cause significant donor site morbidity (10). Various types of flaps have been documented for BCS in the literature (LICAP, TDAP, LTAP, AICAP and MICAP) (11, 12), and the choice depends on the tumour size, location and surgical goals. The LICAP flap, based on the lateral intercostal artery perforator, was first reported for use in breast reconstruction by Hamdi et al. (7). Thus far, it is the most widely used flap type overall (11). This widespread use can be attributed to most BCs being located in the upper outer quadrant, where the proportion of breast tissue is higher. Consistent with the literature, this study found that LICAP was the predominant type used in the cohort of outer-quadrant tumours. Furthermore, this study demonstrated the versatility of LICAP flaps in breast reconstruction: they were utilised for volume replacement in inner-quadrant and centrally located tumours. Furthermore, these flaps were employed for implant salvage and for delayed

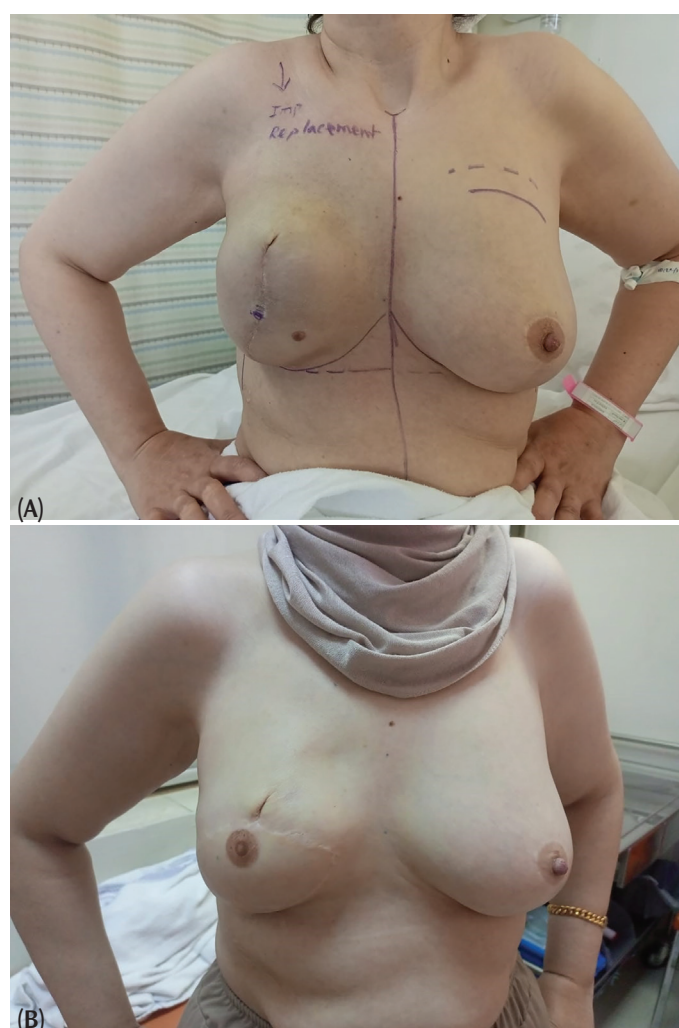


Figure 7. Use of the LICAP flap with a skin island for implant coverage following wound dehiscence and implant extrusion post radiotherapy treatment. (A) Pre-operative photo showing the right breast after skin-sparing mastectomy with implant-based reconstruction, complicated by implant extrusion and dehiscence; (B) Postoperative outcome at 1-year follow-up demonstrating durable coverage and nipple-areola complex tattooing

LICAP: Lateral intercostal artery flap



Figure 8. Use of the LICAP in deformity correction surgery. (A) Pre-operative frontal and lateral views demonstrating a lower pole bird beak deformity in the lower part of the left breast, (B) Clinical outcome at 1-year follow-up, showing restoration of breast contour and symmetry with excellent aesthetic result and deformity corrected along with negative margins

LICAP: Lateral intercostal artery flap

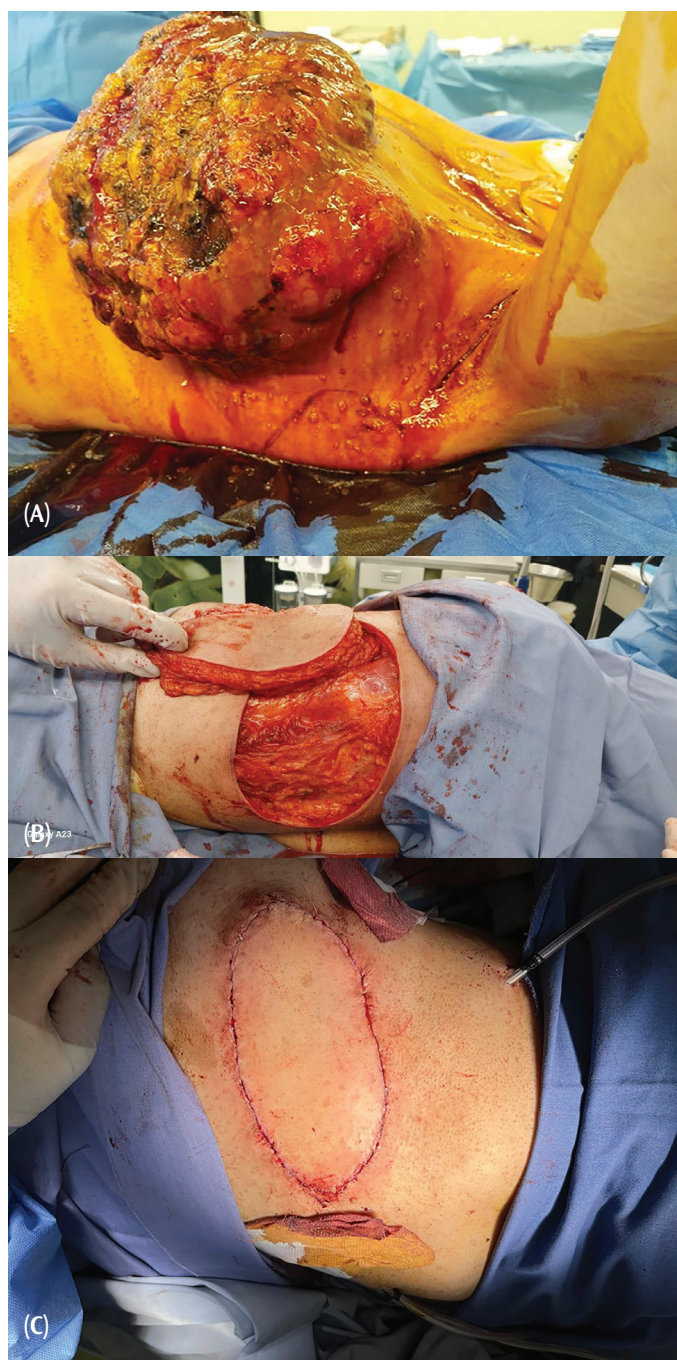


Figure 9. Use of the TDAP for wound closure after a toilet mastectomy for a large fungating mass. (A) Pre-operative view showing an extensive ulcerated fungating tumour involving the right breast, (B) Intraoperative image showing elevation and preparation of TDAP flap for reconstruction of chest wall defect (C) Immediate post-operative result showing the TDAP flap with skin island successfully inset to achieve tension-free closure of the defect

TDAP: Thoracodorsal artery perforator flap

surgery to correct breast deformity. This finding aligns with the literature, in which LICAP flaps have been used for various indications, including immediate reconstruction for volume replacement, implant salvage, wound dehiscence and deformity correction (13-15).

The LTAP flap is based on one or more perforators of the lateral thoracic vessels; it is mainly used in conjunction with the LICAP flap (9, 11) but can also be used alone (9, 11). In this study, LTAP was utilised in only one case involving a large tumour, together with the LICAP flap, to enhance perfusion and volume.

The AICAP flap, based on the anterior intercostal artery perforators, is typically used for tumours in the outer lower quadrant and for immediate reconstruction (16-18). Its use in implant coverage and wound dehiscence has also been recently documented (15, 19, 20). Lower-quadrant tumour resection is linked to the bird's beak deformity. This issue has been addressed in OBS using CWPFs. However, in cases of large tumours, insufficient tissue may still result in poorer cosmetic outcomes. Denning et al. (17) have therefore described a modification of the AICAP harvest technique that makes AICAP a viable option even for large lower-quadrant tumours. This study reports the use of AICAP for volume replacement of an inner lower quadrant tumour.

Ribuffo et al. (21) reported using a combination of LICAP and AICAP to restore breast volume and shape across multiple regions without requiring an implant. This technique could be utilised in OBS for cases involving multifocal or multicentric disease.

The use of MICAP flaps, based on the medial intercostal artery perforator, is less commonly reported in the literature (11, 12, 22). These flaps are employed for inner-quadrant tumours, as demonstrated in this study, in which MICAP was used to replace volume in a case of a lower inner-quadrant tumour. Despite limited data on MICAP use, some reports indicate that it has been utilised for purposes beyond volume replacement, such as implant salvage (14). MICAP has also been reported to be used in complete breast reconstruction after nipple-sparing mastectomy, in combination with LICAP (14).

The TDAP flap is based on one or more subcutaneous perforators that arise from the thoracodorsal artery, usually from its descending branch, supplying the skin and subcutaneous tissue without involving the LD muscle (23). The TDAP harvest is generally more complex and demands more detailed pre-operative Doppler mapping than LICAP (24). The use of TDAP has been reported for volume replacement and implant-based reconstruction, with high reliability and low complication rates and morbidity (25). Additionally, TDAP flaps have been used for implant coverage, salvage and managing wound dehiscence (25-27). In this study, TDAP was used for wound closure and implant coverage when LICAP flaps were not feasible.



Figure 10. Reconstruction of right chest wall defect using TDAP flap following excision of recurrent chest wall lesions. (A) Pre-operative view showing recurrent lesions at the right lateral chest wall, (B) Intraoperative image demonstrating the elevated TDAP flap with adequate perfusion and thickness for defect coverage, (C) Immediate post-operative appearance showing tension free closure of the defect with a well-vascularized skin island

TDAP: Thoracodorsal artery perforator flap

This study reports a low incidence of post-operative complications (5.8%), which is at the lower end of the rates reported in the literature (4.3–15%) (11, 12, 22, 28). Notably, a recent (2025) meta-analysis documented a pooled complication rate of 13% (29). This study also observed 0% re-excision rate and 0% flap loss compared with 1% and 12.9%, respectively, reported in the meta-analysis (29).

The cosmetic outcome was assessed postoperatively by reviewing patients' perceptions of breast volume, shape, and symmetry. Most patients reported excellent (42%) or good (45%) satisfaction levels; none reported poor outcomes. This finding aligns with previous studies that show favourable aesthetic results with CWPF reconstruction compared with mastectomy and volume displacement techniques (5) and high patient satisfaction (30). Nevertheless, an objective assessment of cosmetic outcomes, such as the BREAST-Q score, could have provided a more reliable evaluation and would be as important as assessing patient satisfaction.

Despite the well-documented surgical and cosmetic advantages of CWPFs, their use remains limited across the Arab and MENA regions. Therefore, providing institutional data and outcomes from a national centre encourages broader adoption and integration of CWPF techniques into routine breast reconstructive practice in similar healthcare settings. Consequently, a key strength of this study is its ability to address a significant regional gap. Furthermore, despite a relatively small sample size, this study demonstrates the versatility of CWPF across different indications within the contexts of OBS and BCS.

Study Limitations

The findings of this report are subject to certain limitations. First, the retrospective analysis confines data collection to previously recorded clinical data. Second, as previously discussed, cosmetic outcomes were assessed solely based on patient-reported satisfaction, as standardised objective or surgeon-based evaluation tools (e.g., BREAST-Q or BCCT. core) were not routinely employed during the study period. Additionally, the absence of pre-operative baseline satisfaction assessments limits our capacity to conduct pre- and post-operative comparisons. Moreover, the lack of a comparison group hampers direct comparison with other reconstructive approaches. Finally, the relatively small sample size from a single centre may restrict the generalisability of the reported low complication rate. Therefore, prospective multicentre studies incorporating standardised cosmetic evaluation tools and comparison groups are recommended to further validate these findings.

CWPFs offer a reliable muscle-sparing reconstructive option for patients with BC, yielding favorable surgical, cosmetic, and functional outcomes. This study demonstrates the versatility of CWPFs in BCS and their adaptability to novel clinical applications beyond conventional volume replacement, including implant coverage, salvage, wound closure, and deformity correction. It is the first study to present national data from Jordan, thereby filling a significant gap in the literature and underscoring the importance of adopting CWPF techniques widely across the MENA region. Additionally, this study highlights the benefits of CWPFs in BCS for improving patient satisfaction and cosmetic outcomes without compromising oncological safety.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Review Board of Military Cancer Center Royal Medical Services, Amman, Jordan (approval number: 8/2025, date: 17.06.2025).

Informed Consent: Informed consent was obtained from all participants, and written informed consent for the publication of clinical photographs was acquired from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.H., M.A., A.K., A.B.F., M.B., Concept: S.H., A.K.; Design: M.A., M.I.B.D.; Data Collection or Processing: M.A., A.K., A.B.F., M.B., M.I.B.D.; Analysis or Interpretation: M.A., M.Y.A-N., Literature Search: M.A., A.K.; Writing: S.H., M.A., A.K., M.Y.A-N.

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Rethinking Preoperative MRI in Early Breast Cancer: Who Truly Benefits?

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ABSTRACT

Objective: In light of existing evidence on the use of preoperative magnetic resonance imaging (MRI) in breast cancer (BC) patients undergoing upfront surgery, this study evaluated whether adding MRI to conventional imaging improved the definition of disease extent, subsequent surgical management, and survival outcomes.

Materials and Methods: This retrospective study reviewed patients with stage I–II BC who underwent upfront surgery between January 2014 and September 2025. Patients were divided into an MRI cohort and a non-MRI cohort, and clinicopathologic characteristics, the diagnostic performance of ultrasound and MRI in detecting additional malignant foci, the type of surgery, and recurrence during follow-up were compared.

Results: A total of 261 patients were included, with 149 assigned to the MRI cohort and 112 to the non-MRI cohort. Patients in the MRI group were younger, more often premenopausal, and more likely to have dense breasts. MRI detected additional malignant foci, including ductal carcinoma *in situ* and invasive carcinoma, in 38 patients of 149 (25.48%). MRI findings led to the conversion from planned lumpectomy to mastectomy in 16/149 patients (10.7%), mainly due to the detection of new multicentric disease. With a median follow-up of 30–36 months, there has been no significant difference between the two cohorts concerning local recurrence ($p>0.99$) or distant metastasis ($p = 0.39$).

Conclusion: Preoperative MRI occasionally changed surgical plans but offered no diagnostic advantage over standard imaging, supporting its selective rather than routine use in upfront BC surgery.

Keywords: Breast MRI; early breast cancer; surgical management; ultrasound

KEY POINTS

- Preoperative magnetic resonance imaging (MRI) detected additional malignant or ductal carcinoma *in situ* foci in a subset of patients, but this did not translate into lower re-excision rates or improved early oncologic outcomes.
- Although MRI showed higher sensitivity than ultrasound for identifying malignant lesions, this diagnostic advantage did not reach statistical significance.
- These findings support a selective rather than routine use of preoperative MRI, particularly in patients with dense breasts or inconclusive conventional imaging.

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Introduction

Breast cancer (BC) remains the most diagnosed cancer among women worldwide. According to recent United States Cancer Registry Data, most BC patients are diagnosed at an early stage, 66% of cases present as localized, and 25% are diagnosed at locally advanced stages. The five-year relative survival rate exceeds 99% for localized and 87% for locally advanced disease, reflecting the effectiveness of treatment in early-stage disease (1).

The high survival rates observed in early-stage BC are mainly attributable to breast-conserving surgery (BCS) with negative surgical margins followed by adjuvant irradiation. This approach has been shown to achieve outcomes equivalent to mastectomy (2). Historically, margin positivity after BCS has been reported to range from 17.5% to 59% in invasive lobular carcinoma and from 6.9% to 43% in invasive ductal carcinoma, which, depending on patient factors and preoperative assessment methods, could necessitate re-excision or even conversion to mastectomy (3). However, in contemporary practice and with standardized margin definitions, recent meta-analyses estimate that only 8–10% of BCS cases result in truly positive margins (4). Effective management of BC first requires determining the extent of disease within the breast and establishing an accurate diagnosis.

Current guidelines recommend mammography (MMG) and ultrasound (US) as standard imaging modalities. Magnetic resonance imaging (MRI) is recommended when standard imaging is uncertain and in specific clinical scenarios, such as familial BC associated with germline mutations, invasive lobular carcinoma, suspected multifocality or multicentricity, and in patients with breast implants (5, 6). It is known that MRI has a sensitivity of over 90% for invasive carcinoma and over 70% for ductal carcinoma *in situ* (DCIS) (7). Although breast MRI is currently not the first-line option in the diagnostic workup, accurate assessment of tumor size and extent is essential for optimal surgical planning in BC. Studies have demonstrated that MRI provides greater concordance with pathological tumor size than conventional imaging modalities (MMG and US), particularly in evaluating multifocal and multicentric disease. While US and MMG tend to underestimate tumor size, MRI has been shown to achieve greater accuracy, though it tends to overestimate in certain lesion types, such as non-mass enhancement (8, 9). In contrast to its high sensitivity, preoperative breast MRI has been associated with an increased likelihood of undergoing mastectomy, without reducing re-excision rates after positive margins, as shown in a large meta-analysis that predominantly included retrospective studies (10). However, in a more recent meta-analysis restricted to randomized controlled trials, mastectomy rates were numerically higher in the MRI group

(15% vs. 10%), although this difference did not reach statistical significance (11).

In this study, we aimed to evaluate whether preoperative MRI, in addition to US, improved the detection of additional lesions or DCIS extension, altered surgical decision-making, and affected survival outcomes in BC treated with upfront surgery.

Materials and Methods

This was a retrospective analysis of imaging and pathology reports from patients with BC treated at the Breast Surgery Clinic of Koç University Hospital between January 2014 and September 2025. Eligible stage I–II BC patients, all of whom were treated with upfront surgery—were stratified by preoperative imaging into MRI (US + MMG + MRI) and no-MRI (US + MMG) cohorts for comparative analysis. The Koç University Institutional Review Board (approval no: 2024.262.IRB2.112, date: 09.07.2024) approved this study. BC staging was performed according to the 8th edition criteria of the American Joint Committee on Cancer (12). Data were gathered from various medical records, including operative notes, radiological findings, and pathology reports. All data were obtained by comparing imaging and pathology results.

Statistical Analysis

All statistical analyses were performed using SPSS version 26 (IBM Inc., Armonk, NY, USA). The normality of the data was assessed using the Kolmogorov-Smirnov test. Continuous variables are expressed as median [interquartile range (IQR)] or mean $\pm$ standard deviation, as appropriate based on the data distribution. Comparisons between two independent groups were performed using the Mann-Whitney U test for non-normally distributed variables. For comparisons among more than two groups, the Kruskal-Wallis test was used. Multivariable logistic regression analysis was performed to identify independent predictors of preoperative MRI use. Categorical variables are presented as frequencies and percentages and were compared using the Pearson's chi-square (χ^2) test or Fisher's exact test, as appropriate. A p -value of <0.05 was considered statistically significant.

MMG Protocol

All MMGs were acquired using a digital breast tomosynthesis (DBT) system (Selenia Dimensions, Hologic Inc., Bedford, MA, USA). Standard craniocaudal and mediolateral oblique (MLO) views were obtained, with MLO images acquired in combo mode incorporating DBT. For DBT, low-dose projections were captured over a 15° arc and reconstructed into 1-mm slices to improve visualization of overlapping breast structures. Exposure parameters were automatically adjusted according to breast

thickness and density. The average glandular dose ranged from 1.0 to 1.8 mGy for 2D imaging and from 1.5 to 2.2 mGy for DBT. All images were interpreted by an experienced breast radiologist, and breast density and abnormalities were categorized using the Breast Imaging Reporting and Data System (BI-RADS) criteria (13).

US Protocol

All patients underwent bilateral breast and axillary ultrasonographic examination using a Logiq S8 or Logiq E10S US machine (GE Healthcare, Milwaukee, WI, USA). These US units were equipped with high-frequency linear matrix array transducers ranging from 6 to 15 MHz (50-mm ML6-15 MHz). Examinations were performed by two experienced breast radiologists using a handheld US device. The scanning technique was standardized using radial and anti-radial approaches to systematically scan the entire breast and axillary regions. The breast was divided into quadrants, including the retroareolar region, and scanned clockwise. Any detected abnormalities were documented with their positions noted on a clock-face model, and the distance from the nipple was recorded. Each lesion was measured and categorized according to the BI-RADS (13).

MRI Protocol

All patients in the MRI group underwent multiparametric breast MRI, including DCE-MRI, using either a 1.5T (Siemens Aera, Siemens Healthineers GmbH, Erlangen, Germany) or 3.0T (Siemens Skyra, Siemens Healthineers AG, Forchheim, Germany) system. Examinations were performed in the prone position with a dedicated 16-channel breast coil. The protocol included axial T2-weighted fat-suppressed images and axial dynamic, fat-suppressed 3D T1-weighted gradient-echo sequences acquired before and after contrast injection. A total of six dynamic phases (one pre-contrast and five post-contrast) were obtained using a gradient-echo 3D technique (TR/TE: 4.7/1.8 ms; slice thickness: 1-mm; FOV: 320×320-mm; acquisition time: 60 s per phase). Diffusion-weighted imaging was performed with b-values of 50 and 800 s/mm² using SPAIR fat suppression. A gadolinium-based contrast agent (0.1 mmol/kg) was administered at 2–3 mL/s, followed by a saline flush. Subtraction and MIP images were generated automatically. Images were interpreted by experienced breast radiologists, and lesions were evaluated based on their morphological characteristics and kinetic enhancement patterns (types I–III). BI-RADS was used to classify the findings and guide clinical recommendations (13).

Results

A total of 261 patients were included in the study, divided into 149 in the MRI group and 112 in the non-MRI group. The characteristics of the patients, including breast and tumor features, treatment details, and follow-up outcomes, are shown in Table 1. The median (IQR) age was significantly lower in the MRI

group than in the non-MRI group [51 (range 29–82) vs. 67 (range 35–94) years; $p < 0.001$]. Nulliparity rates were similar between the two groups (21.4% vs. 17.8%; $p = 0.47$). The menopausal distribution differed significantly: premenopausal women were substantially more frequent in the MRI group (49.6% vs. 16.0%), whereas postmenopausal status predominated in the non-MRI group (50.4% vs. 84.0%; $p < 0.001$). Use of oral contraceptives or hormone replacement therapy was higher among MRI patients (25.6% vs. 12.5%; $p = 0.048$). Regarding breast density, dense breast patterns (types C and D) were substantially more common in the MRI group (63.8% vs. 18.7%; $p < 0.001$). A significant difference in tumor stage distribution was observed between the MRI and non-MRI groups ($p < 0.05$). Most patients in the MRI group had T1 tumors (68.46%), whereas the proportion was lower in the non-MRI group (55.36%). Analysis of clinical stage revealed a higher proportion of stage I in the MRI group (57.7% vs. 58.03%). The histopathological subtype distribution also differed significantly, with invasive lobular carcinoma being more prevalent in the non-MRI group (16.1% vs. 6.7%; $p = 0.028$). There was no significant difference in immunohistochemical subtypes between groups (HR+/HER2– 89.9% vs. 90.2%; HER2+ 6.7% vs. 2.7%; triple-negative 3.4% vs. 7.1%; $p = 0.39$). Surgical type did not differ significantly between groups, with BCS performed in 67.1% of MRI patients and 68.8% of non-MRI patients ($p = 0.79$). Among those who underwent BCS, re-excision during the same operation was required in 65% of MRI and 72.7% of non-MRI cases, and second-stage re-excision was rare (0 vs. 1.3%; $p = 0.42$). The median follow-up was 30 months (0–113) in the MRI group and 36 months (0–130) in the non-MRI group ($p = 0.31$). During follow-up, locoregional recurrence occurred in one patient from each group one with areolar recurrence in the MRI group and one with axillary recurrence in the non-MRI group (0.7% vs. 0.9%; $p > 0.99$), while distant metastasis was detected in two MRI (1.4%) and four non-MRI (3.6%) patients ($p = 0.39$).

Multivariable logistic regression analysis demonstrated that breast density was independently associated with preoperative MRI use ($p < 0.001$), as shown in Table 2. Compared with patients with type A breast density, those with type C and type D breast density had significantly higher odds of undergoing MRI [odds ratio (OR): 7.31, 95% confidence interval (CI): 2.31–23.13, $p < 0.001$; OR: 11.80, 95% CI: 2.00–69.57, $p = 0.006$, respectively]. Age, menopausal status, and tumor stage were not significantly associated with MRI use in this study.

As shown in Table 3, clinicopathologic characteristics were compared among patients with additional lesions detected on MRI but missed on US, classified as benign, DCIS, or malignant. Overall, no significant differences were identified between the groups, although a tendency toward younger age and a higher proportion of premenopausal women was observed in cases with DCIS foci.

Table 1. The characteristics of the patients who underwent or did not undergo preoperative breast MRI

	MRI group (n = 149)	Non-MRI group (n = 112)	p-value
Age (median)	51 (29–82)	67 (35–94)	<0.001 ^a
Nulliparity	32 (21.4%)	20 (17.8%)	0.47 ^b
Menopausal status			<0.001 ^b
Premenopausal	74 (49.6%)	18 (16%)	
Postmenopausal	75 (50.4%)	94 (84%)	
OC-HRT			0.048 ^b
Yes	38 (25.6%)	14 (12.5%)	
No	111 (74.4%)	98 (87.5%)	
Density of the breast			<0.001 ^b
Type A	10 (6.7%)	28 (25%)	
Type B	44 (29.5%)	63 (56.2%)	
Type C	66 (44.3%)	19 (16.9%)	
Type D	29 (19.5%)	2 (1.78%)	
T stage			<0.05 ^b
T1	102 (68.46%)	62 (55.36%)	
T2	45 (30.20%)	44 (39.29%)	
T3	2 (1.34%)	6 (5.36%)	
Clinical stage			0.042 ^b
I	86 (57.7%)	65 (58.03%)	
II	63 (42.2%)	47 (41.96%)	
Histopathological sub-type			0.028 ^b
IC (NST)/IDC	109 (73.15%)	76 (67.86%)	
ILC	10 (6.71%)	18 (16.07%)	
Mixed	6 (4.03%)	4 (3.57%)	
Other	24 (16.11%)	14 (12.5%)	
Immunohistochemical sub-type			0.39 ^b
HR positive/HER2 negative	134 (89.93%)	101 (90.18%)	
HER2 positive	10 (6.71%)	3 (2.68%)	
Triple negative	5 (3.36%)	8 (7.14%)	
Type of surgery			0.79 ^b
Breast conserving surgery	100 (67.11%)	77 (68.75%)	
Mastectomy	49 (32.89%)	35 (31.25%)	
Re-excision needed (in lumpectomy group)	n = 100	n = 77	0.42 ^b
Intraoperatively	65 (65%)	56 (72.73%)	
Second surgery	0	1 (1.3%)	
Follow-up (months)	30 (0–113)	36 (0–130)	0.31 ^a
Recurrence			
Locoregional	1 (0.71%)	1 (0.89%)	>0.99 ^c
Distant metastasis	2 (1.42%)	4 (3.57%)	0.39 ^c

^aMann-Whitney U test; ^bPearson's chi-square (χ^2); ^cFisher's exact test; T: Tumor; HR: Hormone receptor; MRI: Magnetic resonance imaging; IC: Invasive carcinoma; IDC: Invasive ductal carcinoma; NST: No special type; ILC: Invasive lobular carcinoma; OC: Oral contraceptive; HRT: Hormone replacement therapy; HER2: Human epidermal growth factor receptor 2

Table 2. Multivariable logistic regression analysis of factors associated with preoperative MRI use

	OR	95% CI	p-value
Age	0.96	0.92–1.01	0.119
Menopausal status (pre vs. post)	1.29	0.39–4.23	0.677
Breast density			<0.001
Type B vs. A	1.48	0.57–3.81	0.417
Type C vs. A	7.31	2.31–23.13	<0.001
Type D vs. A	11.80	2.00–69.57	0.006
T stage			0.492
T2 vs. T1	0.66	0.33–1.31	0.235
T3 vs. T1	0.76	0.05–11.07	0.841
Bold values indicate statistical significance ($p < 0.05$). OR: Odds ratios; CI: Confidence intervals; T: Tumor; MRI: Magnetic resonance imaging			

Among the 149 patients, preoperative MRI led to a change in surgical management from BCS to mastectomy in 16 (10.7%) cases. The individual surgical outcomes of these patients are detailed in Table 4 below (Figure 1). Among these 16 patients, the most common cause was multicentric disease (56.3%), followed by extensive or multifocal non-mass enhancement (25–31%), and, in a smaller proportion, tumor size >50% larger on MRI than on conventional imaging (12.5%).

Forty-nine mastectomy patients who were evaluated by both MRI and US were further analysed in Table 5. MRI demonstrated higher sensitivity, negative predictive value, and overall accuracy than US for detecting malignant lesions. Specifically, MRI achieved a sensitivity of 76.2% and an accuracy of 69.4%, whereas

US achieved sensitivities of 54.5% and 59.2% and accuracies of 69.4% and 69.2%, respectively. Despite these numerical differences favoring MRI, the comparisons of sensitivity and overall diagnostic accuracy did not reach statistical significance ($p = 0.14$ and $p = 0.42$, respectively).

Discussion and Conclusion

Our results indicated that while preoperative MRI identified additional malignant foci, including DCIS and additional malignant tumors, and altered surgical management in around 11% of patients, it did not demonstrate a greater overall diagnostic superiority compared to US, highlighting the need for a selective rather than routine use of MRI in BC treated with upfront surgery.

When comparing patients who underwent MRI with those who did not, several clinicopathologic differences were evident. Patients in the MRI group were generally younger than 50 years and, more likely to be premenopausal. They had higher breast density, consistent with the common practice of using MRI to improve lesion visualization in dense parenchyma. When US and MRI findings were compared with pathological results in patients who underwent mastectomy, MRI demonstrated higher sensitivity and accuracy in detecting malignant foci than US. In our cohort, additional lesions detected only on MRI included benign lesions in 6 (4.01%) patients, DCIS in 18 (12.08%) patients, and malignant invasive foci in 20 (13.4%) patients. Benign and DCIS foci were more frequently observed in younger, premenopausal women. This pattern suggests that MRI tends to reveal both benign and clinically significant lesions, some of which may not be

Table 3. Characteristics of patients according to MRI-detected additional lesion type (benign, malignant, or DCIS) missed on US

	Benign focus ($n = 6/149$)	DCIS focus ($n = 18/149$)	Malign focus ($n = 20/149$)	p-value
Age (median, range)	50.5 (37–72)	42 (35–63)	54.5 (35–72)	0.10 ^a
Menopausal status				0.07 ^b
Premenopausal	4 (66.7%)	14 (77.8%)	8 (40%)	
Postmenopausal	2 (33.3%)	4 (22.2%)	12 (60%)	
Density of the breast				0.42 ^c
Type A	1 (16.7%)	0	1 (5%)	
Type B	1 (16.7%)	3 (16.7%)	6 (30%)	
Type C	3 (50%)	8 (44.4%)	10 (50%)	
Type D	1 (16.7%)	7 (38.9%)	3 (15%)	
Immunohistochemical type				0.65 ^b
HR positive/HER2 negative	6 (100%)	16 (88.8%)	18 (90%)	
HER2 positive	0	2 (11.1%)	2 (10%)	
Triple negative	0	0	0	

^aKruskal-Wallis test; ^bFisher's exact test; ^cPearson's chi-square (χ^2); HR: Hormone receptor; US: Ultrasound; MRI: Magnetic resonance imaging; DCIS: Ductal carcinoma *in situ*; HER2: Human epidermal growth factor receptor 2

Table 4. Patients whose surgical management was changed by MRI findings

Patient	Age (years)	BD	US	MRI	Final pathology	Reasons for management change
Case 1	54	B	Irregular mass 12-mm + Irregular mass 10-mm + Irregular mass 4-mm	Irregular mass 16-mm, irregular mass 15-mm, irregular mass 12-mm, increased periareolar subcutaneous enhancement	Focus 1: IDC 25-mm, Focus 2: IDC 12-mm With DCIS 20%	>50% larger and extensive non-mass enhancement
Case 2	45	D	Irregular mass 5-mm	Irregular mass 7-mm, irregular mass 12-mm, irregular mass 4-mm	Focus 1: IDC 13-mm, Focus 2: IDC 8-mm With DCIS 10%	Multicentric
Case 3	44	B	Irregular mass 9.4-mm	Irregular mass 14-mm, irregular mass 8.5-mm, irregular mass 6-mm	Focus 1: ILC 19-mm, Focus 2: ILC 10-mm, Focus 3: ILC 7-mm, Focus 4: ILC 5-mm, Focus 5: ILC 5-mm	Multicentric
Case 4	57	B	Irregular mass 8.3-mm	Irregular mass 7-mm, irregular enhancing focus 25×8-mm	Focus 1: IC 10-mm (lobular 70%, ductal 30%) Focus 2: IDC 7-mm, Focus 3: IDC 3-mm With DCIS 10%	Multifocal and extensive non-mass enhancement
Case 5	49	C	Irregular mass 35-mm	Irregular mass 22-mm, irregular mass 4-mm, Ductal enhancement lateral to the lesion	IDC 22-mm With DCIS 10%	Multifocal and extensive non-mass enhancement
Case 6	63	C	Multiple lobulated lesions within a 31×5.5-mm area, the largest measuring 8×5-mm	Irregular mass 30-mm, irregular mass 20-mm, irregular mass 4-mm	Focus 1: IDC 30-mm, Focus 2: ILC 9-mm With DCIS 15%	Multifocal and multicentric
Case 7	44	C	Irregular mass 10-mm	Irregular mass 8-mm, ductal enhancement posterior to the lesion	ILC 10-mm, LCIS (pagetoid spread in ducts)	Non-mass extensive enhancement
Case 8	65	B	Regular mass 8-mm, complex breast cyst 11-mm, lobulated mass 14-mm	Regional enhancement from the upper quadrant into the lower inner and outer quadrants with scattered foci	45×38-mm DCIS with multiple invasive foci, the largest 10-m	Non-mass extensive enhancement
Case 9	41	D	Irregular mass 20-mm	Irregular mass 20-mm, architectural distortion 2.5 cm	IDC 20-mm With DCIS 60%	Extensive enhancement with distortion
Case 10	45	C	Irregular mass 8-mm	Irregular mass 8-mm, irregular mass 4-mm	IDC 6-mm With DCIS 95 %	Multicentric
Case 11	67	C	Irregular mass 18-mm, Irregular mass 15-mm, Irregular mass 10-mm	Irregular mass 20-mm, irregular mass 12-mm	Focus 1: IC 19-mm, Focus 2: IC 10-mm With DCIS 1%	Multicentric
Case 12	55	B	Irregular mass 20-mm, Irregular mass 13-mm	Irregular enhancing focus 50×35-mm, architectural distortion, Irregular mass 12.5-mm	IDC 52-mm With DCIS 5%	Multicentric and >50% Larger
Case 13	51	C	Irregular mass 16-mm, Irregular mass 8-mm	Irregular enhancing focus 30×10-mm, ductal enhancement anterior to the lesion	IDC 10-mm With DCIS 15%	Extensive non-mass enhancement
Case 14	75	B	Irregular mass 8.5-mm	Irregular mass 16-mm with additional multi-satellite nodules	ILC 12-mm	Multifocal/multicentric
Case 15	52	C	Irregular mass 17-mm	Irregular mass 20-mm, irregular mass 7-mm, irregular mass 5-mm	Neuroendocrine carcinoma 32-mm and 8-mm with DCIS 10%	Multifocal/multicentric
Case 16	35	D	Irregular cystic lesion 10.6-mm	Irregular mass 9.4-mm + ductal enhancement anterior to the lesion	ILC 9-mm No LCIS or DCIS	Extensive non-mass enhancement

US: Ultrasound; MRI: Magnetic resonance imaging; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma; NST: No special type; ILC: Invasive lobular carcinoma; BD: Breast density

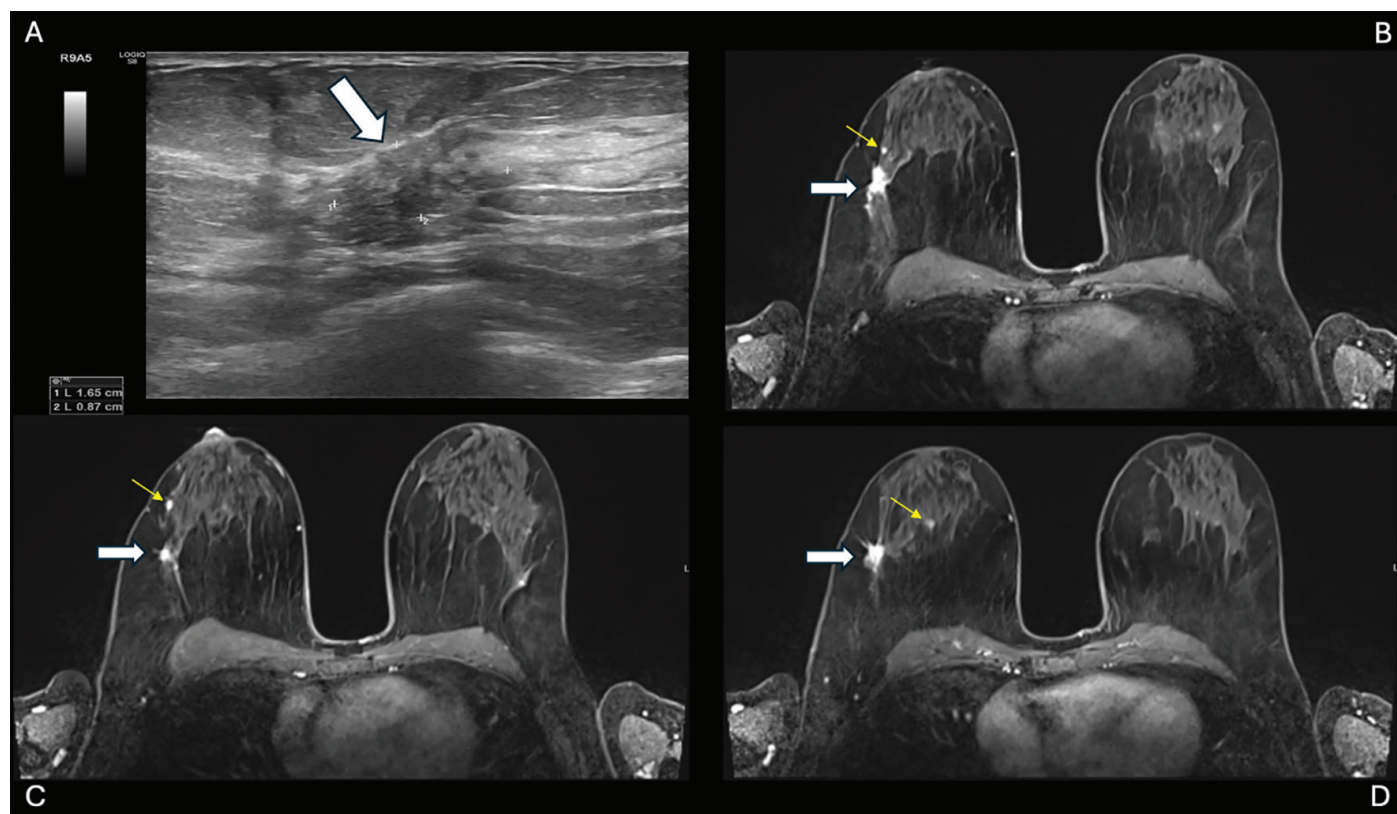


Figure 1. Multifocal invasive ductal carcinoma in a dense breast detected only on MRI. A 51-year-old woman presented with a palpable mass in the right breast. Ultrasound (A) showed a single irregular hypoechoic lesion (bold arrow) at the 9 o'clock position, 5 cm from the nipple, measuring 17×10-mm, with no additional suspicious findings. Breast MRI, performed due to dense parenchyma, confirmed the index circa 20-mm (B) mass (bold arrow) in the mid-outer quadrant and revealed three additional enhancing foci (thin arrows): two up to 5-mm (C) located 2 cm anterior to the index lesion and a 7-mm (D) focus anteromedially, consistent with multifocal disease. Tru-cut biopsy of the index lesion showed invasive ductal carcinoma, and the patient underwent nipple-sparing mastectomy with sentinel lymph node biopsy; final pathology demonstrated two invasive foci measuring 32-mm and 8-mm with approximately 10% surrounding ductal carcinoma *in situ*

MRI: Magnetic resonance imaging

Table 5. Sensitivity of US and MRI in forty-nine patients treated with mastectomy

Parameter	MRI	US	p-value
Sensitivity (%)	76.2	54.5	
Specificity (%)	64.3	63.0	
Positive predictive value (PPV, %)	61.5	54.5	
Negative predictive value (NPV, %)	78.3	63.0	
Accuracy (%)	69.4	59.2	0.42 ^a

^aMcNemar test; US: Ultrasound; MRI: Magnetic resonance imaging

visualized on US, especially in denser parenchyma. These results support a selective use of preoperative MRI in BC, particularly in patients with dense breasts, invasive lobular carcinoma, or inconclusive conventional imaging, as has previously been suggested. Consistent with previous studies, MRI detected non-mass enhancements and small foci that US missed, many of

which represented DCIS or low-grade invasive lesions. Failure to detect these lesions at the time of diagnosis may manifest as locoregional recurrence in the long term (14, 15).

The present study demonstrates that breast density is an independent risk factor for the detection of additional malignant foci on preoperative MRI. This finding is consistent with existing evidence indicating that dense fibroglandular tissue not only increases BC risk but also limits the sensitivity of conventional imaging modalities due to the masking effect (16). In this context, MRI provides a significant advantage by overcoming these limitations and improving lesion detection in dense breasts. Supporting this, the DENSE trial demonstrated that, in women with extremely dense breasts and negative MMG, the addition of MRI significantly increased cancer detection rates and reduced interval cancers by approximately 50% compared to MMG alone. Moreover, tumors detected by MRI were generally smaller and

diagnosed at an earlier stage, highlighting the clinical value of MRI in this high-risk subgroup (17).

After evaluating 149 patients individually, MRI detected additional malignant foci, including DCIS and an invasive component, in 38 (25.48%) patients, and the surgical approach was changed in 16 (10.7%) patients. The main reason for this change was that MRI identified multicentricity in 9 of 16 patients (56.3%), altering the surgical plan for this cohort. In a literature review, Mann et al. (18) reported that preoperative MRI identified additional malignant foci in approximately 32% of patients and led to changes in surgical management in nearly 28% of cases. However, this was not associated with improved oncologic outcomes (18). Similarly, a meta-analysis by Houssami et al. (19) on surgical outcomes demonstrated that preoperative MRI frequently identified additional ipsilateral or contralateral lesions not detected on conventional imaging, many of which were ultimately proven to be DCIS or benign. Although the detection of these MRI-only lesions often led to more extensive surgery and increased mastectomy rates, this escalation in surgical treatment did not translate into improved local control or survival outcomes (19). In the most recent MIPA study, a large multicenter prospective analysis including 5896 patients from 27 centers investigating the impact of preoperative MRI on surgical decision-making and reoperation rates in early-stage BC, which compared patients who underwent MRI with those who did not, the overall mastectomy rate was higher in the MRI group (36.3% vs. 18.0%), corresponding to an approximately 11% absolute increase associated with MRI, which was mirrored in our findings. MRI was more frequently performed in younger patients, those with denser breasts, larger tumors (≥ 20 -mm), and lobular histology. In contrast, the reoperation rate was slightly lower in the MRI group (8.5% vs. 11.7%) (20).

Randomized controlled trials evaluating the impact of preoperative MRI on re-excision rates have shown variable results. In the COMICE trial, the addition of MRI did not reduce re-excision rates compared to standard imaging (10% vs. 11%). In contrast, the MONET trial reported a higher re-excision rate in the MRI group (34% vs. 12%), while the rate of conversion to mastectomy did not differ significantly between groups (21, 22). In the preoperative MRI of the breast trial, a prospective randomized multicenter study evaluating the impact of preoperative MRI on surgical planning, reoperation rates, and neoadjuvant treatment decisions, it was demonstrated that MRI provided additional diagnostic information for 38% of patients and altered surgical management in 18%, significantly reducing reoperation rates (5% vs. 15% in the control group) (23). In the BREAST-MRI trial, a randomized study evaluating the impact of preoperative MRI on surgical and oncological outcomes, MRI led to changes in surgical management toward mastectomy in a subset of patients but did not reduce reoperation rates (8.7%

in both groups) or improve survival (24). The low re-excision rate in our study is attributable to thorough preoperative evaluation and systematic intraoperative assessment of macroscopic margins; furthermore, it can be considered a marker of high-quality care in a dedicated breast center. These results suggest that while MRI may influence surgical planning by detecting additional foci, its routine use does not necessarily translate into improved oncologic outcomes and may increase the risk of overtreatment. Another key finding highlights the critical role of radiologist expertise and the added value of second-look US performed after MRI. The findings, again, are in line with our results, highlighting the importance of careful patient selection and reinforcing the need for shared decision-making when considering MRI as part of preoperative evaluation.

In addition, considering that MRI is not readily accessible in all centers, is associated with higher costs, and cannot be performed in all patients due to technical or clinical limitations, contrast-enhanced mammography (CEM) has recently been investigated as a potential replacement for MRI. While MRI is highly sensitive, CEM is more cost-effective, faster, and accessible. In contemporary practice, CEM may serve as a valuable alternative for patients who cannot undergo MRI due to contraindications, limited access, or time and cost constraints, particularly for local intramammary assessment (25).

This study has several limitations related to its retrospective design and relatively small sample size, which may affect the generalizability of the findings. As this represents a real-world analysis, patients were not prospectively assigned to undergo MRI. The evaluation of re-excision rates is also influenced by institutional practice patterns. As a tertiary referral center, intraoperative macroscopic margin assessment is routinely performed, resulting in an overall re-excision rate below 5%, which is well below the target threshold of 10% recommended by the European Society of Breast Cancer Specialists (26). This low baseline rate may reduce the ability to detect any incremental benefit of MRI in decreasing re-excision rates. Although the study period ran from 2014 to 2025, a substantial proportion of patients were included in more recent years, resulting in a relatively short median follow-up. Therefore, oncological outcomes such as recurrence and survival should be interpreted with caution.

In conclusion, MRI has a selective role in high-risk patients, in cases where breast density causes diagnostic uncertainty, and when there is even the slightest suspicion of additional foci. However, based on our study and the literature, the routine use of preoperative MRI in all BC patients considered for upfront surgery may not be warranted.

Ethics

Ethics Committee Approval: The Koç University Institutional Review Board (approval no: 2024.262.IRB2.112, date: 09.07.2024) approved this study.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ç., M.B., E.D.; Concept: B.Ç., E.D.; Design: B.Ç., S.K.; Data Collection and/or Processing: S.K., Y.H.B., G.Y.; Analysis and/or Interpretation: B.Ç., E.D.; Literature Search: B.Ç., M.B.; Writing: B.Ç., S.K.

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Clinical Outcomes in Initial Hirudotherapy versus Standard Treatment in Idiopathic Granulomatous Mastitis: A Comparative Cohort Study

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ABSTRACT

Objective: Idiopathic granulomatous mastitis (IGM) is a chronic inflammatory disease characterized by a high risk of recurrence and fistula formation. Spontaneous remission has been reported in up to 50% of cases, particularly in mild forms, within 6–24 months without intervention, but inadequate management may allow disease progression. The aim of this study was to compare the clinical outcomes of patients who initially preferred hirudotherapy (leech therapy) with those managed with evidence-based stepwise conventional care.

Materials and Methods: We retrospectively analyzed histopathologically confirmed IGM patients. Patients were divided into two groups: Group 1 who delayed conventional treatment for ≥ 6 months because they initially chose hirudotherapy, and Group 2 who received standardized stepwise management (steroids, aspiration, or surgery). Clinical outcomes included complete remission, overall recurrence/persistence, clinically significant (extensive/severe) recurrence, fistulizing/complicated recurrence, and the need for surgical intervention.

Results: The study included 298 patients, with 41 (13.8%) in Group 1 and 257 (86.2%) in Group 2. Median delay to presentation was significantly longer in Group 1 (15 vs. 1.5 months; $p < 0.001$). Complete remission was achieved in only 4.9% (2/41) of Group 1 compared to 59.1% (152/257) in Group 2 ($p < 0.001$). Overall recurrence/persistence rates were 95.1% in Group 1 versus 21.8% in Group 2 ($p < 0.001$). Among patients who experienced recurrence or persistence, clinically significant (extensive or severe) recurrence occurred in 89.7% (35/39) of Group 1 compared with 42.9% (24/56) of Group 2 ($p < 0.001$), while fistulizing/complicated recurrence was significantly higher in Group 1 (26.8% vs. 5.4%; $p < 0.001$). In multivariable analysis, hirudotherapy use [odds ratio (OR): 6.7; $p < 0.001$] and fistula presence (OR: 9.3; $p < 0.001$) were independent predictors of surgical intervention.

Conclusion: Initial exclusive reliance on hirudotherapy was associated with markedly lower remission rates, substantially higher rates of clinically significant recurrence, longer delays before medical evaluation, and increased surgical needs despite comparable baseline severity. These findings suggest that hirudotherapy alone does not appear to modify the immune-mediated course of IGM and may result in a higher proportion of refractory cases presenting to hospital settings, as milder cases in the community may resolve spontaneously without seeking care. Early adherence to standardized stepwise care may therefore be important to prevent progression to severe recurrence and reduce the need for surgery. However, further prospective studies are required to confirm these findings.

Keywords: Idiopathic granulomatous mastitis; hirudotherapy; spontaneous remission; complete remission; recurrence; fistula

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KEY POINTS

- Initial hirudotherapy (leech therapy) in idiopathic granulomatous mastitis (IGM) was linked to lower complete remission rates and substantially higher recurrence rates compared with standard stepwise treatment.
- Patients who started with hirudotherapy experienced substantially more frequent clinically significant and fistulizing recurrences, along with a higher need for surgical intervention.
- Exclusive reliance on hirudotherapy caused a median treatment delay of 15 months, which appears to contribute to disease progression and worse clinical outcomes.
- Early evidence-based stepwise care appears crucial for minimizing severe recurrence and limiting the need for surgical intervention in IGM.

Introduction

Idiopathic granulomatous mastitis (IGM) is a rare inflammatory breast disease that primarily affects women of reproductive age. The etiology of IGM remains unclear, and it is characterized by non-necrotizing granulomatous inflammation. Patients typically present with a painful mass, abscess, or fistula formation. The clinical presentation of IGM may mimic breast cancer or infectious mastitis, creating a diagnostic and therapeutic challenge (1, 2). IGM is considered a potentially self-limiting condition, with spontaneous remission reported in up to 50% of patients, particularly in mild cases, within 6–24 months without intervention (3). Nevertheless, even though spontaneous resolution is possible in some IGM cases, the disease often follows a prolonged clinical course. IGM is associated with high recurrence rates, and progression to complicated forms may occur when the condition is not adequately managed (3-5).

Multicenter studies have shown that a history of pregnancy, breastfeeding, prior breast infection and smoking are associated with an increased risk of recurrence (3). These observations illustrate the importance of addressing modifiable risk factors during IGM treatment. The pathogenesis of IGM is not fully understood. However, several mechanisms have been proposed, including autoimmune reactions, immune responses to ductal secretions, and possible microbial or traumatic triggers (2).

IGM treatment typically follows a stepwise approach based on clinical severity. Management options may range from observation or local steroid therapy in mild cases to more aggressive approaches such as systemic corticosteroids, immunosuppressive agents, drainage, and surgical interventions in refractory or fistulizing disease (3-6). Although a universal international consensus guideline is lacking, a recent expert consensus report has proposed standardized diagnostic and treatment criteria for IGM, providing a framework for clinical decision-making in regions where the disease is relatively prevalent (5). Nevertheless, treatment strategies remain heterogeneous across centers (3, 4, 7). Early initiation of evidence-based therapy has been associated with improved remission rates and a lower likelihood of surgical intervention (6).

Recent proposals include treatment algorithms based on clinical and ultrasound-based classifications, such as the Pittsburgh classification. These systems categorize disease severity from minimal irritation to widespread involvement, and studies have shown that higher complete response rates are achieved when management follows the recommended algorithm (7).

Cultural beliefs and traditional medicine practices significantly influence health-seeking behavior in certain regions of Türkiye and the Middle East. Despite well-documented potential complications such as secondary bacterial infections, hirudotherapy (medicinal leech therapy) is widely perceived as a natural, low-risk, and religiously compatible treatment modality (8, 9). In addition, traditional beliefs may delay patients' presentation to medical care, which can result in more advanced disease at diagnosis and poorer outcomes (10). Hirudotherapy has shown efficacy in specific conditions, including venous congestion and microvascular disorders (8, 11). However, despite its frequent use, the role of hirudotherapy as an initial treatment modality in inflammatory breast diseases such as IGM has not yet been systematically evaluated in comparative clinical studies.

The aim of this retrospective study was to compare clinical outcomes between patients who initially opted for exclusive hirudotherapy for ≥ 6 months and those who received timely institutionally preferred stepwise conventional treatment after a biopsy-confirmed diagnosis of IGM. The ≥ 6 -month threshold was selected to identify patients who had meaningfully delayed evidence-based care, rather than those who had only briefly explored traditional remedies, and is consistent with the lower bound of the reported spontaneous remission window for IGM (6–24 months), beyond which persistent disease is unlikely to resolve without intervention (3). All patient data were extracted retrospectively from hospital records, outpatient files, and telephone follow-up conducted after the care period had concluded; no prospective data collection or intervention assignment was performed. We hypothesized that prolonged reliance on hirudotherapy would be associated with delayed access to evidence-based care, increased disease severity, higher complication rates, and greater need for surgical intervention.

Materials and Methods

This retrospective cohort study included female patients diagnosed with IGM by needle core biopsy between January 2020 and December 2024. The study was approved by the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: E-10840098-772.02-3000, date: 24.06.2021) and conducted in accordance with the Declaration of Helsinki.

Patient Selection and Diagnostic Criteria

A total of 313 female patients were screened. In all cases, the diagnosis of IGM was confirmed by histopathological examination of tissue obtained via ultrasound-guided tru-cut biopsy. Ultrasound was the primary imaging modality for all patients, while magnetic resonance imaging was reserved for cases with suspected extensive disease or complex fistulizing patterns.

According to institutional protocols before establishing the diagnosis of IGM, tuberculosis (purified protein derivative test, culture, polymerase chain reaction, and chest imaging when indicated), malignancy, sarcoidosis, Wegener's granulomatosis, fungal or bacterial infections, and other secondary granulomatous causes were ruled out.

Patients were included if they had biopsy-proven lobulocentric non-caseating granulomatous inflammation consistent with IGM and had at least 12 months of follow-up. Patients with infectious, malignant, and systemic granulomatous etiologies and secondary granulomatous mastitis (tuberculosis, sarcoidosis, fungal or bacterial infections, cystic neutrophilic granulomatous mastitis, or other identifiable causes) were excluded from the study.

Data were collected from electronic hospital records, outpatient files and telephone follow-up interviews. Three patients (1%) were lost to follow up and excluded from analysis. Therefore, the analyzable cohort consisted of 310 patients. Of these, 12 patients who continued treatment outside the city were recorded for follow-up data but were not included in the standard care group, resulting in a comparative cohort of 298 patients. The patient selection process is illustrated in Figure 1.

Patient Groups

Patients were categorized based on their initial treatment preference following biopsy-confirmed diagnosis.

Group 1 (Leech Therapy Group, $n = 41$)

This group consisted of patients who exclusively underwent hirudotherapy for ≥ 6 months after diagnosis and declined conventional medical treatment during that period.

Hirudotherapy was performed in non-medical traditional settings by independent practitioners. The number of sessions, duration of application, and leech species were not standardized, as these interventions occurred outside institutional clinical control (8, 10). Hirudotherapy exposure was verified through two complementary sources: (1) institutional records documenting the absence of any conventional treatment during the ≥ 6 -month post-diagnosis period; and (2) direct patient contact. Patients who did not attend scheduled post-biopsy follow-up appointments were actively contacted by telephone by the study team. This active outreach confirmed hirudotherapy use and allowed collection of outcome data for non-attending patients. Exposure was therefore corroborated by the documented absence of institutional treatment and was not based solely on patient self-report.

Seven patients initially declined in-person hospital follow-up after diagnosis. Outcome information for these patients was obtained through telephone interviews conducted at least 12 months after their last known hospital visit. They were included in the outcome analyses based on the available follow-up data (recurrence, persistence, fistula development, or remission status).

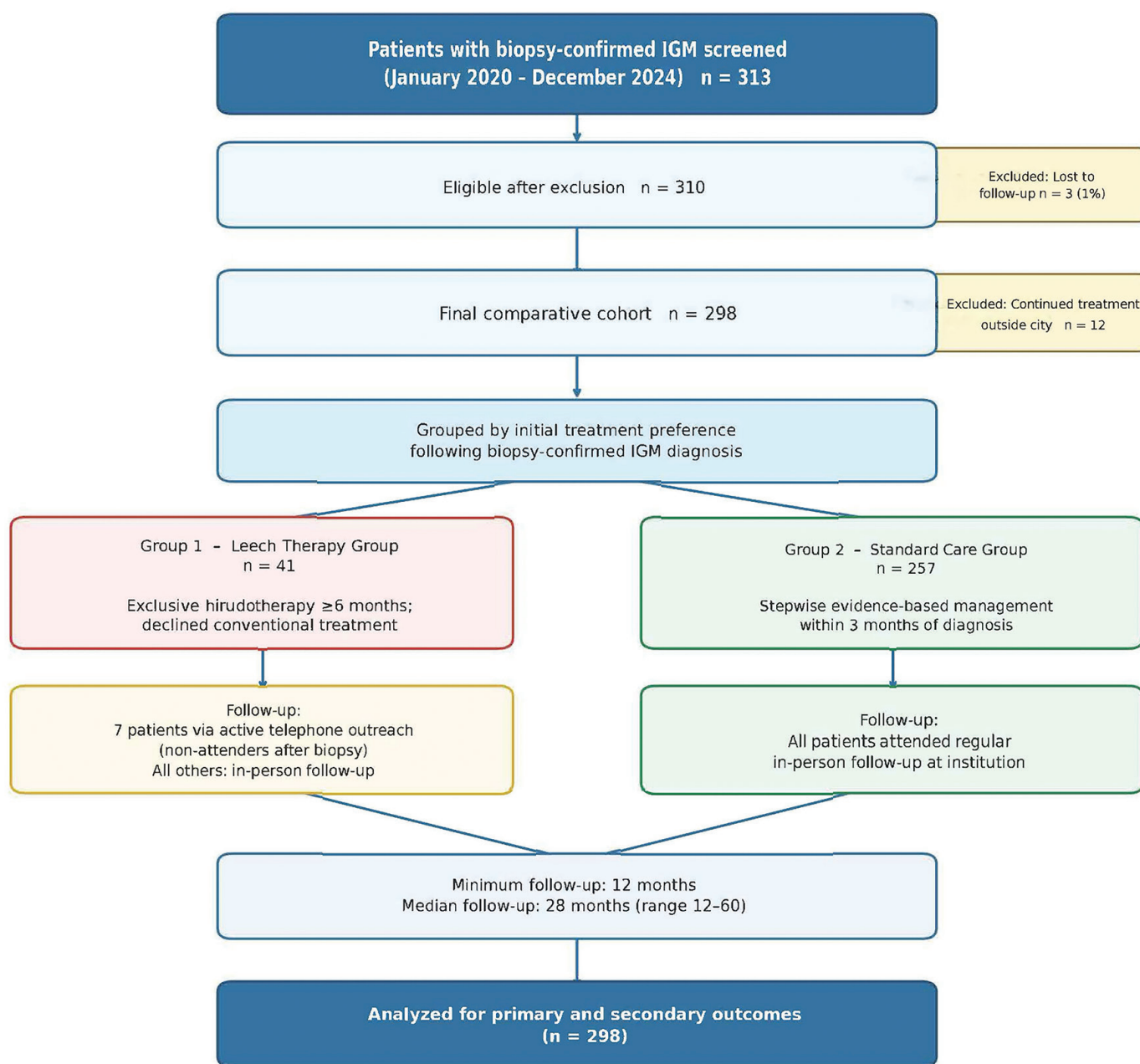
Group 2 (Standard Care Group, $n = 257$)

The second group consisted of patients who received stepwise evidence-based management within three months of diagnosis and attended regular, in-person follow-ups.

Initial Clinical Severity Classification at Patient Presentation

Patients were classified into three severity groups at the time of initial presentation according to severity and corresponding treatment approach. The classification reflected the stepwise treatment approach used in routine clinical practice and was defined retrospectively, as follows (5, 7, 8):

- Mild severity (limited mass, minimal inflammation, no fistula/abscess/ulceration, mild or absent skin changes, no multifocality): patients managed with observation (watch-and-wait) or only with topical/intralesional steroids (12, 13);
- Moderate severity (prominent mass, moderate inflammation, possible localized abscess or skin changes, no fistula/ulceration, limited multifocality): Systemic steroids (dose of 0.5–0.8 mg/kg/day methylprednisolone, followed by gradual tapering over 8 to 12 weeks based on clinical response) or intralesional steroids as first-line therapy, combined with aspiration for abscess drainage when indicated;
- Severe/complicated (fistula/sinus presence, multiple abscesses, widespread inflammation, skin ulceration, multifocal/bilateral involvement, treatment resistance, or high recurrence risk):



* 12 patients excluded from comparative analysis (continued treatment outside city) but were retained for follow-up data recording purposes.

Figure 1. Patient selection flowchart. CONSORT-style diagram illustrating the screening, exclusion, and group allocation of patients included in the comparative cohort analysis. Patients were grouped based on their initial treatment preference following biopsy-confirmed IGM diagnosis. Active telephone outreach was performed for patients who did not attend scheduled follow-up after biopsy, ensuring complete outcome ascertainment

IGM: Idiopathic granulomatous mastitis

Systemic steroids as first-line therapy with the addition of immunosuppressive agents (methotrexate or azathioprine) in resistant cases. Aspiration or drainage was performed when abscess formation was present and surgical intervention (wide local excision or drainage) was performed as a last resort in refractory cases (14, 15).

To ensure consistency across participating centers, the initial clinical severity classification was performed according to a predefined standardized protocol applied by the participating surgeons at each center. All cases were assessed using the same severity criteria based on clinical findings, imaging reports, and pathology data.

Data Collection and Outcome Measures

Demographic characteristics (age, bilaterality, multifocality), time from diagnosis to first conventional treatment, total disease duration and the need for surgical intervention were recorded. Clinical outcomes included complete remission (complete clinical and radiological resolution) and recurrence or persistence of disease (new episode or ongoing disease) after treatment. For analytical purposes, recurrence events were further evaluated according to clinical severity. Clinically significant recurrence was defined as extensive or severe recurrence, including persistent severe inflammatory attacks, refractory disease course, multiple recurrences, or fistulizing/complicated presentations, such as sinus tract formation with abscess. These events were analyzed as a subgroup of overall recurrence.

Statistical Analysis

Continuous variables are presented as median (range) or mean $\pm$ standard deviation, and categorical variables as frequencies (%). Inter-group comparisons were performed using the Mann-Whitney U test, chi-square test, or Fisher's exact test as appropriate. Independent predictors of surgical intervention were identified using multivariable binary logistic regression (backward stepwise). A p -value <0.05 was considered statistically significant. All analyses were conducted using SPSS, version 28.0 (IBM Inc., Armonk, NY, USA).

Results

For comparative analysis, 298 patients were included after excluding 12 patients who continued treatment in different cities. The final comparative analysis included two groups: Group 1 (Leech Therapy Group, $n = 41$) and Group 2 (Standard Care Group, $n = 257$).

Baseline Characteristics at Initial Presentation

Baseline demographic and clinical characteristics are summarized in Table 1. The two groups were comparable with respect to age, body mass index, smoking status, parity, number of deliveries, time since last delivery, breastfeeding history, and duration of breastfeeding (all $p > 0.05$). The distribution of initial clinical severity (mild, moderate, or severe/complicated) did not differ significantly between groups (χ^2 test, $p = 0.92$), indicating similar baseline clinical status.

Leech Therapy Group Follow-up Details

Seven patients initially declined in-person hospital attendance after diagnosis. Among these patients, four later presented with complicated fistula formation, two continued leech therapy due to recurrent abscess episodes, and one reported symptom improvement and did not seek further hospital care. All remaining patients attended in-person hospital follow-up. No

additional loss to follow-up occurred beyond the three patients excluded during cohort formation.

Follow-up Duration

All patients had a minimum follow-up of 12 months. The median follow-up duration was 28 months (range 12–60) in the full cohort. Median follow-up was 26 (12–58) months in the standard care group and 32 (12–60) months in the leech therapy group ($p = 0.008$). The longer median follow-up in the leech group reflects the extended disease duration and delayed presentation, as well as the inclusion of late-presenting cases.

Median time from diagnosis to presentation was 15 (6–24) months in the leech therapy group versus 1.5 months in the standard care group ($p < 0.001$). Total disease duration was significantly longer in the leech therapy group (median of 22 months vs. 9 months; $p < 0.001$).

Clinical Outcomes

Clinical outcomes are presented in Table 2. Complete remission was markedly lower in the leech therapy group compared with the standard care group (4.9% vs. 59.1%, $p < 0.001$). Overall recurrence or persistent disease was significantly more frequent in the leech therapy group than in the standard care group (95.1% vs. 21.8%, $p < 0.001$). Among patients with recurrence, clinically significant recurrence (extensive or severe recurrence) occurred in 35 of 39 patients (89.7%) in the leech therapy group compared with 24 of 56 patients (42.9%) in the standard care group ($p < 0.001$). Fistulizing or complicated recurrence represented a subset of these events and was significantly more frequent in the leech therapy group (26.8% vs. 5.4%, $p < 0.001$) (Figure 2).

Multivariable logistic regression analyses identified initial exclusive leech therapy [odds ratio (OR) 6.7, 95% confidence interval (CI) 2.9–15.6, $p < 0.001$] and presence of fistula at presentation (OR 9.3, 95% CI 3.1–28.1, $p < 0.001$) as independent predictors of surgical intervention. Other covariates were not statistically significant.

Discussion and Conclusion

This study provides one of the first comparative cohort analyses examining the clinical impact of exclusive initial hirudotherapy in biopsy-proven IGM. The principal finding was the markedly lower remission rate and substantially higher recurrence and surgical intervention rates among patients who initially relied on hirudotherapy, despite similar baseline demographic and disease severity characteristics.

Complete remission was achieved in only 4.9% of the leech therapy group compared with 59.1% in the standard care group ($p < 0.001$), while overall recurrence/persistence occurred in 95.1% versus 21.8% ($p < 0.001$). The markedly higher recurrence/

Table 1. Baseline characteristics at initial presentation

Characteristic	Leech therapy (n = 41)	Standard care (n = 257)	p-value
Age, median (range), years	36 (24–52)	37 (22–58)	0.51
BMI, mean ± SD, kg/m ²	27.8±4.2	27.4±4.5	0.62
Smoking (current or former), n (%)	8 (19.5%)	48 (18.7%)	0.89
Parity (≥1 delivery), n (%)	35 (85.4%)	220 (85.6%)	0.97
Number of deliveries, median (range)	2 (0–5)	2 (0–6)	0.78
Time since last delivery, median (range), years	6 (1–18)	7 (1–20)	0.44
History of breastfeeding, n (%)	32 (78.0%)	198 (77.0%)	0.88
Duration of breastfeeding, median (range), months	18 (0–60)	16 (0–72)	0.55
Initial severity classification, n (%)			0.92*
- Mild	12 (29.3%)	75 (29.2%)	
- Moderate	14 (34.1%)	90 (35.0%)	
- Severe/complicated	15 (36.6%)	92 (35.8%)	

*Chi-square test; SD: Standard deviation; BMI: Body mass index

Table 2. Clinical outcomes

Outcome	Leech therapy (n = 41)	Standard care (n = 257)	p-value
Complete remission, n (%)	2 (4.9%)	152 (59.1%)	<0.001
Overall recurrence or persistence, n (%)	39 (95.1%)	56 (21.8%)	<0.001
Extensive or severe recurrence*, n (%)	35 (85.4%)	24 (9.3%)	<0.001
Fistulizing/complicated recurrence†, n (%)	11 (26.8%)	14 (5.4%)	<0.001

*Subset of overall recurrence or persistence; †Subset of extensive or severe recurrence

persistence in the leech therapy group is consistent with known risk factors for IGM recurrence, including potential delays in effective immunomodulatory therapy, and is consistent with multicenter data linking recurrence to factors such as history of pregnancy, breastfeeding, prior breast infection, and smoking (3). Importantly, the distribution of initial clinical severity did not differ significantly between groups ($p = 0.92$), suggesting that the observed divergence in outcomes cannot be explained by differences in baseline disease burden. Patients in the leech therapy group experienced a substantial delay in presentation for conventional care, accompanied by significantly prolonged total disease duration compared to the standard care group (1, 2).

IGM is widely regarded as an immune-mediated inflammatory condition characterized by granulomatous lobulitis (2). Early initiation of corticosteroid or immunomodulatory therapy has been associated with better disease control and lower risk of progression to fistulizing or refractory forms (16). In contrast, hirudotherapy does not directly target the underlying granulomatous inflammatory cascade. Medicinal leeches have a well-established role in reconstructive and plastic surgery, where they are used to relieve venous congestion in replanted

digits, pedicled and free flaps, and nipple-areola complex congestion following breast surgery (8, 11). Their anticoagulant and vasodilatory secretions, including hirudin, calin, and destabilase, are effective in reversing localized venous stasis in these vascular contexts (11). The perception of hirudotherapy as a broadly applicable, natural, and low-risk treatment may stem in part from its genuine efficacy in such settings, combined with its long-standing use in traditional Unani and Islamic medicine frameworks (10). However, these mechanisms are mechanistically distinct from the immune-mediated granulomatous inflammation that drives IGM pathology. While medicinal leeches have recognized utility in selected surgical contexts (7, 10), their biological effects, which are primarily anticoagulant with limited local anti-inflammatory activity, are unlikely to modify the immune-driven pathology of IGM.

Spontaneous remission is a well-recognized feature of IGM. Several studies report spontaneous resolution in up to 50% of patients, particularly in mild forms without any intervention, typically within 6–24 months (3-5). This natural course has important implications when interpreting outcomes of non-evidence-based therapies. Mild cases that resolve spontaneously in the community may never present to hospital, whereas

patients with persistent disease are more likely to eventually seek medical care. In the present cohort, patients who initially relied on hirudotherapy presented after a prolonged delay (median 15 months), suggesting that the hospital-based hirudotherapy group may have been enriched with more persistent or treatment-resistant cases. Consistent with this interpretation, among the 39 patients with recurrence or persistence in the leech therapy group, 35 (89.7%) developed clinically significant forms, including fistulizing or extensive/severe recurrence.

The markedly higher rates of fistulizing/complicated and extensive/severe recurrence in the leech therapy group further support the hypothesis that delaying evidence-based treatment may permit progression to more destructive disease phenotypes (3). Multivariable analysis demonstrated that exclusive initial leech therapy was independently associated with the need for surgical intervention (OR 6.7), even after adjustment for baseline severity and other covariates. The presence of fistula at presentation was the strongest predictor (OR 9.3), consistent with prior literature showing fistulizing disease as a marker of advanced inflammatory burden (9).

In Türkiye, hirudotherapy is not reimbursed by the social security institution, even when performed in public facilities, and remains fully out-of-pocket for patients, as the law excludes unlicensed traditional, complementary, and alternative medicine practices (17). Patients who prefer hirudotherapy often seek it directly through unregulated or traditional providers, leading to significant therapeutic delays. Consequently, those who eventually present to hospital are more likely to present with complicated IGM (e.g., fistulizing or severe-persistent disease), as evidenced by the high rate of serious/complicated recurrence at nearly 90% in the leech therapy group. This may contribute to progression to more severe IGM forms and increase the burden on the healthcare system through higher surgical intervention rates, prolonged hospitalizations, and greater treatment costs associated with fistulizing or refractory disease.

These findings must be interpreted within the context of several limitations. The retrospective design introduces potential selection bias, and the leech therapy sub-group was small, making up only about 14% of the whole study population. It is possible that patients who experienced spontaneous resolution following hirudotherapy never presented to hospital, which may

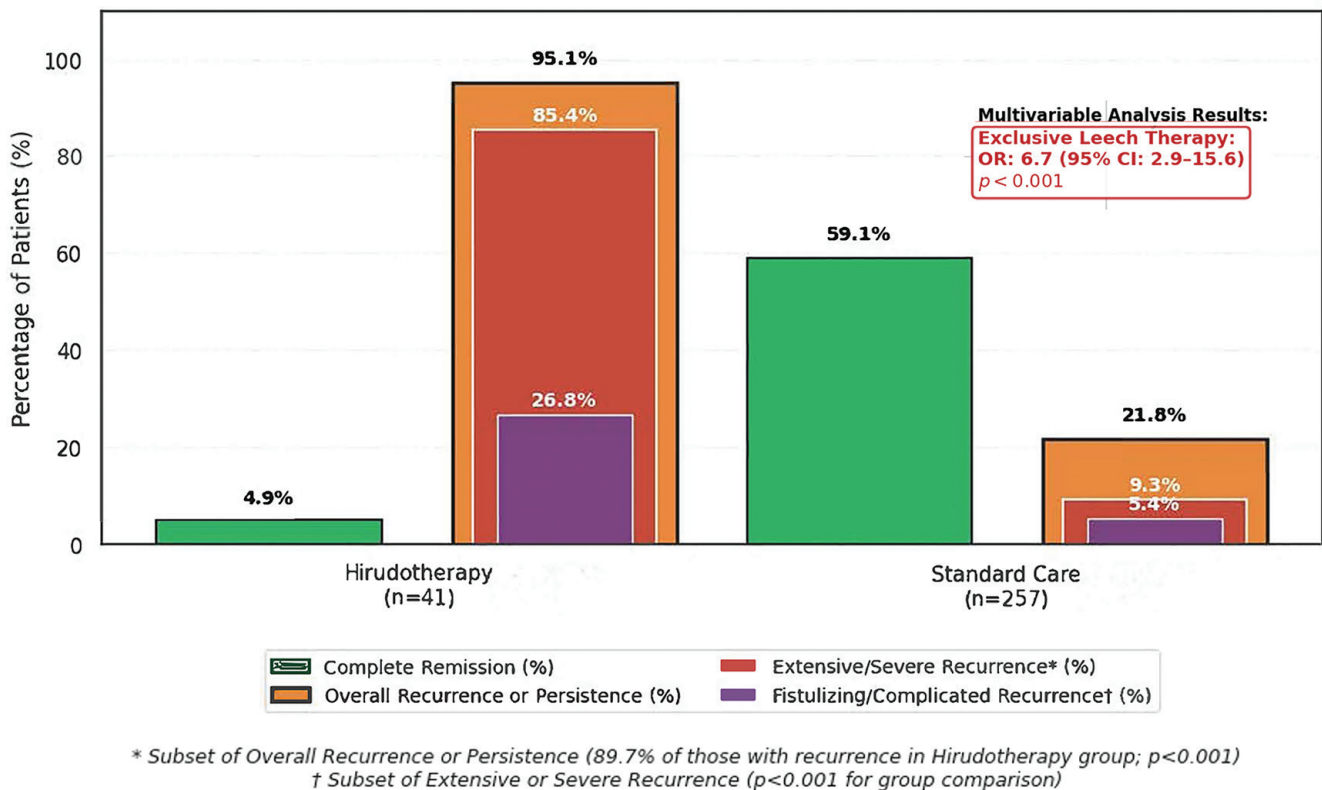


Figure 2. Comparison of remission and recurrence patterns in biopsy-proven IGM according to initial treatment strategy (hirudotherapy vs. standard care). Bars represent percentages of the total cohort. Hirudotherapy was associated with lower remission and higher rates of complicated recurrence, including clinically significant recurrence in 89.7% of those with recurrence ($p < 0.001$)

IGM: Idiopathic granulomatous mastitis; OR: Odds ratio; CI: Confidence interval

have increased the incidence of refractory cases in this group. As reported in multiple review and case series, spontaneous resolution without intervention occurs in up to 50% of IGM cases (16). This phenomenon is likely to occur similarly across both groups, given the comparable baseline severity distributions and the fact that our cohort captured consecutive biopsy-proven cases.

Undetected spontaneous resolutions in the community cannot be completely excluded. However, it is unlikely that such cases disproportionately affected the leech therapy group. Patients in this group presented with prolonged delay before seeking conventional care, and high rates of fistulizing/complicated and extensive/severe recurrence were observed. These findings argue against the possibility that the leech cohort appeared more refractory solely because of unrecognized spontaneous resolutions.

Follow-up for seven patients in the leech group was obtained via telephone interviews, introducing potential reporting bias. However, all included patients had at least 12 months of follow-up. Baseline characteristics were comparable between the groups, supporting the internal validity of the study. Marked differences were observed in remission rates, recurrence patterns, disease duration, and the need for surgical intervention. These findings suggest that the observed results are unlikely to be explained by selection bias alone.

Our findings suggest that prolonged exclusive reliance on non-evidence-based treatment in IGM may be associated with delayed access to effective immunomodulatory therapy, increased disease persistence, and higher surgical burden. Early and culturally sensitive patient counseling may therefore be important to prevent avoidable therapeutic delay and progression to complicated disease.

Relying solely on hirudotherapy as the first treatment for IGM was associated with poorer clinical outcomes. Remission rates were lower, recurrence was higher, especially fistulizing and severe forms, and more patients required surgery. Delays in initiating evidence-based therapy may allow the disease to progress to more complicated stages. Timely initiation of standard treatment therefore appears essential. Clinicians should inform patients about the risks of delaying therapy, and culturally sensitive education and early referral pathways may help bridge traditional practices with evidence-based medical care. Prospective studies are needed to understand the long-term impact of delayed treatment.

Ethics

Ethics Committee Approval: The study was approved by the Istanbul Medipol University Non-Interventional Clinical Research

Ethics Committee (approval no: E-10840098-772.02-3000, date: 24.06.2021) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: This retrospective study was conducted using de-identified data obtained from medical records.

Footnotes

Authorship Contributions

Concept: M.T., K.C., M.B.A., M.Ö., A.G., R.C.A.O., H.K.; Design: M.T., K.C., M.B.A., M.Ö., A.G., R.C.A.O., H.K.; Data Collection and/or Processing: M.T., K.C., M.B.A., M.Ö., A.G., R.C.A.O.; Analysis and/or Interpretation: M.T., K.C., M.B.A., M.Ö., A.G., R.C.A.O., H.K.; Literature Search: M.T., K.C., M.B.A., M.Ö., A.G., R.C.A.O., H.K.; Writing: M.T., K.C., M.B.A., M.Ö., A.G., R.C.A.O., H.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Baseline Quality of Life and Its Predictors among Jordanian Women with Breast Cancer: Findings from an Ongoing Randomized Controlled Trial

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ABSTRACT

Objective: Breast cancer is the most common cancer among women in Jordan. Survivors often experience impaired quality of life (QoL) due to various sociodemographic and clinical factors. Understanding QoL at the time of diagnosis is essential for developing effective interventions. This study aimed to assess baseline QoL and to identify predictors of QoL among Jordanian women with breast cancer prior to any intervention.

Materials and Methods: This cross-sectional analysis examined baseline data from an ongoing randomized controlled trial registered with Australian New Zealand clinical trials registry. Two hundred women with breast cancer completed the Arabic versions of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-BR23 questionnaires at study entry, prior to randomization and intervention. Sociodemographic and clinical variables were collected and analyzed using SPSS version 24. Multiple regression analysis was performed to identify predictors of QoL.

Results: The mean age of participants was 48.0±8.3 years. The global QoL score was 57.4/100. Higher scores were observed for role and social functioning, whereas emotional functioning had the lowest scores. The most frequently reported symptoms were insomnia, fatigue, and pain. Multivariate linear regression identified younger age (positively associated) and total breast symptoms (negatively associated) as significant independent predictors of QLQ-C30 global QoL. For QLQ-BR23, the overall model was significant, although no individual predictor reached statistical significance.

Conclusion: Jordanian women with breast cancer experience moderate impairment in QoL at study entry, primarily influenced by symptom burden and age. These baseline findings provide a foundation for interpreting intervention effects in the ongoing randomized controlled trial. Routine assessment of symptoms and culturally sensitive supportive care are recommended to improve patient outcomes.

Keywords: Quality of life; breast cancer; Jordan; predictors; EORTC QLQ-C30; EORTC QLQ-BR23; baseline data; randomized controlled trial

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KEY POINTS

- Significant Quality of Life Impairment Identified: Jordanian women with breast cancer face moderate but notable impairment in their quality of life, underscoring a critical patient care gap.
- Key Predictors Revealed: Clinical factors (e.g., cancer stage, treatment type) and the burden of symptoms are significant predictors of this compromised quality of life.
- Pronounced Emotional Distress: Emotional functioning is particularly affected, alongside a high symptom burden, highlighting specific areas for targeted intervention.
- Urgent Call for Integrated Care: There is a crucial need for culturally sensitive and integrated supportive care strategies to effectively improve these patients' well-being.

Introduction

Breast cancer continues to be the most frequently diagnosed malignancy among women worldwide and represents a major public health concern in Jordan, where it constitutes nearly 40% of all cancers diagnosed among females (1, 2).

Although advances in screening programs and therapeutic interventions have substantially improved survival outcomes, the disease and its treatments—including chemotherapy, axillary lymph node dissection, and endocrine therapy—often lead to considerable physical, psychological, and social challenges for patients (3-6).

Consequently, health-related quality of life (HRQoL) has become an essential patient-centered outcome in breast cancer survivorship research. HRQoL reflects multiple dimensions of well-being, including physical functioning, symptom burden, emotional status, social relationships, and spiritual aspects of life (4, 5, 7).

In Middle Eastern countries, including Arab societies, women with breast cancer frequently experience poorer HRQoL compared with global averages. This may be attributed to delayed diagnosis, limited access to comprehensive supportive care services, and sociocultural factors that influence psychological coping and illness perception (4, 8).

Previous systematic reviews have identified several determinants that may affect HRQoL among breast cancer survivors. These include sociodemographic characteristics, clinical status, treatment-related variables, and psychosocial conditions (3, 4, 7, 9-12).

Evidence from Jordan suggests that women with breast cancer may experience elevated levels of psychological distress, increased symptom burden, and varying degrees of social isolation. Cultural factors, such as the importance of family gatherings and concerns related to eating difficulties during chemotherapy-induced dysphagia, may further complicate patients' experiences (3, 7). In addition, interventions such as complete decongestive therapy following axillary lymph node dissection have demonstrated potential benefits in reducing breast cancer-related lymphedema and improving QoL (6).

This section discusses the specific predictors of QoL among Jordanian women with breast cancer. Existing cross-sectional studies suggest associations between QoL and factors such as demographic characteristics, symptom distress, spirituality, and religious beliefs; however, comprehensive data are still scarce (10, 11). Moreover, regional reviews indicate that research addressing QoL among Arab women remains insufficient, particularly in countries such as Jordan, Bahrain, Tunisia, and the United Arab Emirates (4, 8). Psychological distress following diagnosis is also widely reported and may significantly compromise patients' well-being, highlighting the importance of supportive interventions including mindfulness-based approaches and social support programs (7).

Therefore, the present study aims, using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23 instruments, to assess the QoL of Jordanian women diagnosed with breast cancer and to explore its association with sociodemographic, clinical, treatment-related, and psychosocial variables.

The findings may contribute to the development of culturally appropriate interventions and inform health policies aimed at improving QoL among this population.

Materials and Methods

Study Design and Setting

This study presents a cross-sectional analysis of baseline data collected as part of an ongoing randomized controlled trial (RCT) (ANZCTR 12619000095167), which was prospectively registered. The parent RCT evaluates the effectiveness of a psychoeducational intervention program to improve QoL among Jordanian women diagnosed with breast cancer. This baseline analysis was conducted at Al-Bashir Hospital, a tertiary referral center in Amman, Jordan, between January and June 2019, prior to the delivery of any intervention. This study focuses on characterizing QoL and its predictors at study entry, to inform the subsequent interpretation of intervention effects.

Participants

Two hundred Jordanian women diagnosed with breast cancer and who were receiving treatment were recruited from oncology

inpatient clinics for the parent RCT. Eligible participants (confirmed diagnosis, ongoing treatment, and ability to complete questionnaires; no psychiatric illness or comorbid chronic systemic diseases) were randomly assigned by the primary investigator to the intervention or control groups using a randomized block design. However, this study reports only baseline data collected prior to randomization and intervention

Sample size was calculated using STATA software (power = 0.80, α = 0.05, moderate effect size, 9 predictors; minimum n = 119). To account for 10% attrition, 220 participants were approached. Of these, 10 were excluded due to comorbidities, and 10 questionnaires were excluded due to missing data, yielding 200 complete responses. No demographic differences existed between included and excluded participants.

Baseline Data Analysis Stating

This study focuses exclusively on baseline data collected before randomization and intervention. No intervention effects are reported in this analysis.

Instruments

Eligible participants completed a comprehensive 55-item questionnaire assessing socio-demographic characteristics (age, educational level, employment status, marital status, monthly income, duration of marriage, occupation, number of children, menopausal status); medical history (chronic diseases, family history); and treatment details (methods, surgery type, post-operative details, histopathology type, stage, and grade). Breast cancer stage was determined according to the American Joint Committee on Cancer 8th edition staging system, based on the TNM classification (tumor size, lymph node involvement, and metastasis).

The study utilized validated Arabic versions of the EORTC QLQ-C30 and QLQ-BR23 questionnaires.

EORTC QLQ-C30 (30 items): This core questionnaire assesses global health status/QoL, five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, nausea/vomiting, pain), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). The Arabic version of the QLQ-C30 has been widely validated across various Arabic-speaking populations, demonstrating its reliability and validity in these contexts (13-15).

EORTC QLQ-BR23 (23 items): This breast cancer-specific module includes scales for functional aspects (body image, sexual functioning, future perspective) and for symptoms (arm symptoms, breast symptoms, systemic therapy side effects, upset by hair loss). The Arabic version of the QLQ-BR23 has

also been psychometrically validated, confirming its suitability for assessing QoL in Arabic-speaking breast cancer patients (13, 14, 16).

Cronbach's alpha indicated that each subscale had high reliability: EORTC QLQ-C30 = 0.87 and EORTC QLQ-BR23 = 0.86.

Each item was scored on a 4-point Likert scale (1 = "not at all" to 4 = "very much"), except for global health status/QoL items (1 = "very poor" to 7 = "excellent"). Raw scores were transformed to a 0–100 scale, where higher scores indicate better functioning, more severe symptoms, or higher QoL, depending on the scale. The questionnaires were administered by trained female nurses in face-to-face interviews to minimize bias.

Ethical Approval and Informed Consent

Ethical approval was obtained from the Jordan Ministry of Health's local ethical research committee (ethics committee no: 9694, date: 05.07.2018) and Universiti Sains Malaysia (protocol code: USM/JEPeM/18080386, date: 24 December 2018). Written informed consent was obtained from all participants prior to enrollment. The consent process included a detailed explanation of the purpose of the study, procedures, risks, and of the right to withdraw at any time without affecting their medical care. Participants were assured of confidentiality and that data would be used for research purposes only. Participation was voluntary, and the confidentiality of data was ensured. The study was conducted in accordance with the Declaration of Helsinki.

Procedure

Permission to use the EORTC QLQ-C30 and QLQ-BR23 questionnaires was obtained from the main author. A female researcher approached eligible women in oncology clinic waiting areas, provided a brief explanation of the study obtained written informed consent, administered the questionnaires to obtain implicit consent through completion, and collected them immediately, while maintaining participant confidentiality and anonymity. Trained research assistants fluent in Arabic ensured accurate interpretation and documentation of responses, particularly for participants with limited literacy or visual impairments.

Statistical Analysis

Data were analyzed using SPSS version 24. Descriptive statistics were used to summarize socio-demographic and clinical characteristics and QoL scores. Instrument reliability was assessed using Cronbach's α . Independent t-tests, one-way analysis of variance, and multivariate linear regression identified predictors of QoL scores. All statistical analyses were two-sided, with $p < 0.05$ considered statistically significant.

Results

Comparison of Baseline Characteristics

At baseline, independent-samples t-tests revealed no statistically significant differences in QLQ-C30 or QLQ-BR23 scores between patients. These findings confirm baseline homogeneity, bolstering internal validity for assessment.

Participant Characteristics

The study included 200 participants (mean age 48.0 ± 8.3 years; range 26–69 years), most of whom were married housewives with secondary education or less (58%). The mean monthly household income was 348.7 ± 209 Jordanian Dinar, with 74% having medical insurance. Detailed socio-demographic and clinical characteristics are presented in Tables 1 and 2 (QoL scores overview).

Further analysis of QLQ-C30 and QLQ-BR23 data revealed distinct patterns in patient functioning and symptom burden.

EORTC QLQ-C30 Findings

On the QLQ-C30, patients reported the highest functioning in the role and social domains, whereas emotional functioning was

considerably lower. Insomnia, fatigue, and pain were the most prevalent symptoms, with financial difficulties also a notable concern.

EORTC QLQ-BR23 Findings

The breast cancer-specific QoL assessment indicated relatively higher scores for sexual functioning and body image. However, patients reported the lowest scores in future perspective, reflecting concerns about their long-term health and prognosis. Key symptoms related to breast cancer and its treatment included hair loss, arm symptoms, and systemic therapy side effects, which highlight treatment-related toxicities.

Predictors of QoL

As shown in Table 3, a multivariate linear regression analysis identified two significant independent predictors of QLQ-C30 global QoL: younger age [positively associated, $\beta = (-0.152)$, $p < 0.05$] and total breast symptoms [negatively associated, $\beta = (-0.280)$, $p < 0.05$] for both tools. Other clinical variables, such as cancer stage and chemotherapy dose, were included in the model but were not statistically significant independent predictors in this baseline analysis.

	Baseline QLQ-C30			Baseline QLQ-BR23		
Patient group	Mean (SD)	Test statistic	p-value	Mean (SD)	Test statistic	p-value
Control	58.96 (19.8)	t(198) = 1.13	0.257	24.67 (9.3)	t(198) = 0.960	0.340
Intervention	55.82 (19.3)			23.36 (10.2)		
Age (years)						
26-36 years	57.95 (16.5)	f(3,196) = 0.10	0.984	23.97 (11.2)	f(3,196) = 1.40	0.249
37-46 years	57.87 (18.8)			24.87 (9.7)		
47-56 years	56.72 (20.8)			22.41 (9.2)		
≥57 years	57.68 (20.5)			26.05 (10)		
Educational attainment level						
Literacy	56 (17)	f(2,197) = 0.15	0.864	21.86 (8.3)	f(2,197) = 1.02	0.362
Secondary and less than high school	58.01 (19.2)			23.80 (9.9)		
Diploma, bachelor/higher	56.73 (21.4)			25.19 (9.9)		
Patients employment status						
Housewife	57.76 (19.3)	f(2,197) = 1.83	0.163	23.95 (9.7)	f(2,197) = 1.20	0.303
Private sector employed	64.59 (18.5)			28.23 (8)		
Government employed	51.03 (21.9)			22.49 (10.3)		
Marital state/social state						
Never married	61.10 (14.9)	t(31.40) = 0.1.20	0.249	24.58 (7.1)	t(32.40) = 0.120	0.708
Ever married	56.94 (20.1)	adj.		23.94 (10)	adj.	
Medical health insurance						
No	52.19 (14.1)	t(132.2) = 2.70	0.008	22.97 (8.9)	t(132.2) = 0.90	0.371
Yes	59.22 (20.9)	adj.		24.38 (10)	adj.	

SD: Standard deviation; QLQ-BR23: Quality of life questionnaire-breast cancer 23; QLQ-C30: Quality of life questionnaire-core 30; adj.: Adjective

Table 4 shows that no individual predictor reached significance for QLQ-BR23 (all $p > 0.05$), although the overall model was significant. The overall regression model was statistically significant; no individual predictor (including type of surgery or chemotherapy) reached statistical significance independently ($p > 0.05$). These findings ensure consistency between the reported statistical data and the summary presented in the abstract.

Summary of Bivariate Findings

Bivariate analyses confirmed no significant differences in QoL scores by patient group, age, or education. However, significant associations were identified with clinical factors such as smoking history, appetite loss, and nipple discharge, which informed the subsequent multivariate models.

Discussion and Conclusion

These findings represent the baseline characteristics of participants enrolled in an ongoing RCT. This study assessed QoL among Jordanian women diagnosed with breast cancer and identified a moderate overall impairment, with the greatest burden observed in emotional functioning and treatment-related symptoms, particularly fatigue, insomnia, and pain. These findings are consistent with evidence from the Eastern Mediterranean and Middle East, where breast cancer survivors frequently report compromised QoL driven primarily by symptom burden and disease severity rather than sociodemographic characteristics (4, 17), and are further supported by studies on psychological distress and its associated factors among Jordanian women with breast cancer (18).

Table 2. Clinical characteristics and associations with QoL scores of the sample ($n = 200$)

	Baseline QLQ-C30			Baseline QLQ-BR23		
	Mean (SD)	Test statistic	p -value	Mean (SD)	Test statistic	p -value
History of smoking						
Active smoker	50.66 (21.3)	$f(2,197) = 4.96$	0.008	21 (7.2)	$f(2,197) = 1.31$	0.273
Past smoker	45.92 (18.6)			22.44 (11.6)		
Never smoked	59.31 (19.03)			24.51 (9.7)		
History of loosed appetite						
No	59.87 (20.9)	$t(161.6) = 3.02$	0.003	24.95 (9.6)	$t(161.6) = 2.02$	0.045
Yes	51.99 (15.2)	adj.		21.99 (9.7)		
Nipple discharge						
No	59.53 (19.6)	$t(198) = 3.16$	0.002	25.02 (9.5)	$t(198) = 2.99$	0.003
Yes	48.82 (17)			19.99 (9.6)		
Breast cancer stage						
1 st	54.90 (23.1)	$f(2,197) = 1.72$	0.181	25.49 (10.9)	$f(2,197) = 3.26$	0.041
2 nd	59.90 (17.8)			25.46 (9.9)		
3 rd	54.75 (20.8)			21.93 (9)		

SD: Standard deviation; QLQ-BR23: Quality of life questionnaire-breast cancer 23; QLQ-C30: Quality of life questionnaire-core 30; QoL: Quality of life; adj.: Adjective

Table 3. Multivariate predictors of QLQ-C30 global QoL ($n = 200$)

Predictor	B	SE	β	t(df)	p -value
Constant	122.458	11.196		10.938	<0.001
Age	-0.359	0.145	-0.152	-2.475	0.014
Total breast symptoms	-3.725	0.801	-0.280	-4.653	<0.001

Full model: employment $p = 0.057$, insurance $p = 0.051$; SE: Standard error; QLQ-C30: Quality of life questionnaire-core 30; QoL: Quality of life

Table 4. Multivariate predictors of QLQ-BR23 QoL ($n = 200$)

Predictor	B	SE	β	t(df)	p -value
Constant	48.393	5.649		8.567	<0.001
Total breast symptoms	-0.830	0.449	-0.127	-1.851	0.066

Model overall significant; no single strong predictor; SE: Standard error; QLQ-BR23: Quality of life questionnaire-breast cancer 23; QoL: Quality of life

The profound “lived experiences” of specific and challenging treatment side effects, such as chemotherapy-induced oral mucositis, further underscore this significant symptom burden. For instance, fatigue and insomnia are commonly reported as highly distressing symptoms, significantly impacting the daily lives and overall well-being of breast cancer patients (19).

The prominence of fatigue, sleep disturbance, and pain aligns with regional systematic reviews, showing these as the most prevalent and persistent concerns in breast cancer populations (17, 20).

Such symptoms exert cumulative effects on physical, affective, and cognitive functioning, thereby explaining the reduced emotional well-being observed in this cohort. Effective coping strategies, including psychoeducation programs, have proven beneficial in enhancing coping among Jordanian women diagnosed with breast cancer (21). Similar symptom-driven impairments have been consistently reported in studies using the EORTC QLQ-C30 and QLQ-BR23 instruments (14, 22).

Clinical characteristics such as advanced disease stages, mastectomy, and chemotherapy were significantly associated with poorer QoL scores; specific breast- and treatment-related symptoms identified through multivariate regression were also significantly associated with poorer QoL scores. This suggests that the physiological impact of the disease and its interventions is a primary driver of QoL decrements. Indeed, older age, long-term survival, postmenopausal status, and a minimum education level have all been associated with increased pain, further highlighting the complex interplay of factors affecting QoL (4, 22). Further regression analyses identified specific breast-related and treatment-related symptoms—including appetite loss, weight loss, itching, bowel or excretory disturbances, and breast ulceration—as independent predictors of reduced QoL. Comparable findings have been reported in multicenter reference-value studies, which show that symptom severity accounts for substantial variability in QoL outcomes among breast cancer patients (22).

Despite notable emotional and symptomatic impairment, social and role functioning remained relatively preserved—a pattern observed in prior Jordanian and regional studies, possibly reflecting strong family support and cultural coping strategies (23).

Indeed, studies have shown the effectiveness of psychoeducation intervention programs in enhancing coping strategies among Jordanian women diagnosed with breast cancer (24).

In collectivist cultures, family engagement in caregiving and decision-making sustains social roles despite compromised physical or emotional functioning—a buffering effect corroborated by prior Jordanian research, though not directly assessed here (23).

Sexual functioning exhibited less impairment than that reported in Western populations. This observation warrants cautious interpretation, as cultural norms related to privacy, modesty, and disclosure may bias self-reporting of sexual health issues, potentially resulting in underreporting rather than genuine absence of impairment (4, 22).

Clinically, these results underscore the need for routine assessments of QoL and symptoms in breast cancer management. Implementing systematic screening for fatigue, insomnia, and pain—coupled with timely referrals to supportive, rehabilitative, and palliative care services—could alleviate symptom burden and enhance patient well-being. Evidence-based approaches, encompassing structured physical activity regimens, psychoeducational initiatives, and targeted pharmacological and non-pharmacological symptom management strategies, have evidenced QoL enhancements in breast cancer cohorts (4, 14, 22). In particular, psychoeducation programs have proven efficacious in strengthening coping mechanisms among Jordanian women with breast cancer. Furthermore, cultural and religious beliefs profoundly influence perceptions of illness and coping mechanisms, often promoting resilience and collective support which can mitigate some psychological distress (24).

In light of Jordan’s sociocultural context, supportive interventions incorporating patients’ values, beliefs, and spiritual resources could enhance emotional adaptation. Although not evaluated here, spirituality’s well-established role in coping among Middle Eastern cancer patients merits further investigation into its influence on QoL (17, 23).

Implications for Nursing Research

This study underscores the substantial influence of clinical characteristics and symptom burden—particularly fatigue, insomnia, pain, and appetite disturbances—on QoL among Jordanian women with breast cancer. Nursing research should prioritize targeted interventions to alleviate these symptoms, alongside longitudinal and interventional studies that examine symptom trajectories and psychosocial needs and evaluate culturally tailored strategies to promote emotional well-being and overall QoL. Future research should explore the specific impact of various surgical procedures on social health, as distinct breast surgeries may differentially affect QoL, necessitating tailored supportive care strategies. Specifically, the effectiveness of interventions such as cognitive behavioral therapy, aerobic training, music therapy, and resistance training in improving sleep quality among women with breast cancer warrants exploration within the Jordanian cultural context.

Study Limitations

This study has several limitations, including its cross-sectional design, which precludes causal inferences; single-center

recruitment, which limits generalizability; and reliance on self-reported data, which may introduce response biases influenced by cultural norms. Prospective, longitudinal, multicenter studies incorporating validated measures of social support, coping mechanisms, and spiritual well-being are recommended. This analysis reports only baseline data; intervention effects will be examined in subsequent publications from the ongoing RCT.

This study reveals moderate impairment in QoL among Jordanian women with breast cancer, particularly in emotional functioning and treatment-related symptoms. Symptoms—especially fatigue, insomnia, pain, and breast-specific ones—emerged as the primary drivers of reduced QoL, outweighing sociodemographic factors. Clinical factors, such as disease stage and treatment type, also contributed to QoL variations. These findings underscore the need for routine symptom monitoring and culturally sensitive supportive nursing practices in breast cancer care to enhance patient-reported outcomes. The baseline data reported here will inform the interpretation of intervention effects in the ongoing RCT.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Jordan Ministry of Health's local ethical research committee (ethics committee no: 9694, date: 05.07.2018) and Universiti Sains Malaysia (protocol code: USM/JPEM/18080386, date: 24 December 2018).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Mo.A., M.Y., J.A.S., F.M.A., A.A., A.M., M.A., B.A., S.A-Q.; Concept: Mo.A., M.Y., J.A.S., F.M.A., A.A., A.M., M.A., B.A., S.A-Q.; Design: Mo.A., M.Y., J.A.S., F.M.A., A.A., A.M., M.A., B.A., S.A-Q.; Data Collection and/or Processing: Mo.A., M.Y., J.A.S., F.M.A., A.A., A.M., M.A., B.A., S.A-Q.; Analysis and/or Interpretation: Mo.A., M.Y., J.A.S., F.M.A., A.A., A.M., M.A., B.A., S.A-Q.; Literature Search: Mo.A., M.Y., J.A.S., F.M.A., A.A., A.M., M.A., B.A., S.A-Q.; Writing: Mo.A., M.Y., J.A.S., F.M.A., A.A., A.M., M.A., B.A., S.A-Q.

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Clinical Management After Rupture of Silicone Gel-Filled Breast Implants in a Surgically Treated Cohort: A Retrospective Study

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ABSTRACT

Objective: Breast implant rupture is clinically significant complication that is often asymptomatic making diagnosis challenging. The primary objective of this study was to describe the clinical presentation, preoperative imaging findings, and operative findings in this surgically selected cohort. A secondary objective was to assess the apparent concordance of magnetic resonance imaging (MRI) and ultrasound findings with intraoperative rupture status in this surgically selected cohort. Additional exploratory analyses examined symptom categories, implant age, and implant placement in relation to operative and imaging findings.

Materials and Methods: This retrospective observational study evaluated a cohort of women with suspected or confirmed silicone breast implant rupture who underwent operative management at the Department of Plastic Surgery, Faculty of Medicine, Comenius University, University Hospital Bratislava, Ružinov, between 2020 and 2025. Because only patients who proceeded to surgery were included, the cohort represents a selected referral population rather than an unselected surveillance population.

Results: The mean patient age was 50.6 years, with a mean implant age of 14.7 years. Within this surgically selected cohort, MRI demonstrated higher apparent sensitivity and positive predictive value than those of ultrasound; however, diagnostic performance varied across subgroups and the findings should be interpreted cautiously because of the small sample size and selection bias. In patients with local symptoms, the apparent diagnostic performance was lower, particularly for ultrasound.

Conclusion: Breast implant rupture showed heterogeneous clinical presentations in this retrospective cohort of surgically treated patients, ranging from asymptomatic, imaging-detected rupture to cases associated with local symptoms, capsular contracture, or systemic complaints. MRI showed a higher apparent concordance with intraoperative rupture status than ultrasound in this selected cohort; however, the findings are limited by selection and verification bias. Subgroup analyses were exploratory, and clinical management should remain individualized; prospective studies are needed to guide evidence-based imaging and treatment strategies.

Keywords: Breast implant; implant rupture; magnetic resonance imaging; ultrasonography

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KEY POINTS

- Breast implant rupture frequently remains asymptomatic and is often detected incidentally on imaging, underscoring the importance of reliable diagnostic tools.
- Magnetic resonance imaging showed higher apparent diagnostic performance than ultrasound, but these findings are limited by selection and verification bias.
- In patients with local symptoms, apparent diagnostic performance was lower, particularly for ultrasound.
- Clinical management should remain individualized, and prospective studies are needed to guide evidence-based imaging and treatment strategies.

Introduction

Breast implants are among the most commonly used medical devices in plastic and reconstructive surgery (1). Despite continuous technological progress, a breast implant remains a foreign object within the body and carries a risk of complications. The most frequent include capsular contracture (CC), seroma, hematoma, infection, implant migration or malposition, and implant rupture (2, 3). Implant rupture is a clinically important complication whose incidence increases with the length of time since implantation. Reported rates range from 1–10% within the first 10 years, with a marked rise in risk after 15 years (4). Implant rupture involves a breach of the implant shell, allowing silicone gel or saline to escape into the periprosthetic space and surrounding tissues. Rupture of saline implants is usually easy to recognize because it results in a sudden loss of breast volume. In contrast, ruptures of silicone implants often present with subtle or absent clinical signs. They are frequently detected incidentally during imaging examinations such as magnetic resonance imaging (MRI) or ultrasound, since many cases remain asymptomatic (5).

A frequent underlying cause is the gradual wear of the implant shell. Repeated micro-deformations, friction against the periprosthetic capsule, and external forces can weaken the capsule's structure and lead to micro-tear formation. Another factor that can lead to rupture is trauma, such as a direct impact on the chest, injury from a car accident, or iatrogenic damage during procedures such as breast biopsy or mammography; these events may cause abrupt shell failure (6).

Implant rupture can occur in two forms: intracapsular, in which the silicone remains confined within the fibrous capsule, and extracapsular, in which the gel escapes into surrounding tissues. If an intracapsular rupture is identified, surgical removal and replacement of the implant are generally advised, even in asymptomatic patients, due to the risk of progression to extracapsular rupture and related complications, such as granulomatous reactions or silicone nodules (4, 7). An extracapsular rupture is a more severe form of implant damage in which silicone gel escapes from the periprosthetic capsule into the breast tissue or the lymphatic system. Patients may report breast enlargement, changes in shape, pain, localized induration, or palpable nodules in the breast or axilla. In some

cases, an inflammatory reaction may occur, accompanied by redness and tenderness in the affected area. A typical finding is the presence of so-called silicone nodules (siliconomas), which develop as a granulomatous response to the leaked silicone (4). Silicone may migrate to regional lymph nodes, particularly the axillary nodes, leading to a condition known as silicone lymphadenopathy. The prolonged presence of silicone in these tissues can complicate differential diagnosis, as palpable nodes may resemble malignancy (8).

A related phenomenon, known as “gel bleed,” refers to the microscopic leakage of silicone molecules through an intact implant shell. This process has been linked to the development of granulomatous inflammation and CC (7, 9). With long-term exposure, gel bleed can lead to the accumulation of silicone in regional lymph nodes, resulting in silicone lymphadenopathy (8). In some cases, gel bleed is believed to play a role in the development of systemic symptoms, such as those described in breast implant illness (BII) or in the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). BII refers to a cluster of systemic symptoms that patients associate with the presence of breast implants, including fatigue, muscle and joint pain, brain fog, and depressive symptoms. ASIA syndrome is a broader term describing autoimmune or inflammatory manifestations triggered by an adjuvant, including silicone (10, 11). Accompanying complications significantly increase the risk of implant rupture. CC can increase mechanical stress on the implant shell (9), while recurrent seromas and hematomas may foster an environment that promotes fibrosis and gradual weakening of the implant structure (12, 13). The management of implant rupture primarily relies on surgical intervention. Treatment options include simple implant removal, capsulectomy, or replacement with a new implant, depending on the presence of complications, the patient's overall clinical condition and individual preferences (2, 14).

The primary objective of this study was to describe the clinical presentation, preoperative imaging findings, and operative findings in this surgically selected cohort. A secondary objective was to assess the apparent concordance of MRI and ultrasound findings with intraoperative rupture status in this surgically selected cohort. Additional exploratory analyses examined symptom categories, implant age, and implant placement in relation to operative and imaging findings.

Materials and Methods

This retrospective observational study evaluated a surgically treated cohort of women with suspected or confirmed silicone breast implant rupture who subsequently underwent operative management at the Department of Plastic Surgery, Faculty of Medicine, Comenius University, University Hospital Bratislava, Ružinov, between 2020 and 2025. The study was approved by the Ethics Committee of University Hospital Bratislava in November 16, 2022 under reference number EC/158/2022. Because only patients who proceeded to surgery were included, the cohort represents a selected referral population rather than an unselected surveillance population.

Patient Selection

Eligible patients were women aged 18 years or older who had a history of breast augmentation or implant-based breast surgery, had suspected or documented implant rupture on preoperative imaging or clinical evaluation, and subsequently underwent surgery. Patients were included only if operative records were available for review. Histopathology data were collected when available as part of routine clinical management. Patients were excluded if they were younger than 18 years or if the surgery was performed for reasons unrelated to suspected implant rupture, such as elective cosmetic revision performed without concern for implant rupture, or surgery performed solely for acute infection. A total of 43 women met the inclusion criteria and were included in the analysis.

Data Collection

Clinical data were retrospectively extracted from the Medea hospital information system at UNB Ružinov. Sources included outpatient records, preoperative imaging reports, operative reports, discharge summaries, and follow-up documentation. The following variables were collected when available: patient age, indication for surgery, presenting symptoms, implant age, implant placement, imaging modality used before surgery, intraoperative findings, and histopathologic findings.

Because most patients were referred from external institutions, imaging examinations were performed using heterogeneous protocols. Detailed technical parameters, including MRI field strength, coil type, imaging sequences, slice thickness, ultrasound probe frequency, and radiologist subspecialty expertise, were not consistently available and therefore could not be analyzed in a standardized manner.

Imaging Assessment, Reference Standard, and Histopathology

Preoperative imaging consisted of MRI, ultrasound, or both, depending on the referring pathway and clinical context. Imaging classification was based on the final preoperative radiologic

report available in the medical record. Cases were categorized as imaging-positive when rupture was described or suspected in the report, and as imaging-negative when rupture was not reported. Given the retrospective, multicenter nature of imaging acquisition, standardized rereading of all original imaging studies using a uniform protocol was not feasible. Therefore, the imaging analysis reflects real-world preoperative assessments rather than controlled diagnostic imaging studies.

The reference standard for implant rupture was the intraoperative finding documented in the surgical report. Rupture status was classified as “confirmed” when rupture was identified intraoperatively, and as “not confirmed” when the implant was found to be intact.

Histopathologic examination was evaluated separately from the confirmation of implant rupture. Histology was used to document, when present, silicone leakage, siliconomas, granulomatous reactions, or related tissue changes, but it was not used as the primary reference standard for diagnosing implant rupture.

Statistical Analysis

Analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Descriptive statistics were used to summarize patient demographics, implant characteristics, presenting symptoms, imaging findings, operative findings, and histopathologic results. Continuous variables are presented as means (with ranges) and categorical variables as counts and percentages. For preoperative imaging, intraoperative findings were used as the reference standard. Because the study included only surgically treated patients with suspected or clinically relevant pathology, the dataset is affected by selection bias and verification bias, and is enriched for positive cases. As a result, specificity and negative predictive value could not be reliably estimated, and any measure of overall diagnostic accuracy must be interpreted with substantial caution. Accordingly, imaging results are presented as an apparent within-cohort concordance with intraoperative findings, rather than as estimates of performance in routine screening or surveillance practice. Given the limited sample size, all subgroup analyses were considered exploratory and hypothesis-generating. No multivariable modeling was performed because the sample size was insufficient to allow robust adjustment for confounding.

Results

A total of 43 women were included in the study. Age at the time of surgery ranged from 26 to 77 years, with a mean age of 50.6 years. The interval between implantation and surgical intervention ranged from 2 to 39 years, with a mean duration of

14.7 years. Preoperative imaging consisted of MRI in 25 patients, ultrasound in 16 patients, and both modalities in 1 patient. One patient underwent emergency surgery for systemic symptoms and had no prior imaging. Implant placement was reported as subglandular in 11 patients, submuscular in 17 patients, and dual-plane in 4 patients. In 11 patients (25.6%), implant placement was not documented in the surgical reports.

Fourteen patients were asymptomatic at presentation, and implant rupture was detected incidentally on imaging in all of them, including 10 cases identified by MRI and 4 by ultrasound. All 14 cases were confirmed intraoperatively. Histologic evidence of silicone leakage into the capsule was present in 8 of these 14 patients. Fifteen patients presented primarily with CC. In this subgroup, preoperative imaging suggested implant rupture in 13 cases, including 7 identified by MRI and 6 by ultrasound. Intraoperative rupture was confirmed in 11 of these patients, whereas 4 implants were found to be intact at surgery. Eleven patients presented with local symptoms, including breast pain, swelling, or redness. Fever was present in 3 of these 11 patients, with temperatures of up to 38 °C in 2 patients and of 39 °C in 1 patient. In this subgroup, MRI suggested implant rupture in 5 patients, of whom 3 had rupture confirmed intraoperatively. Ultrasound suggested rupture in 4 patients, of whom 2 had rupture confirmed intraoperatively. Histologic evidence of silicone leakage into the capsule was found in 4 patients.

Three additional patients presented with systemic symptoms that were clinically attributed to possible BII. Preoperative imaging suggested implant rupture in all 3 patients: 2 cases detected on MRI and 1 case on ultrasound. Intraoperative rupture was confirmed in 1 of 3 patients, and histologic evidence of silicone leakage was documented in 1 patient.

Possible ASIA syndrome was included in the differential diagnosis for one patient presenting with local symptoms, recurrent fever up to 39 °C, and enlarged left axillary lymph nodes. Although ultrasound suggested implant rupture, rupture was not confirmed intraoperatively. Histologic examination demonstrated a siliconoma. This individual case is presented descriptively and does not allow causal inference.

Imaging Findings and Intraoperative Confirmation

Within this surgically selected cohort, MRI showed higher apparent sensitivity and positive predictive value than ultrasound for intraoperatively confirmed implant rupture. Because the study included only surgically treated patients and lacked a non-operated comparison group, the specificity and negative predictive value could not be reliably estimated. The reported imaging metrics, therefore, reflect performance within a surgically selected population and should not be extrapolated to routine surveillance settings. Table 1 summarizes the comparison between MRI and ultrasound. MRI showed an apparent sensitivity of 95.0% and a positive predictive value of 79.2%, whereas ultrasound showed an apparent sensitivity of 80.0% and a positive predictive value of 57.1%. Within-cohort agreement was defined as the proportion of imaging assessments concordant with intraoperative rupture status among patients who underwent that imaging modality.

Imaging Findings According to Implant Placement

Exploratory subgroup analyses were performed based on implant placement. In the subglandular subgroup, MRI showed an apparent sensitivity of 87.5%, with 1 false-negative case. Ultrasound did not correctly identify implant rupture in this subgroup, resulting in 2 false-positive findings and 1 false-negative finding. In the dual-plane subgroup, all MRI-assessed cases were correctly identified. No patients in this subgroup underwent ultrasound examination. Because of the very small number of patients, these findings should be interpreted only descriptively. Among patients with submuscular implants, MRI showed an apparent sensitivity of 100%, although false-positive findings reduced agreement within the cohort. Ultrasound also demonstrated relatively high apparent sensitivity in this subgroup but lower within-cohort agreement. In the subgroup with undocumented implant placement, all surgically confirmed ruptures were detected preoperatively; however, false-positive findings were also present. No clear association between implant placement and imaging performance can be established from these data.

Table 1. Comparison of imaging method parameters: MRI vs. ultrasound			
Statistics	Results (%)		
	MRI	Ultrasound	Total
Within-cohort agreement	76.0	50.0	65.9
Specificity	Not estimable		
Sensitivity	95.0	80.0	90.0
PPV	79.2	57.1	71.1
NPV	Not estimable		
Specificity and NPV are not estimable because there are no true-negative cases. PPV: Positive predictive value; NPV: Negative predictive value; MRI: Magnetic resonance imaging			

Imaging Findings According to Presenting Symptoms

Exploratory analyses were also performed according to the presenting symptom category. In asymptomatic patients, no false-negative imaging findings were observed. In patients with local symptoms, apparent imaging concordance was lower, particularly for ultrasound. In patients presenting with CC, MRI demonstrated higher apparent sensitivity and greater within-cohort agreement than ultrasound. In patients with systemic symptoms, apparent sensitivity remained high, but within-cohort agreement was low due to false-positive findings. These subgroup findings are based on small numbers and should be considered descriptive and hypothesis-generating.

Impact of Implant Age on Presenting Symptoms

Implant age appeared to be associated with differences in clinical presentation. In our cohort, most individuals who reported localized symptoms (breast discomfort, shape changes, or palpable irregularities) had implants 15 years old or younger ($n = 9/11$). In contrast, patients who developed CC predominantly had implants older than 15 years ($n = 9/15$), indicating that longer implant duration may contribute to more advanced or structurally significant complications. This represents a descriptive observation without statistical testing and should therefore be interpreted cautiously.

Discussion and Conclusion

Breast implant ruptures showed heterogeneous clinical presentations in this surgically treated cohort, ranging from asymptomatic cases detected on imaging to patients with local complaints, CC, or systemic symptoms. In our patient group, clinical symptoms were often ambiguous, making both diagnosis and treatment planning more challenging. This aligns with existing literature, which describes a broad range of presentations, from asymptomatic implant ruptures detected only on imaging to cases in which patients report notable discomfort.

In the present study, MRI showed greater apparent concordance with intraoperative rupture status than ultrasound. This is in line with prior reports indicating that MRI is sensitive for detecting implant rupture, including intracapsular rupture that may occur without obvious clinical signs (4, 7). Similarly, the study by Secco et al. (15) describes MRI as a more reliable diagnostic modality than ultrasound.

However, not all studies have found a large difference between MRI and ultrasound. Spit et al. (16) reported that ultrasound was nearly as effective as MRI in detecting silicone leakage and proposed ultrasound as an initial imaging modality, with MRI reserved for inconclusive cases. Thus, diagnostic accuracy (as within-cohort agreement) depends not only on the imaging technique itself but also on the radiologist's level of experience.

In our cohort, imaging was performed at multiple external institutions before referral, resulting in heterogeneous protocols and incomplete technical data that may have influenced the observed performance.

The study by Rukanskienė et al. (17) demonstrated that ultrasound reliably assesses breast implant integrity and can serve as the initial imaging modality in suspected rupture. In contrast, MRI is most appropriate when ultrasound results are inconclusive (17). Similarly, the study by Telegrafo and Moschetta (18) suggested that ultrasound may serve as the initial imaging modality in patients with breast implants. When an intracapsular rupture is suspected on ultrasound, additional assessment with MRI is recommended. In contrast, if ultrasound clearly identifies an extracapsular rupture, surgical removal of the implant can be considered without the need for further diagnostic examinations (18). Importantly, the diagnostic performance observed in this study must be interpreted within the context of a surgically selected cohort. Due to the absence of true negative cases, specificity and negative predictive value could not be reliably assessed. As a result, the reported accuracy and sensitivity reflect performance in patients already selected for surgical management and should not be directly extrapolated to routine clinical practice.

In our cohort, implant rupture was detected preoperatively in 14 asymptomatic patients and was confirmed intraoperatively, illustrating the recognized phenomenon of silent rupture. However, this study was not designed to evaluate surveillance strategies or screening policies. Current recommendations regarding imaging follow-up should therefore be interpreted based on external guidelines and outcome data rather than as conclusions drawn from this cohort (19, 20). Despite familiarity with Food and Drug Administration guidelines, the study by Henry et al. (21) found that surgeon adherence remains low, largely because the guidelines are often viewed as unnecessary or insufficiently supported by evidence. Similarly, patient compliance is poor. Mehta et al. (22) reported that only about 20% of patients underwent follow-up screening within 5–6 years after surgery, highlighting the challenges of screening.

In symptomatic patients, false-positive imaging findings were more common, particularly on ultrasound. This may reflect the operator-dependent nature of ultrasound as well as the influence of edema, fibrosis, or scarring on image interpretation. MRI also demonstrated false-positive findings but appeared to perform better overall in this cohort. These findings are consistent with the broader literature suggesting that MRI is often more reliable for assessing implant rupture, especially when ultrasound findings are inconclusive (23). The relationship between systemic symptoms and implant rupture remains incompletely understood and cannot be specifically evaluated within the design of this study.

The observed relationship between implant age and clinical presentation is also in line with previously reported trends. Local symptoms were more often observed in patients with younger implants, whereas CC was more frequent in those with older implants. This is consistent with evidence showing that both contracture and implant rupture are more likely with increasing time since implantation and that contracture reflects a chronic process of capsular remodeling rather than an immediate consequence of rupture (24-26). Another noteworthy finding concerns differences between implant generations. Patients with older implants (2nd- and 3rd-generation) experienced higher rates of both intracapsular and extracapsular ruptures than those with newer, highly cohesive 5th-generation implants. This supports the current preference for cohesive gel implants, which reduce the risk of silicone leakage into surrounding tissues and lower the likelihood of related complications (27-29). However, these findings should be interpreted with caution, as newer implant generations have shorter follow-up periods, limiting direct comparability.

With regard to clinical management, the findings of this study suggest that surgical treatment may be appropriate in selected patients with implant rupture, particularly those with symptoms. However, given the retrospective design and the surgically selected cohort, the data do not support definitive recommendations for routine explantation in all cases. Management should therefore remain individualized, taking into account symptoms, imaging findings, comorbidities, and patient preferences (30, 31).

This study has several important limitations. First, the retrospective design and the relatively small sample size limit the strength of the conclusions. Second, the inclusion of only surgically treated patients introduces selection bias and precludes the reliable assessment of specificity and negative predictive value. Third, the cohort was heterogeneous with respect to implant characteristics, clinical presentation, and available data. Additionally, implant placement was not documented in the operative report in 25.6% of patients, reflecting an inherent limitation of retrospective data collection, in which variables not considered relevant at the time of surgery were not consistently recorded. This is a recognized challenge in retrospective studies and underscores the need for standardized, prospective documentation of implant characteristics in future research. Moreover, the heterogeneity of imaging protocols is a significant limitation, as MRI examinations performed across multiple external institutions varied in field strength, coil configuration, and sequence selection, and were interpreted by radiologists with differing levels of subspecialty expertise in breast imaging. Similarly, ultrasound examinations were performed using various probe frequencies and techniques. This heterogeneity in protocols may have contributed to variability in diagnostic performance and may have limited the ability to draw

conclusions about optimal imaging protocols. Furthermore, subgroup analyses were based on small numbers and should be considered exploratory. Finally, the absence of a non-surgical control group limits the ability to assess the broader clinical significance of imaging findings and systemic symptoms.

Taken together, these findings provide descriptive insight into the clinical and imaging features of breast implant rupture in a surgically managed population. Larger prospective studies that include both symptomatic and asymptomatic patients, as well as operated and non-operated controls, are needed to better define the role of imaging and to inform evidence-based management strategies.

Breast implant rupture showed heterogeneous clinical presentation in this retrospective cohort of surgically treated patients, ranging from asymptomatic imaging-detected rupture to cases associated with local symptoms, CC, or systemic complaints. MRI showed a higher apparent concordance with intraoperative rupture status than did ultrasound in this selected cohort. However, because the study included only patients who underwent surgery, the findings are subject to selection and verification bias, and should not be extrapolated to routine screening or surveillance populations. Subgroup analyses were exploratory and did not support definitive conclusions regarding imaging strategy or routine surgical management. Clinical decision-making should remain individualized, taking into account symptoms, imaging findings, comorbidities, and patient preferences. Larger prospective studies that include broader patient populations are needed to clarify the role of imaging and to guide evidence-based management of silicone breast implant rupture.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University Hospital Bratislava in November 16, 2022 under reference number EC/158/2022.

Informed Consent: Given the retrospective observational nature of the study and the use of existing anonymized data, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T.T., M.C., D.M., M.B.; Concept: M.T.T., M.C., S.H., D.M., M.B.; Design: M.T.T., M.C., S.H., D.M., M.B.; Data Collection and/or Processing: M.T.T., M.C., S.H., D.M.; Analysis and/or Interpretation: M.C., S.H.; Literature Search: M.T.T., M.C., S.H., D.M., M.B.; Writing: M.T.T., M.C., S.H., D.M., M.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Simplified LYMPHA for Prevention of Breast Cancer-Related Lymphedema After Axillary Dissection: Initial Feasibility Experience from South Asia

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ABSTRACT

Objective: Breast cancer-related lymphedema is an important survivorship concern after axillary lymph node dissection. Conventional LYMPHA and immediate lymphatic reconstruction can reduce this risk, but adoption in low- and middle-income settings is limited by the need for microsurgical personnel, equipment, additional operating time, and cost. This study reports an initial feasibility assessment of simplified LYMPHA (S-LYMPHA) performed by breast surgical oncologists using indocyanine green guidance.

Materials and Methods: This was a prospective, single-arm feasibility cohort study. Consecutive eligible patients undergoing planned axillary lymph node dissection or completion axillary dissection after a positive intraoperative sentinel node assessment were enrolled from July 2024 to September 2025. Arm circumferences were measured preoperatively and at 3 and 6 months, at three fixed points. After confirmation that axillary dissection was required, methylene blue and indocyanine green were injected into the ipsilateral upper limb. Arm lymphatics were identified, preserved, and invaginated into a suitable axillary venous tributary after nodal dissection. The primary outcomes of this interim report were technical feasibility, short-term safety, and clinical lymphedema at 6 months.

Results: Thirty-seven patients underwent attempted S-LYMPHA. The median age was 51 years. Nineteen patients (51.4%) received neoadjuvant chemotherapy and 26 patients (70.3%) underwent mastectomy. Sixteen patients (43.2%) required axillary dissection after nodal metastasis was detected on intraoperative sentinel node assessment. Arm lymphatics were identified in all patients. The mean number of lymphatics identified was 2.6 (range 1–5), and the mean number of lymphovenous anastomoses created was 1.5 (range 1–3). More than one anastomosis was performed in 16 (43.2%) patients. At a uniform 6-month follow-up, one patient had clinical lymphedema, corresponding to an observed incidence of 2.7% (exact 95% confidence interval, 0.07–14.16). No dye-related adverse reaction or local complication attributable to the lymphatic reconstruction was observed.

Conclusion: S-LYMPHA was technically feasible and safe in this initial South Asian feasibility cohort. These early data should be interpreted as evidence of implementability and short-term safety rather than proof of lymphedema prevention. Larger comparative cohorts with longer follow-up are required to define efficacy, durability, and oncologic safety.

Keywords: Breast cancer; breast cancer-related lymphedema; LYMPHA; S-LYMPHA; axillary lymph node dissection; immediate lymphatic reconstruction; low-resource setting

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KEY POINTS

- Simplified LYMPHA (S-LYMPHA) is feasible in resource constrained settings.
- S-LYMPHA can reduce potential breast cancer-related lymphedema.

Introduction

Breast cancer is the most common malignancy among women in India, and improvements in survival have made long-term treatment-related morbidity increasingly important. Breast cancer-related lymphedema (BCRL) remains one of the most feared sequelae of axillary treatment, especially after axillary lymph node dissection (ALND) and regional nodal irradiation (1, 2). BCRL may present months to years after treatment, with progressive arm swelling, heaviness, pain, cellulitis, functional limitations, psychosocial distress, and financial burden.

Immediate lymphatic reconstruction, commonly referred to as LYMPHA, was developed to preserve lymphatic drainage at the time of axillary dissection by creating lymphovenous bypasses between transected arm lymphatics and adjacent venous tributaries (3, 4). Early series and institutional experiences have reported low lymphedema rates after LYMPHA, but implementation remains difficult in many South Asian and other low-resource settings because conventional LYMPHA usually requires microsurgical expertise, an operating microscope, specialized instruments, additional operative time, and added cost (3-5).

Simplified LYMPHA (S-LYMPHA) was subsequently described as a less resource-intensive adaptation that can be performed by an oncologic surgeon using loupe magnification and an invagination technique rather than formal supermicrosurgical suturing (6). This manuscript reports our early prospective experience with S-LYMPHA. In response to the preliminary nature of the data, the present report is framed as an IDEAL Phase IIa feasibility study, with emphasis on technical success, early safety, and short-term clinical outcomes rather than on definitive efficacy.

Materials and Methods

Study Design and Setting

This was a prospective, single-arm feasibility cohort study of preventive lymphatic reconstruction in patients undergoing ALND for breast cancer. The study was conducted at participating breast surgical oncology centres following approval by the Saifee Hospital Ethics Committee (approval no: SH/DNB/SUR/07/2024/019, date: 30.07.2024). Written informed consent was obtained from all patients.

Participants

Consecutive adult patients with histologically confirmed breast cancer were eligible if ALND was planned preoperatively or if

it became necessary intraoperatively, after metastatic disease was identified during sentinel lymph node assessment. Patients undergoing completion ALND after a positive frozen-section or touch-imprint cytology were also eligible.

Exclusion criteria were: previous axillary surgery on the affected side; previous axillary radiotherapy; pregnancy or lactation; known allergy to methylene blue or indocyanine green; inability to complete follow-up measurements; and clinical inflammatory breast cancer requiring treatment pathways in which reliable arm lymphatic mapping or immediate reconstruction was judged unsuitable.

Perioperative Treatment and Physiotherapy

Recommendations for neoadjuvant chemotherapy, breast procedure, ALND, and adjuvant treatment were decided by the multidisciplinary team based on disease stage, receptor status, response to therapy, and institutional protocols. Radiotherapy was recommended when indicated by standard oncologic criteria, including nodal burden and receipt of breast-conserving surgery; however, data on completion of adjuvant radiotherapy and on radiation fields are not mature enough for analysis in this 6-month feasibility report. All patients received standard postoperative advice regarding shoulder and arm mobility. Overhead abduction was restricted until removal of the drain. Compression garments and formal physiotherapy were prescribed for symptomatic patients or those considered at higher risk after clinical review.

S-LYMPHA Technique

Procedures were performed by a two-surgeon team. Indocyanine green fluorescence imaging was performed using the Stryker SPY-PHI system. Before surgery, the baseline circumferences of both arms were recorded at three predefined points: at 10 cm above the elbow, at 5 cm below the elbow, and at the wrist.

After the decision for ALND had been confirmed, 1 mL of methylene blue was injected into the volar aspect of the ipsilateral upper arm, approximately 5 cm proximal to the axillary fold into the intradermal, subcutaneous, and deeper tissue planes. An additional 1 mL of indocyanine green was injected intradermally proximal to the methylene blue injection sites. After 15–20 minutes, the arm lymphatics were traced toward the axilla using fluorescence imaging. Identified lymphatics were dissected carefully, clipped distally, and preserved at the maximum feasible length.

Following standard ALND, a suitable venous tributary was selected and mobilized toward the lymphatics. The S-LYPMPHA technique, as described by Ozmen et al. (6), was performed by invaginating one or more lymphatics into the venous tributary using a U-stitch and stay sutures with 6–0 polypropylene. When possible, intraoperative fluorescence imaging was used to confirm lymphatic flow into the venous tributary. When multiple suitable lymphatics were available, more than one lymphatic was invaginated into the same venous tributary or into separate tributaries, according to local anatomy (Figures 1 and 2).

A suction drain was placed in the axilla below the lymphovenous approximation, and a separate drain in the breast or chest wall was placed when required. Care was taken to avoid direct suction trauma to the anastomosis.

Outcome Definitions and Follow-up

The primary outcomes for this interim analysis were technical feasibility, defined as successful identification of arm lymphatics

and completion of at least one lymphovenous anastomosis, and short-term safety, defined as dye-related adverse events or local complications attributable to the reconstruction. Clinical lymphedema was assessed at 3 and 6 months.

Clinical BCRL was defined as an ipsilateral increase of more than 2 cm at any measured point compared with baseline and symptomatic BCRL as symptoms such as heaviness, tightness or functional discomfort; and absence of a comparable proportional increase in the contralateral arm.

Statistical Analysis

This feasibility analysis was descriptive. Continuous variables are presented as mean (range) or median, as appropriate. Categorical variables are presented as numbers and percentages. The observed incidence of lymphedema was reported with an exact binomial 95% confidence interval. No formal hypothesis testing was performed because the present report did not include a comparator arm and was not powered to evaluate efficacy.

Results

Patient and Treatment Characteristics

Thirty-seven patients underwent attempted S-LYPMPHA during the study period. Baseline and treatment characteristics are summarized in Table 1. The median age was 51 years. Nineteen patients (51.4%) had received neoadjuvant chemotherapy. Twenty-six patients (70.3%) underwent mastectomy, including one who underwent bilateral mastectomy with ALND on the affected side and sentinel lymph node biopsy on the contralateral side. Sixteen patients (43.2%) initially underwent sentinel lymph node biopsy and subsequently required ALND after nodal metastasis was detected on intraoperative assessment.

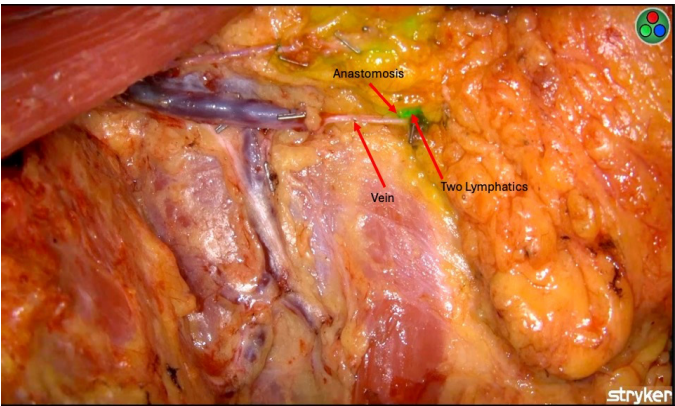


Figure 1. Two arm lymphatics invaginated into a single tributary of the axillary vein

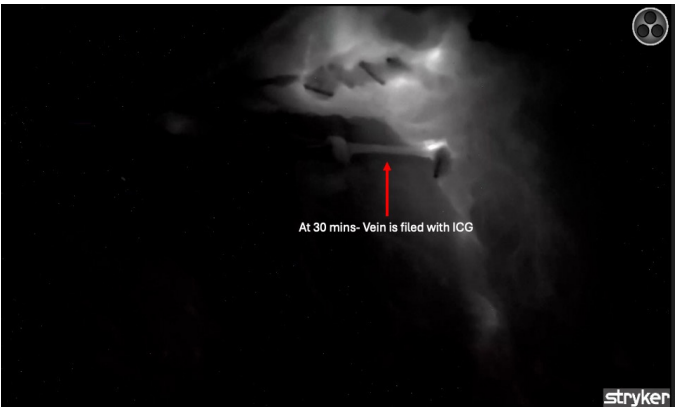


Figure 2. Fluorescence imaging 30 minutes after the procedure demonstrating lymphatic flow into the venous tributary

Table 1. Baseline and treatment characteristics	
Variable	Value
Age	Median 51 years (30–65 years)
Neoadjuvant chemotherapy	19/37 (51.4%)
Breast operation	Mastectomy 26/37 (70.3%); breast conservation 11/37 (29.7%)
Indication for ALND	Planned ALND 21/37 (56.8%); ALND after positive intraoperative sentinel node assessment 16/37 (43.2%)
Mean lymph nodes removed	15 (range, 10–42)
Mean positive lymph nodes	3.1 (range, 0–24)
Body mass index mean	24.5+/-3.8
Radiotherapy	Incomplete
ALND: Axillary lymph node dissection	

Technical Feasibility and Short-term Safety

Arm lymphatics were identified using fluorescence guidance in all 37 patients. At least one lymphovenous anastomosis was completed in every patient. The mean number of arm lymphatics identified was 2.6 (range, 1–5), and the mean number of lymphovenous anastomoses created was 1.5 (range, 1–3). More than one anastomosis was performed in 16 patients (43.2%). No local complications attributable to the reconstructive step or no dye-related adverse reactions were observed (Table 2).

Lymphedema Outcomes

All patients included in this analysis had arm measurements available at the 6-month postoperative visit. Seventeen patients developed clinical lymphedema (>2 cm increase in arm circumference), corresponding to an observed 6-month incidence of 46%; one patient (2.7%) had symptomatic BCRL (Table 3). However 16 out of these 17 patients also showed increase in contralateral arm measurements. Hence it is actually weight gain and not true lymphedema.

Discussion and Conclusion

This initial prospective experience suggests that S-LYMPHA can be implemented in our breast surgical oncology setting with high technical success and no observed reconstruction-specific adverse events. Primary outcome feasibility: arm lymphatics were identified in all patients, and at least one lymphovenous anastomosis could be completed in every case by the operating team without reliance on a separate microsurgical service.

The observed 6-month symptomatic lymphedema incidence of 2.7% is encouraging but must be interpreted cautiously. BCRL often appears beyond the first postoperative year, particularly when regional nodal irradiation and higher body mass index are present (1, 2). A short follow-up interval can therefore underestimate the eventual incidence.

Conventional LYMPHA has shown favorable outcomes in multiple early series, but implementation barriers are substantial in low-resource settings. Boccardo et al. (4) described primary preventive lymphovenous reconstruction after axillary surgery, and later reports showed durable feasibility (7). Feldman et al. (8) reported a low lymphedema incidence after LYMPHA in a single-institution experience. Ozmen et al. (6) described S-LYMPHA and reported lymphedema in 3% of patients undergoing S-LYMPHA compared with 19% after ALND alone. Our present data should be viewed as an early implementation experience, consistent with the technical feasibility reported elsewhere, not as proof that the same magnitude of benefit has been reproduced.

This distinction is particularly relevant for South Asia. Patients frequently present with larger tumours and more advanced nodal disease, and ALND remains common. In node-positive disease, level III nodal involvement may be encountered depending on burden in levels I and II (9). A feasible preventive strategy that breast oncologic surgeons can perform could therefore be valuable if its efficacy is confirmed in larger controlled studies. Further studies should also compare S-LYMPHA with other arm lymphatic preservation techniques such as axillary reverse mapping (10).

Study Limitations

This study has several important limitations. First, it is a single-arm feasibility cohort study without a comparison group; therefore, it cannot establish that S-LYMPHA reduces lymphedema. Second, the cohort is small. Third, the follow-up period analyzed is limited to 6 months, whereas BCRL commonly develops between 1 and 3 years after axillary treatment. Fourth, radiotherapy details are incomplete because most patients are still undergoing treatment. Validated patient-reported outcome measures, such as LYMPH-Q, were not administered. Fifth, the assessment relied on symptoms and circumference measurements rather than limb-volume calculation, perometry, or bioimpedance. Because of these limitations, the current report should be interpreted as evidence of feasibility and short-term safety.

S-LYMPHA was feasible and safe in this initial cohort of patients undergoing ALND for breast cancer. The procedure can be performed by trained breast surgical oncologists using indocyanine green guidance and an invagination technique. The short-term lymphedema rate was low, but the absence of a comparison group, a small cohort size, and a 6-month follow-up preclude drawing conclusions about efficacy. Longer follow-up periods and comparative evaluations are necessary before S-LYMPHA can be recommended as a proven lymphedema-prevention strategy.

Table 2. Technical and perioperative outcomes	
Outcome	Result
Successful arm-lymphatic identification	37/37 (100%)
Completion of at least one lymphovenous anastomosis	37/37 (100%)
Number of lymphatics identified	Mean 2.6 (range, 1–5)
Number of anastomoses created	Mean 1.5 (range, 1–3)
Dye-related adverse events	0/37
Local complications attributable to S-LYMPHA	0/37
S-LYMPHA: Simplified LYMPHA	

Table 3. Six-month arm-circumference measurements

No.	Baseline arm circumference*	6-month arm circumference*	Increase >2 cm	Symptomatic BCRL
1	R 27/25/16; L 28/25/16	R 29.5/25/17; L 27/25/16.	Yes	Yes
2	L 33/29/18; R 32/30/18	L 31/25/16.6; R 31/25.5/16.5	No	No
3	L 33/24/15; R 33/25/15	L 34/25/15; R 33/25/15	No	No
4	L 35/28/19; R 35/28/19	L 33/28/18; R 30.4/25.4/17.7	No	No
5	L 35/26/18; R 34/21/17	L 34.2/27.9/16.5; R 33/27.9/17.7	No	No
6	R 26/24/15; L 26/24/15	R 26.5/20/12; L 26/20/12	No	No
7	R 26/21/16; L 24/21/16	R 25.5/22.8/15; L 25.5/22.8/15	No	No
8	L 30/23/15; R 31.5/22/15	L 27/22/17; R 26/23/18	Yes	No
9	R 27.5/23.5/16; L 27/23/16	R 23/22/16; L 23/22/16	No	No
10	L 29/21/15; L 28/20/15	L 31/29/15; R 31/29/15	Yes	No
11	L 30/24/15; R 28/24/15	L 33/27/19; R 33/26/19	Yes	No
12	L 29/24/16; R 28/24/16	L 28/24/16; R 28/24/16	No	No
13	L 19/17/13; R 19/17/13	L 18/17/13; R 18/18/13	No	No
14	L 28.5/24/16; R 27/23.5/16.5	L 30/25/16; R 31/25/17	No	No
15	L 25/21/16; R 24/22/17	L 35/26/18; R 34/26/19	Yes	No
16	L 27/21/14; R 27/21/14	L 25/23/16; R 25/23/16	Yes	No
17	R 36/26/17; L 34/25/16	R 35/26/17; L 33/24/16	No	No
18	L 24/20/15; R 24/20/15	L 26.5/21/14.5; R 26.5/21/14.5	Yes	No
19	L 26/23/16; R 26/22/16	L 26/22/16; R 27/23/16	No	No
20	R 28/24/16; L 27/24/16	R 29/25/16.5; L 28/24/16	No	No
21	L 29/24/15; R 26/24/15	L 27/24/16; R 27/25/17	No	No
22	L 29/23/17; R 27/23/17	L 32/26/17; R 31/26/17	Yes	No
23	R 28/22/16; L 27/22/16	R 26/24/16; L 26/24/16	Yes	No
24	L 26/23/18; R 27/23/18	L 31/22/15; R 31/24/15	Yes	No
25	R 28/23/16; L 28/23/16	R 32.5/24.5/16.5; L 31/24.5/15.5	Yes	No
26	L 30/25/14; R 32/26/15	L 30/25/16; R 31/26/16	Yes	No
27	L 33/28/18; R 32/26/18	L 34/28/18; R 32/26/18	No	No
28	R 28/21/14; L 28/22/14	R 29/22/16; L 28/21/16	No	No
29	R 30/25/16; L 30/24/16	R 28/25/17; L 27/24/17	No	No
30	L 28/22/15; R 28/22/14	L 26.5/22/13; R 25.5/22/13.5	No	No
31	L 25/22/15; R 25/23/15	L 27/23/16; R 27.5/23/16	Yes	No
32	R 29/24/15; L 29/24/15	R 32/25/16; L 33/25/16	Yes	No
33	R 26/24/15; L 27/24/15	R 29/25/16.5; L 30/26/17	Yes	No
34	R 28/23/15; L 26/23/15	R 27/22/16; L 27/23/17	No	No
35	L 28/23/15; R 28/23/15	L 30/26/16; R 30/26/16	Yes	No
36	L 35/26/15; R 35/26/15	L 37/27/17; R 36/26/16	Yes	No
37	R 32/24/15; L 31/24/15	R 32/22/15; L 32/22/15	No	No

*: Measurements are shown as 10 cm above the elbow, 5 cm below the elbow, and at the wrist. The affected side is listed first. BCRL: Breast cancer-related lymphedema

Ethics

Ethics Committee Approval: The study was conducted at participating breast surgical oncology centres following approval by the Saifee Hospital Ethics Committee (approval no: SH/DNB/SUR/07/2024/019, date: 30.07.2024).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.R.G., J.R.A., I.R., E.T., N.C.; Concept: N.R.G., J.R.A., I.R., E.T., N.C., E.K., A.G., R.S., E.A.; Design: N.R.G., J.R.A., I.R., E.T., N.C., R.S., E.A.; Data Collection and/or Processing: N.R.G., J.R.A., I.R., E.T., R.S.; Analysis and/or Interpretation: N.R.G., J.R.A., I.R., E.T., E.K., A.G., R.S., E.A.; Literature Search: N.R.G., J.R.A., I.R., E.T., E.K., R.S., E.A.; Writing: N.R.G., J.R.A., I.R., E.T., E.K., R.S., E.A.

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The Ratio of the Resected Specimen Volume to Breast Volume, as Measured by Three-Dimensional Surface Imaging, Is Associated With Aesthetic Outcome After Breast-Conserving Surgery

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ABSTRACT

Objective: An objective method to predict aesthetic outcomes after breast-conserving surgery (BCS) has not been established. The ratio of the resected specimen volume to breast volume (S/B ratio) may be a reasonable option for this purpose.

Materials and Methods: We recruited 32 breast cancer patients who underwent BCS. Preoperative breast volumes were measured using three-dimensional surface imaging (3DSI) and computed tomography (CT). The volume of the surgical specimens was estimated by the length, width, and height of the specimen. The S/B ratio was calculated from these values. The association between the S/B ratio and aesthetic outcome evaluated by an expert panel or by patient-reported outcomes was analyzed 1 year after BCS.

Results: There was a statistically significant association between the S/B ratio and aesthetic outcome evaluated by the expert panel when we used 3DSI to measure the preoperative breast volume ($p = 0.01$). An S/B ratio of $<12.3\%$ may represent a preliminary cut-off for predicting an excellent aesthetic outcome. This association was not observed when CT was used to measure breast volume ($p = 0.09$). Furthermore, there was no significant association between the S/B ratio and patient-reported outcome.

Conclusion: When 3DSI is used for breast volume measurement, the S/B ratio is associated with the aesthetic outcome after BCS. This advantage of 3DSI may be due to the upright position of the patients during the breast volume measurement.

Keywords: Breast neoplasms; breast-conserving surgery; aesthetic outcome; three-dimensional surface imaging

KEY POINTS

- The ratio of the resected specimen volume to breast volume (S/B) may help predict the aesthetic outcome after breast-conserving surgery.
- Breast volume measurement using three-dimensional surface imaging is useful for evaluating the aesthetic outcome.
- An S/B ratio of $<12.3\%$ may represent a preliminary cut-off for predicting an excellent aesthetic outcome.

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Introduction

Breast-conserving surgery (BCS) is a major procedure for the treatment of breast cancer. Approximately half of breast cancer patients undergo BCS in Japan (1). The aim of BCS is to prevent patients from suffering a sense of breast loss and to improve quality of life. Therefore, maintaining the shape of the breast is essential. If the breast is affected extensively by the disease and a good cosmetic outcome is not expected, mastectomy and breast reconstruction should be considered. For adequately judging whether BCS should be performed or not, reliable objective indicators are needed.

The ratio of the resected breast volume to whole breast volume may be a reasonable predictor of the aesthetic outcome after BCS. Many studies have investigated the impact of the ratio of the breast tumor volume to whole breast volume on aesthetic outcomes (2-5), and some of those studies have shown promising outcomes (6-8). Further studies are necessary in this area.

Recently, personal computers have improved in performance and become more affordable. These advances allow us to use a three-dimensional (3D) camera and process the resulting 3D images easily. Others attempted to use 3D cameras to evaluate the shape of the treated breast (9), but the results were unsatisfactory because the postoperative breast was evaluated at an unspecified time after the BCS (10).

In this study, we aimed to reveal the reliability of the ratio of the resected specimen volume to breast volume (S/B ratio) as an indicator of the aesthetic outcome after BCS. To achieve this, we prospectively recruited patients who underwent BCS and evaluated the association between the aesthetic outcome and the S/B ratio determined using 3D surface imaging (3DSI) or computed tomography (CT) to measure breast volume.

Materials and Methods

Ethical Statement

This study was approved by the Nihon University Itabashi Hospital Ethical Review Board (approval no: RK-220208-4, date: 10 February 2025) and was performed in accordance with the principles of the Declaration of Helsinki. We obtained written informed consent from all participants.

Study Participants

We recruited female breast cancer patients to investigate the usefulness of 3DSI for BCS. 3D imaging data were obtained before the operation. In addition, we obtained the demographic characteristics of the patients, clinical and pathological features of the breast cancer, and CT images.

3DSI Measurement of Breast Volume

We used the K3 3D camera system (Kiisya Corporation, Tokyo, Japan) to measure breast volume according to the manufacturer's manual (11). Briefly, 3D images were taken with the patient in the sitting position. The region of interest was outlined on the acquired image and retrieved using the equipped software. Using this software, the retrieved region was sectioned at a 1 cm interval, the size of the area from each section was obtained, and these values were summed to calculate the volume. Measurements were performed by two authors (HG and SF) independently, and the mean value was adopted. Approximately 10 minutes were required to obtain 3D images, including patient preparation and data saving, and an additional 10 minutes were needed to calculate breast volume. No additional costs were incurred for image acquisition.

CT Measurement of Breast Volume

CT scanning was performed preoperatively from the external acoustic meatus to the inferior margin of the ischial tuberosities for staging in each patient. The patients were placed in the supine position. In general, contrast medium was not used. Osirix® (Pixemo SARL, Swiss) software was used to calculate the breast volume measured by CT according to the manual. Briefly, the CT data were imported into this software, the margins of the sectioned breast image were traced in each slice, and the breast volume was calculated by summing the values of the traced area and multiplying by a section interval of 5 mm. The breast margins were defined as the breast skin surface and the outer lines of the muscle and bones of the thorax. Similar to the 3DSI measurement, the same two authors performed these measurements independently, and the mean value was adopted.

The Volume of the Resected Specimen

The surgically resected specimen was regarded as a column with an ellipse-shaped bottom. The long and short diameters of the bottom end and the height of the specimen were measured. The volume of the resected specimen was calculated using the following formula:

$$\text{Specimen volume} = (\text{long diameter})/2 \times (\text{short diameter})/2 \times \pi \times \text{height}$$

Panel Assessment of Aesthetic Outcome

One year after BCS, the cosmetic outcome of the surgery was evaluated by a panel of 12 members comprising experienced 8 nurses and 4 surgical oncologists who had over 10 years of clinical experience. One of these panelists assessed the aesthetic outcome in person for each participant. None of the members were involved in the surgical treatments, and all were blinded to the treatment histories of the patients. The aesthetic outcome was evaluated as shown in Table 1 (12).

Patient-Reported Outcomes

At the same time as the panel assessment of the aesthetic outcome, the patients completed the “satisfaction with breasts” module of the BREAST-Q, which is one of the most commonly used instruments for measuring patient-reported outcomes in breast cancer treatment (13). This module included 11 items. The summed scores for each item were converted to an equivalent transformed score according to the conversion table provided by BREAST-Q, and this score ranged from 0 to 100. Higher scores indicated better patient satisfaction with the surgical outcome. Furthermore, the patients completed the “adverse effects of radiation” module of the BREAST-Q, which consists of six items. In this module, each item was analyzed as a stand-alone measure, with the patient’s response used directly as the item score. No composite or transformed scores were calculated.

Statistical Analysis

The relationship between 3DSI and CT breast volume measurements was investigated using Pearson’s correlation coefficients. Linear regression analysis was used to generate regression lines. The association between the S/B ratio and panel assessment or patient-reported outcomes was analyzed using ordinal logistic regression analysis. Receiver operating characteristic (ROC) analysis was used to evaluate the ability of the S/B ratio to predict the aesthetic outcome. The statistical package R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; <http://www.R-project.org>) was used for the statistical analyses. $p<0.05$ was considered significant.

Results

From May 2022 to July 2024, we recruited 39 breast cancer patients who underwent BCS. Of these, 7 patients were excluded from the analysis for various reasons (Figure 1). Although one patient lacked breast volume measurements by CT because of breast compression with an elastic bandage to achieve hemostasis, this patient was included in the study. Therefore, 32 patients were included in the analysis. However, CT-based breast volume measurements were available for only 31 patients.

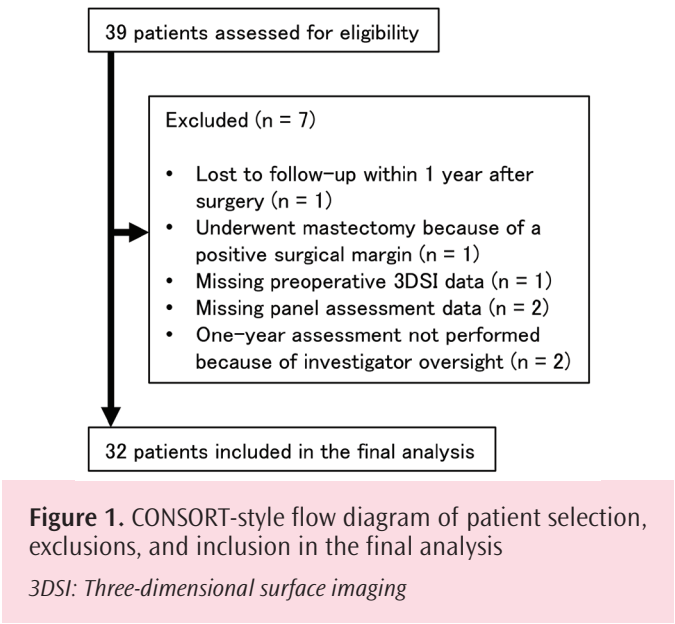
The clinical and pathological characteristics of the patients are summarized in Table 2. The mean age of the patients was 59 years, the mean tumor size was 24.7 (range 10–75) mm, and the stage was 0 or I in 84.4% of the cases. Eleven cases (34.3%) had ductal carcinoma *in situ*-predominant lesions, defined as lesions in which the intraductal carcinoma component was larger than the invasive component. There were no cases with multifocal lesions. Five patients (15.6%) received adjuvant chemotherapy, and 24 patients (75.0%) received endocrine therapy. All patients underwent

radiation therapy. Of these, four patients (12.5%) received boost radiation therapy, and two patients (6.3%) received supraclavicular radiation therapy.

The distributions of the 3DSI- and CT-measured breast volumes of the study patients are shown in Figure 2. The median (mean, range) breast volumes measured by 3DSI and CT were 428.9 (473.8, 160.0–1012.0) mL and 360.1 (396.9, 92.9–983.3) mL, respectively. The association between the 3DSI- and CT-measured breast volumes is summarized in Figure 3, and the Pearson’s correlation coefficient was 0.68. The distribution of the surgically resected specimen volume is demonstrated in Figure 4; the median (range) volume was 45.5 (12.4–254.3) mL.

The relationship between the aesthetic outcome assessed by the expert panel and the S/B ratio measured by 3DSI or CT is shown in Figure 5. The low S/B ratio measured by 3DSI was significantly associated with a better aesthetic outcome [odds ratio per 1% increase in the S/B ratio, 1.14; 95% confidence interval (CI), 1.04–1.26; $p = 0.01$]. The proportional-odds assumption was evaluated using the nominal test and was not violated ($p = 0.653$). This tendency remained significant even after removal of the one patient who lacked CT-measured breast volume data

Table 1. Aesthetic outcome of the treated breast	
Excellent	Treated breast was nearly identical to untreated breast.
Good	Treated breast was slightly different from untreated breast.
Fair	Treated breast was clearly different from untreated breast but not severely distorted.
Poor	Treated breast was severely distorted.



due to elastic bandage compression. On the other hand, the low S/B ratio measured by CT showed the same trend, but the association with aesthetic outcome failed to reach statistical significance ($p = 0.09$).

Figure 6 shows the ROC curve assessing the ability of the S/B ratio measured by 3DSI to predict the aesthetic outcome determined by the panel assessment. Because ROC analysis requires a binary outcome, the four-category aesthetic assessment was dichotomized into an excellent outcome (8 cases) versus a good, fair or poor outcome (24 cases). The optimal cut-off S/B ratio distinguishing between the excellent aesthetic outcome and non-excellent outcome was determined by the Youden index to be 12.3%, with a sensitivity of 62.5%, a specificity of 100% and an area under the curve of 0.78 (95% CI, 0.62–0.94).

The patients were administered the “satisfaction with breast” module in BREAST-Q. However, we did not detect any significant association between the patients’ answers and the S/B ratio measured by 3DSI (Figure 7). According to the “adverse effects of radiation” module of the BREAST-Q, 22 patients (68.7%) reported being a little bothered by at least one item, and 1 patient (3.1%) reported being a lot bothered by at least one item. Overall, 23 patients (71.8%) reported any bother from radiation.

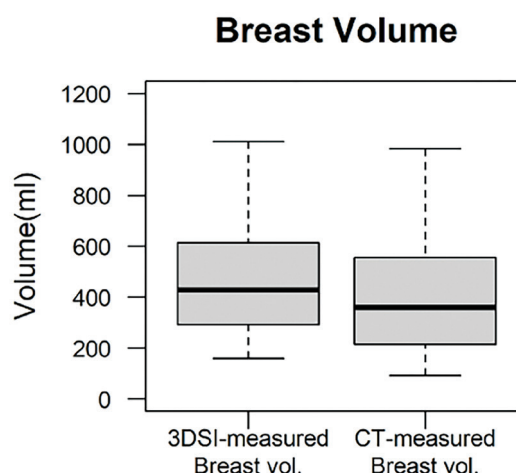


Figure 2. Distribution of the breast volumes measured by 3DSI versus CT. The median (range) volumes were 428.9 (160.0–1012.0) and 360.1 (92.9–983.3) mL when measured using 3DSI and CT, respectively. The horizontal lines within the boxes represent the median. The upper and lower sides of the boxes represent the 75th and 25th percentiles, respectively. The upper and lower whiskers extend to the largest value within 1.5×IQR above the 75th percentile and the smallest value within 1.5×IQR below the 25th percentile, respectively

3DSI: Three-dimensional surface imaging; CT: Computed tomography; IQR: Interquartile range

Table 2. Clinical characteristics of the study patients

No. of patients		32	
Mean age (range), years		59	(35–79)
Mean height (range), cm		160.0	(144.1–172.6)
Mean weight, kg		56.5	(37.2–82.9)
Mean body mass index (range)		22.0	(15.7–31.4)
Laterality	Right	14	43.8%
	Left	18	56.3%
Stage	0	4	12.5%
	I	23	71.9%
	II	5	15.6%
Mean tumor size (range), mm ^{\$^1\$}		24.7	(10–75)
Histology	Invasive ductal carcinoma	25	78.1%
	Mucinous carcinoma	3	9.4%
	DCIS	4	12.5%
DCIS-predominant lesion ^{\$^2\$}		11	34.3%
Chemotherapy		5	15.6%
Endocrine therapy		24	75%
Boost radiation therapy		4	12.5%
Supraclavicular radiation therapy		2	6.3%

^{\$^1\$}: The size was measured microscopically. These tumors included both invasive and *in situ* lesions; ^{\$^2\$}: A DCIS-predominant lesion was defined as a lesion in which the intraductal carcinoma component was larger than the invasive component. There were no cases with multifocal lesions; DCIS: Ductal carcinoma *in situ*

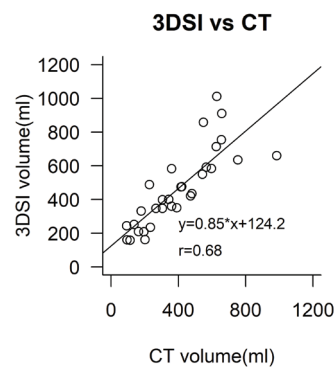


Figure 3. The relationship between the breast volume measured by 3DSI and that measured by CT. The correlation between the two breast volumes was moderate ($R = 0.68$)
3DSI: Three-dimensional surface imaging; CT: Computed tomography

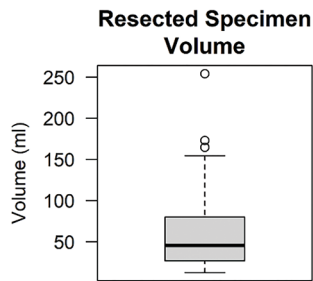


Figure 4. Distribution of the volumes of the resected specimen. The median (range) volume was 45.5 (12.4–254.3) mL. The boxplot parameters are the same as those in Figure 2

Discussion and Conclusion

We found that the S/B ratio is a reliable indicator of the cosmetic outcome after BCS based on the close association between the S/B ratio and aesthetic outcome as determined by a panel assessment. Furthermore, 3DSI-measured breast volume is more useful than CT-measured breast volume in this setting.

It is reasonable to expect the S/B ratio to be predictive of aesthetic outcomes after BCS. Several prior studies used the tumor volume rather than the resected specimen volume to evaluate aesthetic outcomes (2, 3, 6). Although tumor volume is easy to estimate preoperatively, there is a distinct difference between the tumor volume and resected specimen volume, and this discrepancy is likely to differ significantly among surgeons. Another issue is how to handle the case of multiple lesions or microcalcification. We believe that use of the S/B ratio should be evaluated extensively before using the tumor volume. On the other hand, the S/B ratio has an important limitation, as it cannot be accurately determined preoperatively. Future studies should investigate the association between the extent of disease and resected specimen volume.

Our study suggests that the ideal S/B ratio associated with an excellent aesthetic outcome after BCS is less than 12.3%. This estimate should be interpreted with caution because we have not yet performed a validation study. To our knowledge, two other studies reported similar thresholds, 10% and 14.6%, for evaluating the aesthetic outcome after BCS, as shown in Table 3 (6, 14). However, their approaches to measuring the breast and

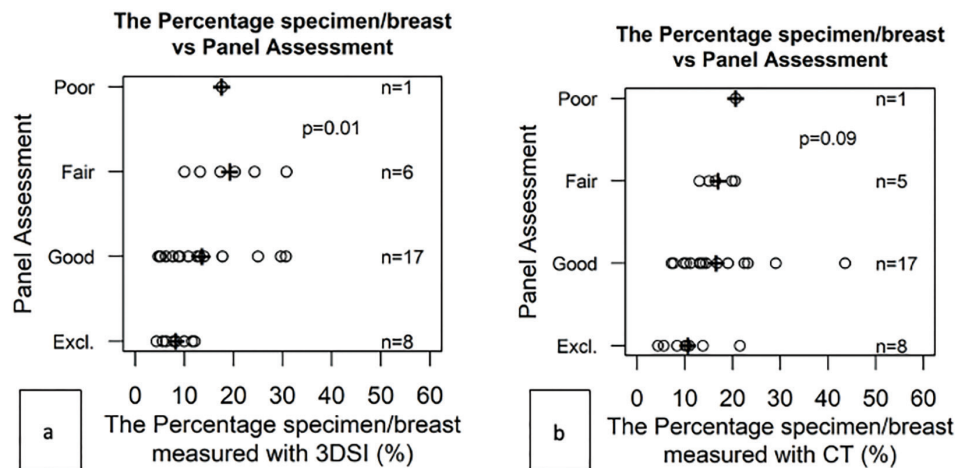


Figure 5. The association between the S/B ratio measured by 3DSI or CT and aesthetic outcome determined by the panel assessment. This association was statistically significant when breast volume was measured by 3DSI (a, $p = 0.01$) but not when measured by CT (b, $p = 0.09$). The plus signs indicate the mean of each category. “n” indicates the number of cases in each category

S/B: Specimen volume to breast volume; 3DSI: Three-dimensional surface imaging; CT: Computed tomography

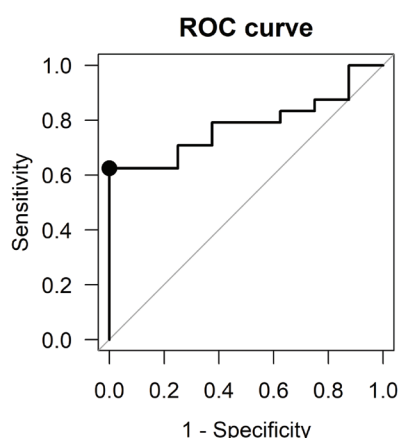


Figure 6. Receiver operating characteristic curve assessing the ability of the S/B ratio to predict an excellent cosmetic outcome based on the panel assessment. The black dot represents the Youden index

S/B: Specimen volume to breast volume; ROC: Receiver operating characteristic

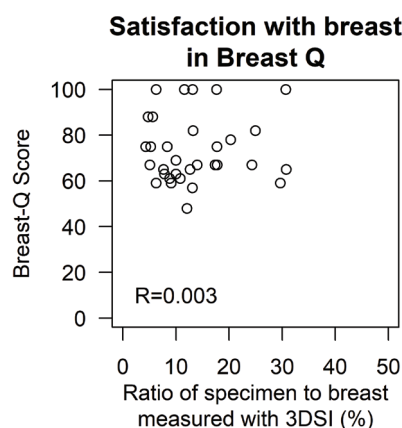


Figure 7. The association between the S/B ratio measured by 3DSI and the score for the “satisfaction with breast” module in BREAST-Q. The association was not significant ($r = 0.007$)

S/B: Specimen volume to breast volume; 3DSI: Three-dimensional surface imaging

specimen volumes and evaluating cosmetic outcomes differed from ours. More studies are necessary in this area.

Similar to several other studies (9, 15-18), we showed that the 3DSI-measured breast volume is useful for predicting aesthetic outcomes after breast surgery. Kim et al. (16) reported that 3DSI-measured breast volume is more useful than mastectomy specimen weight for predicting the ideal implant size for breast reconstruction. We used 3DSI, CT, magnetic resonance imaging, mammography, and resected mastectomy specimen to measure breast volume and found that the measured volumes were similar among the different modalities (11). However, breast volume measured by 3DSI is distinctly different from that measured by the other modalities because the patient is positioned exclusively upright during 3DSI measurement. Colman et al. (19) reported differences in breast volume between the prone and standing positions ranging from approximately 8% to 22%. Because cosmetic assessment is performed for patients in the upright position, 3DSI-measured breast volume should be used to assess aesthetic outcomes after breast surgery. To our knowledge, our study is the first to show the usefulness of 3DSI for predicting aesthetic outcomes after BCS.

In contrast to the assessment of aesthetic outcomes by the nurse/surgeon panel, our study failed to show an association between the S/B ratio and patient-reported outcomes. Whereas Vos et al. (7) successfully demonstrated a positive association between a small tumor size and patient-reported aesthetic outcomes, other reports failed to reveal such an association (4, 5). Johansen et al. (20) reported a significant but relatively weak level of concordance between patients' and clinicians' evaluations of the cosmetic results. We believe that patients' evaluations of aesthetic outcomes are complicated by many factors including adjuvant chemotherapy, endocrine therapy, and radiation therapy. In particular, radiation therapy is a well-known confounder or effect modifier of aesthetic outcomes, and 71.8% of our patients were affected. This treatment possibly plays a more significant role in patient satisfaction than panel-based assessments. Importantly, the S/B ratio alone cannot determine aesthetic outcomes after BCS, and should not be regarded as a standalone tool for clinical decision-making.

Table 3. Comparison of S/B ratio among relevant studies

Study group	Sample size	Measurement of specimen volume	Measurement of breast volume	S/B ratio
Cochrane et al. (6)	151	Estimated from tumor size	Mammography	10%
Hashem et al. (14)	36	Actual specimen size	Mammography	14.6%
Present study	32	Actual specimen size	3DSI	12.3%

3DSI: Three-dimensional surface imaging; S/B: Specimen volume to breast volume

Our study has some limitations. The number of patients was small. The patient-reported outcomes did not support the outcomes of the panel assessment. Because each participant was evaluated by a single panelist, inter-rater reliability could not be assessed. Future studies should include independent assessments by multiple panelists for each participant to evaluate the reproducibility of the aesthetic assessment. Aesthetic outcomes after BCS are influenced by several factors, including tumor location, absolute breast size, body mass index, and boost radiation. Because of the limited sample size, we were unable to adjust for these potential confounding factors in the present analysis. We did not evaluate aesthetic outcomes beyond 1 year after surgery. The breast size of our cohort was relatively small, with a median volume of 428.9 mL. Although this study was performed prospectively, some data were missing. The volume of the resected specimen was estimated based on the resected specimen's length, width, and height, instead of actual volume measurements. Because multiple statistical associations were examined without adjustment for multiple comparisons, our findings should be interpreted with caution, and confirmation in a larger independent cohort is warranted. However, we believe that our conclusions were not impaired significantly even after consideration of all these limitations.

In conclusion, the S/B ratio is a useful indicator of cosmetic outcomes after BCS. Furthermore, 3DSI-measured breast volume is more useful than CT-measured breast volume for this evaluation. More studies are needed to achieve the same conclusions with patient-reported outcomes and to investigate the utility of the relationship between the extent of disease and the resected sample volume for predicting cosmetic outcomes preoperatively in BCS patients.

Ethics

Ethics Committee Approval: This study was approved by the Nihon University Itabashi Hospital Ethical Review Board (approval no: RK-220208-4, date: 10 February 2025) and was performed in accordance with the principles of the Declaration of Helsinki.

Informed Consent: We obtained written informed consent from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.F., H.G., Y.H., K.T.; Concept: Y.H., K.T.; Design: K.T.; Data Collection and/or Processing: S.F., H.G.; Analysis and/or Interpretation: S.F., K.T.; Literature Search: Y.H., K.T.; Writing: K.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Versatility of Lateral Intercostal Artery Perforator Flaps in Partial Breast Reconstruction: First National Experience of Peru

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ABSTRACT

Objective: Oncoplastic breast surgery (OBS) allows wide oncologic resections without compromising breast symmetry. In small-breasted patients with minimal ptosis, volume displacement techniques have limited applicability. Lateral intercostal artery perforators (LICAP)-based perforator flaps allow immediate or delayed partial breast reconstruction for lateral and central defects, preserving muscle and minimizing donor-site morbidity. This study aimed to evaluate the safety and outcomes of LICAP-based flaps and to report the first national experience in Peru.

Materials and Methods: A retrospective observational study was conducted from August 2023 to August 2025 in patients who underwent OBS with perforator-based flap reconstruction, including LICAP, bilobed LICAP, and combined LICAP-lateral thoracic artery perforator (LTAP) flaps.

Results: Twenty patients were included. The mean age was 56.8 years (range, 27–81 years), and 65% were postmenopausal. Indications included invasive ductal carcinoma (85%), ductal carcinoma *in situ* (5%), and phyllodes tumor (10%). Tumor location: upper outer quadrant (65%), central (20%), upper inner quadrant (10%). Clinical stage IIA was the most frequent (55.5%), and tumors measuring 3–4 cm were observed in 45% of cases. Luminal B was the predominant subtype (40%), and 35% of patients received neoadjuvant chemotherapy. Procedures included bilobed LICAP (35%), LICAP+LTAP (30%), and LICAP (25%). The mean operative time was 134 minutes (range, 90–195 minutes), and the mean pathological tumor size was 3.57 cm (range, 0–7 cm). Negative margins were achieved in 95% of patients. Surgical complications (Clavien-Dindo grade I) occurred in 15%. During a median follow-up of 22.5 months (range, 10–24 months), no locoregional recurrences were observed.

Conclusion: LICAP-based volume replacement OBS is a versatile, safe, and reproducible technique that may expand the indications for breast-conserving surgery in selected patients and yields encouraging short-term outcomes comparable to those reported in international series.

Keywords: Oncoplastic breast surgery; LICAP flap; partial breast reconstruction; bilobed flap; breast-conserving surgery

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KEY POINTS

- Lateral intercostal artery perforators (LICAP)-based perforator flaps are a safe and versatile option for partial breast reconstruction in lateral and central breast defects.
- These flaps preserve muscle, minimize donor-site morbidity, and can be performed immediately or in a delayed setting.
- In this first national series from Peru, 94% of patients achieved negative margins with low complication rates (11%, all minor).
- The techniques, including LICAP+lateral thoracic artery perforator and bilobed LICAP modifications, allow reconstruction in small breasts with minimal ptosis and expand eligibility for breast-conserving surgery.
- Oncologic and aesthetic outcomes were comparable to international series, supporting LICAP-based flaps as a reproducible oncoplastic strategy.

Introduction

Breast-conserving surgery (BCS) is the standard of care for early-stage breast cancer and, when combined with radiotherapy, has been associated with higher overall survival rates compared with mastectomy (1). Oncoplastic breast surgery (OBS) techniques in BCS are indicated when tumor resection is expected to result in deformity and poor aesthetic outcomes. These techniques are broadly classified into volume displacement techniques, ideal for patients with large and/or ptotic breasts (grade 2 or 3), and volume replacement techniques, applied to small- to moderate-sized breasts with mild ptosis (grade 1) or no ptosis, as well as to cases where patients do not desire contralateral symmetrization surgery (2). Partial breast reconstruction using mammoplasty techniques and regional flaps has been widely described as a strategy to avoid mastectomy and total breast reconstruction, both of which are associated with more complex procedures, higher complication rates, and no demonstrated oncologic advantage over BCS (3).

Muscle-sparing regional flaps based on chest wall perforators for partial breast reconstruction were first described by Hamdi et al. (4), who demonstrated the use of lateral intercostal artery perforators (LICAP) located between the 5th and 8th intercostal spaces, approximately 2.5–3.5 cm from the anterior border of the latissimus dorsi muscle. These perforators allow the design of a flap that can be extended toward the dorsal region to reconstruct lateral breast defects; however, their use is limited in the central and medial quadrants because of the limited length of the vascular pedicle. To overcome this limitation, several modifications to the original flap design described by Hamdi et al. (4) have been proposed.

The bilobed LICAP flap, described by Paulinelli et al. (5), is a double transposition flap that enables volume replacement in the central breast region, using donor tissue from the upper outer quadrant of the breast and a lateral thoracic flap based on LICAP perforators, thereby preserving breast contour and symmetry. Another modification described by Meybodi et al. (2) involves an “S”-shaped incision along the breast contour, which avoids visible dorsal scarring and eliminates the need for patient repositioning during flap dissection. This approach also allows

tension-free closure and has been associated with a reduced rate of surgical site infections (2).

Additionally, McCulley et al. (6) described flaps based on the lateral thoracic artery perforator (LTAP), which is located between the 3rd and 5th intercostal spaces along the posterolateral breast border; the most consistent and dominant perforator was found 8–12 cm inferior to the axillary fold. These flaps can be used alone or in combination with LICAP-based flaps, increasing tissue mobilization and reconstructive volume for lateral breast defects.

The aim of this study is to present, to our knowledge, the first national experience in Peru with LICAP-based volume replacement techniques and their modifications in OBS.

Materials and Methods

Study Design

We conducted a retrospective, observational case series between August 2023 and August 2025. Patients who underwent OBS with perforator-based volume replacement flaps (LICAP, bilobed LICAP, and LICAP+LTAP) were identified in institutional records. All procedures were performed by a single surgeon with national certification and international OBS training (Spain and Brazil) at the Department of Breast Surgery, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru.

Surgical indications were determined by a multidisciplinary surgical committee. Inclusion criteria were: women over 18 years of age with tumors located in the lateral or central breast quadrants; a poor tumor-to-breast volume ratio; minimal or no ptosis; a preference against contralateral breast surgery; and no prior breast irradiation. Diagnosis and neoadjuvant/adjuvant treatment of breast cancer and phyllodes tumors followed the National Comprehensive Cancer Network guidelines, with the primary objective of enabling BCS while minimizing deformity.

Surgical Technique

Preoperative markings for the oncoplastic pattern design were performed with the patient in the supine position. Breast ptosis was assessed and key measurements were obtained,

including the midclavicular point-to-nipple distance, nipple-to-inframammary fold distance, and nipple-to-sternal notch distance. The locations of LICAP and LTAP perforators were initially identified using anatomical landmarks. Patients were then placed in the supine position, and the exact locations of the perforators were confirmed using color Doppler ultrasound. Under general anesthesia, local infiltration was performed in the tumor resection area using Klein solution combined with tranexamic acid, as described by Ziegler Rodríguez et al. (7).

The choice of surgical technique was based on the following indications. The LICAP flap (as described by Hamdi et al. (4) was used in cases of tumors located in the lateral breast quadrants and/or when a large skin island was required for reconstruction of the surgical defect. The technique described by Meybodi et al. (2) was selected for patients who did not desire a visible scar in the dorsal region, which was avoided by using an “S”-shaped incision along the breast contour. This incision also facilitated the identification and dissection of the LTAP perforator. In these cases, both the LICAP and LTAP perforators were used, primarily for defects in the superolateral breast quadrants because of the length of the LTAP pedicle. Skeletonization of LICAP perforators was not required for propeller or turnover flap transposition. The LICAP perforator marking area was preserved as a skin island that was de-epithelialized after flap inset. Flap viability was assessed intraoperatively based on clinical signs, such as dermal bleeding

and capillary refill. The bilobed LICAP flap technique described by Paulinelli et al. (5) was indicated in cases of central tumors involving or located close to the skin, which required excision of the nipple-areolar complex (NAC). In these cases, reconstruction of the NAC was performed as a second-stage procedure using the Hammond flap technique (8).

In two cases with involvement of the superomedial breast quadrant (multifocal disease and heterogeneous response to neoadjuvant therapy), a modification of the original bilobed LICAP technique was performed. This involved mobilization of the upper breast quadrant toward a more medial position, using non-absorbable fixation sutures to the pectoral fascia. Part of the flap lobe was de-epithelialized to replace the resected volume. The nipple-areola complex was repositioned using a round block technique, allowing areolar expansion and preventing contour deformities. A schematic algorithm summarizing the indications and the surgical decision-making process for selecting LICAP, bilobed LICAP, or combined LICAP+LTAP reconstruction is presented in Figure 1.

Donor sites were meticulously closed in all cases using quilting sutures. A single 14 Fr closed-suction drain was placed at each of the donor and recipient sites. An additional drain was inserted in cases requiring axillary lymphadenectomy. Drains were removed when the output was <30 mL over 24 hours (Figure 1).

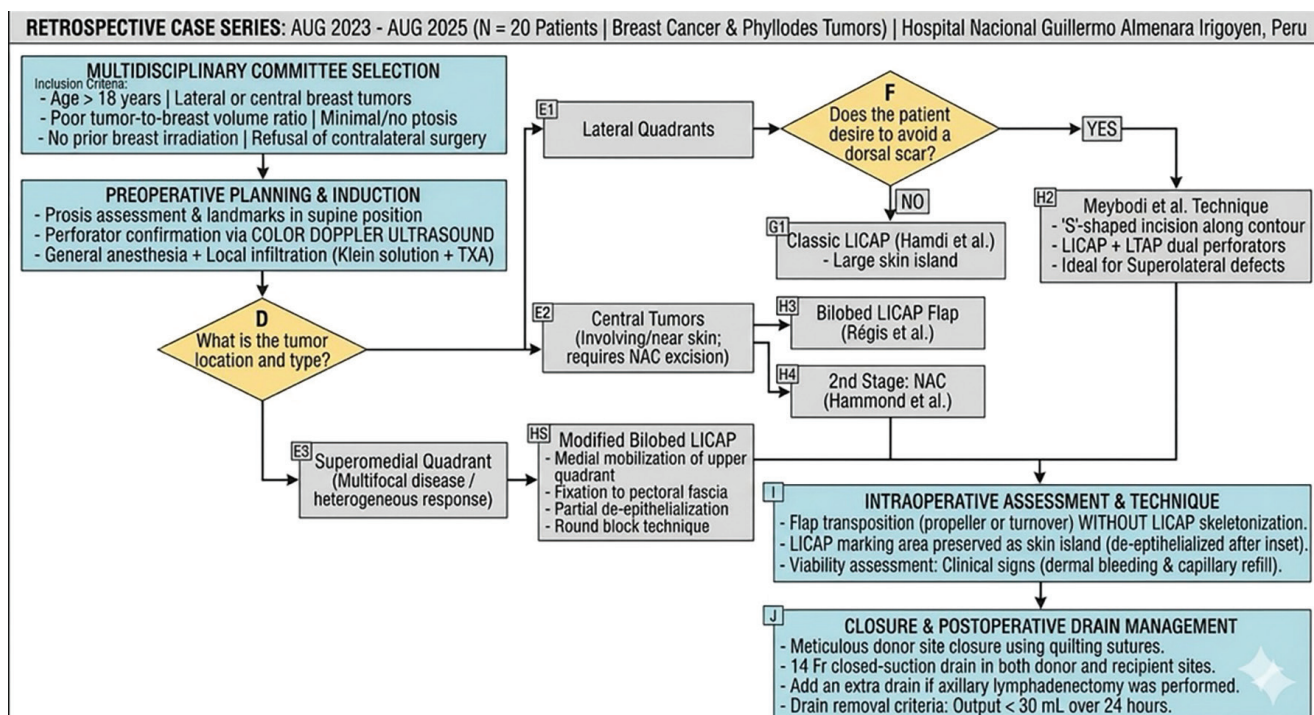


Figure 1. Surgical decision-making algorithm for LICAP-based oncoplastic breast reconstruction and perioperative management
NAC: Nipple-areola complex; LICAP: Lateral intercostal artery perforator; LTAP: Lateral thoracic artery perforator; TXA: Tranexamic acid; Fr: French gauge

Patient-Reported Outcome Measures

Patient-reported outcomes were assessed using the BREAST-Q breast-conserving therapy module. The questionnaire was completed by all eligible patients (100% response rate) after an informed discussion and confirmation of understanding of the following items, at 6 weeks after completion of adjuvant radiotherapy or at 6 weeks after surgery in patients who did not require adjuvant radiotherapy. The following domains were evaluated: psychosocial well-being, sexual well-being, physical well-being, satisfaction with breasts, satisfaction with outcome, and satisfaction with care. Scores for each domain were reported as the median and interquartile range (Q1-Q3) because the data were not normally distributed.

Statistical Analysis

Descriptive statistics were used to summarize the data. Continuous variables are presented as mean $\pm$ standard deviation and range, while categorical variables are expressed as frequencies and percentages. All analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA).

Ethics

The study was exempted from formal review by the Hospital Nacional Guillermo Almenara Irigoyen Ethics Committee of the Red Prestacional Almenara (ethics review no: 209, date: May 5, 2026). This exemption was granted in compliance with institutional regulations that exclude retrospective, descriptive, and non-experimental studies from formal evaluation. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Patient data were strictly anonymized and handled confidentially, and standard informed consent for surgical procedures was obtained from all patients prior to treatment.

Results

Between August 1, 2023, and August 31, 2025, 20 patients underwent BCS using OBS with LICAP flap-based volume replacement techniques. The mean age was 56.8 years (range, 27–81 years) and 65% of patients were postmenopausal. Four patients (20%) had comorbidities, including hypertension, hypothyroidism, and neuromyelitis optica (Table 1).

The surgical indications were invasive ductal carcinoma in 17 cases (85%), ductal carcinoma *in situ* in 1 case (5%), and phyllodes tumor in 2 cases (10%). Tumors were located in the upper outer quadrant (65%), central quadrant (20%), and upper inner quadrant (10%). The most frequent clinical stage was IIA (55.5%); initial clinical tumor size of 3–4 cm was observed in 45% of patients, and clinically node-negative disease was present in 70% of patients. The most common immunophenotype was

Luminal B (40%). Seven patients (35%) received neoadjuvant chemotherapy, with one achieving a pathological complete response (with residual ductal carcinoma *in situ*) (Table 1).

Preoperative planning included mammography and breast ultrasound in 94.4% of cases. The procedures performed were: 7 cases (35%) of bilobed LICAP flap (Figure 2); 5 cases (25%) of LICAP flap (Figure 3); 6 cases (30%) of LICAP+LTAP flap (Meybodi technique) (Figure 4); and 2 cases (10%) of bilobed LICAP flap associated with nipple-areola complex reconstruction (Hammond flap) (Figure 5). The mean operative time was 134 minutes (range 90–195 minutes) (Table 2).

The mean pathological tumor size was 3.57 cm (range, 0–7 cm). Surgical margin specimens were evaluated on permanent sections. Negative margins were achieved in 95% of cases. One patient (5%) had positive margins and subsequently underwent completion mastectomy, with multifocal disease identified on final pathology. Regarding axillary management, 11 patients (68.7%) underwent sentinel lymph node biopsy (SLNB) alone, 2 patients (12.5%) underwent SLNB followed by axillary lymph node dissection (ALND), and 4 patients (25%) underwent ALND alone. Three sentinel lymph nodes were identified in 50% of patients undergoing SLNB (Table 2).

The overall surgical complication rate was 15% ($n = 3$), all classified as Clavien-Dindo grade I. Two patients developed partial wound dehiscence, which was managed with local wound care; another presented with superficial erythema at the suture site and was treated with a short course of oral antibiotics. No cases of fat necrosis or late complications were observed (Table 2).

The BREAST-Q breast-conserving therapy questionnaire was administered six weeks after completion of adjuvant radiotherapy or, for patients who did not require adjuvant radiotherapy, six weeks after surgery. The following domains were assessed: psychosocial well-being (median 83; Q1-Q3, 80–91), sexual well-being (median 70; Q1-Q3, 66–84), satisfaction with breasts (median 88; Q1-Q3, 71–100), physical well-being (median 76; Q1-Q3, 75–85), satisfaction with outcome (median 91; Q1-Q3, 67–100), and satisfaction with care (median 100; Q1-Q3, 100–100) (Table 2).

A total of 18 patients (90%) received adjuvant therapy, including radiotherapy (RT) combined with endocrine therapy (ET) (40%) and chemotherapy combined with radiotherapy and endocrine therapy (35%). At a median follow-up of 22.5 months (range, 10–24 months), no locoregional recurrences were observed. One patient developed a distant recurrence (brain metastasis) and was treated with whole-brain radiotherapy and chemotherapy (Table 2).

Table 1. Patient demographics and tumor characteristics of patients who underwent LICAP, bilobed LICAP, LICAP+LTAP-based partial breast reconstruction

Variables	LICAP	Bilobed LICAP	LICAP+LTAP	Total
n (%) or mean (range)				
Age	67.0 (60–73)	56.6 (41–81)	48.5 (27–62)	56.8 (27–81)
Hormonal status				
Pre-menopausal	1 (20.0)	3 (33.3)	3 (50)	7 (35.0)
Post-menopausal	4 (80.0)	6 (66.7)	3 (50)	13 (65.0)
Comorbidities				
None	5 (100.0)	7 (77.8)	4 (66.7)	16 (80.0)
Neuromyelitis optica	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.0)
Hypothyroidism	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
Hypertension	0 (0.0)	1 (11.1)	1 (16.7)	2 (10.0)
Ptosis				
No ptosis	3 (60.0)	5 (55.5)	2 (33.2)	10 (50.0)
G1	1 (20.0)	3 (33.3)	3 (49.8)	7 (35.0)
G2	1 (20.0)	1 (11.1)	1 (16.6)	3 (15.0)
G3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor location				
Upper outer	5 (100.0)	3 (33.3)	5 (83.3)	13 (65.0)
Lower outer	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.0)
Lower inner	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper inner	0 (0.0)	2 (22.2)	0 (0.0)	2 (10.0)
Central	0 (0.0)	4 (44.4)	0 (0.0)	4 (20.0)
Diagnosis				
DCIS	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.0)
IDC	5 (100.0)	9 (100.0)	3 (50.1)	17 (85.0)
ILC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phyllodes	0 (0.0)	0 (0.0)	2 (33.4)	2 (10.0)
ER				
Positive	5 (100.0)	6 (75.0)	3 (100.0)	14 (87.5)
Negative	0 (0.0)	2 (25.0)	0 (0.0)	2 (12.5)
PR				
Positive	2 (40.0)	3 (37.5)	0 (0.0)	5 (31.25)
Negative	3 (60.0)	5 (62.5)	3 (100.0)	11 (68.75)
HER2 receptor				
Positive	0 (0.0)	3 (37.5)	1 (33.3)	4 (25)
Negative	0 (0.0)	5 (62.5)	2 (66.6)	12 (75)
Clinical stage				
0	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.5)
IA	1 (25.0)	0 (0.0)	0 (0.0)	1 (5.5)
IIA	2 (50.0)	5 (55.6)	2 (40.0)	11 (55.5)
IIIA	1 (25.0)	2 (22.2)	2 (40.0)	3 (16.6)
IIIB	0 (0.0)	2 (22.2)	0 (0.0)	2 (11)
DCIS: Ductal carcinoma <i>in situ</i> ; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; ER: Estrogen receptor; PR: Progesterone receptor; LICAP: Lateral intercostal artery perforators; LTAP: Lateral thoracic artery perforator				

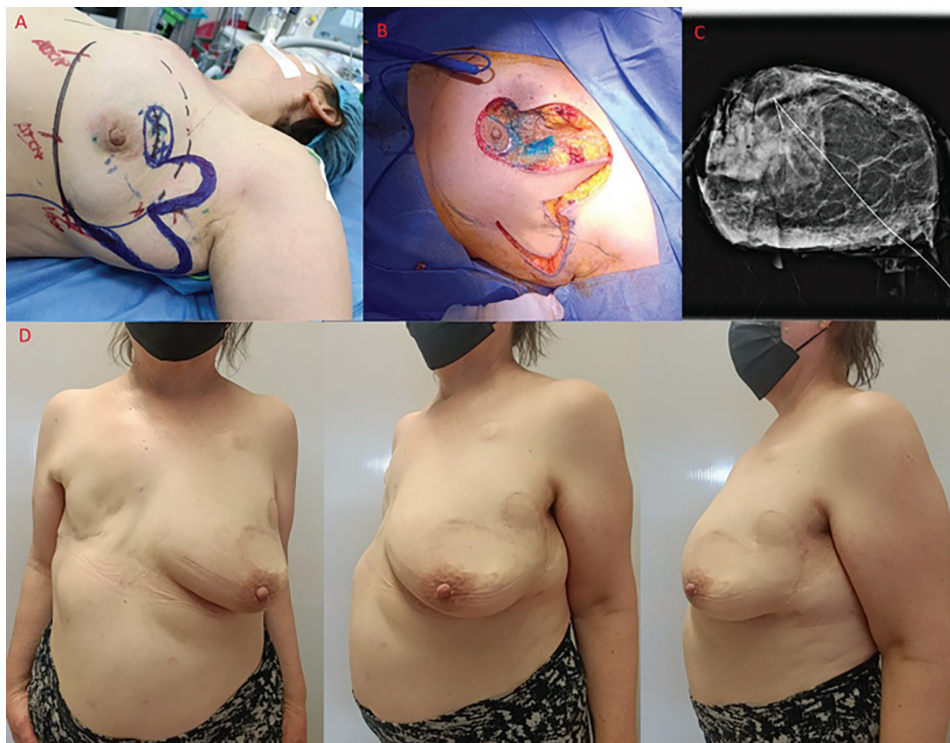


Figure 2. A. Preoperative bilobed LICAP flap design. B. Intraoperative defect following tumor resection with nipple-areola complex excision. C. Specimen mammography confirming complete lesion excision. D. Twelve-month postoperative follow-up after adjuvant radiotherapy (frontal, oblique, and lateral views), demonstrating preserved breast contour and satisfactory aesthetic outcome

LICAP: Lateral intercostal artery perforator



Figure 3. LICAP flap reconstruction for a lateral breast defect. A. Preoperative flap design. B. Intraoperative defect following tumor resection. C. Volume replacement using a LICAP flap. D. Clinical appearance at 10-month follow-up after adjuvant radiotherapy (frontal, oblique, and lateral views), demonstrating preserved breast contour and satisfactory aesthetic outcome

LICAP: Lateral intercostal artery perforator

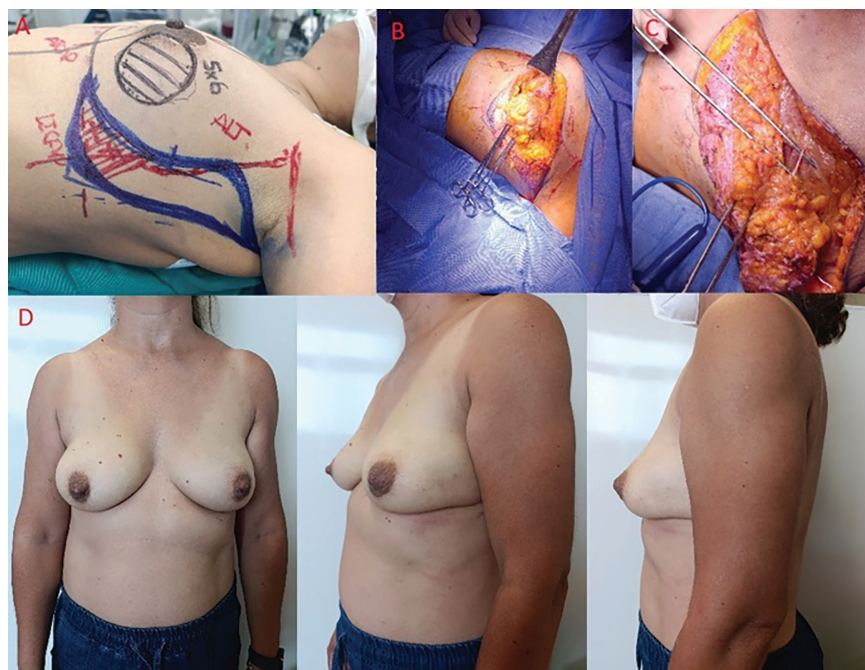


Figure 4. Combined LICAP-LTAP flap reconstruction using the Meybodi technique. A. Preoperative flap design. B. Intraoperative defect following tumor resection with flap elevation. C. Identification of the LTAP perforator during flap dissection. D. Clinical appearance at 10-month follow-up after surgery (frontal, oblique, and lateral views), demonstrating preserved breast contour and satisfactory aesthetic outcome

LICAP: Lateral intercostal artery perforator; LTAP: Lateral thoracic artery perforator



Figure 5. Bilobed LICAP flap with secondary nipple-areola complex reconstruction using the Hammond flap. A. Post-neoadjuvant chemotherapy mammogram. B. Preoperative flap design. C. Clinical appearance after primary breast reconstruction. D. Clinical appearance at 6-month follow-up after adjuvant radiotherapy and secondary Hammond flap reconstruction (frontal, oblique, and lateral views), demonstrating preserved breast contour and satisfactory aesthetic outcome.

LICAP: Lateral intercostal artery perforator

Table 2. Surgical and treatment details of patients who underwent LICAP, bilobed LICAP, LICAP+LTAP-based partial breast reconstruction

Variables	LICAP	Bilobed LICAP	LICAP+LTAP	Total
n (%) or mean (range) or Q1-Q3				
Axillary surgery				
SLNB	5 (100.0)	5 (55.6)	1 (33.3)	11 (64.7)
ALND	0 (0.0)	3 (33.3)	1 (33.3)	4 (23.5)
SLNB+ALND	0 (0.0)	1 (11.1)	1 (33.3)	2 (11.8)
Pathological T (cm)	3.0 (2.5–3.5)	3.8 (1.0–7.0)	3.6 (0.0–6.0)	3.6 (0–7)
Margin				
Negative	5 (100.0)	8 (88.9)	6 (100.0)	19 (95.0)
Positive	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
Surgery time (minutes)	115 (90–130)	120 (95–140)	105 (80–195)	134 (90–195)
Surgical complications				
No	5 (100.0)	8 (88.9)	4 (66.7)	17 (85.0)
Yes				
Surgical site infection	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
Partial wound dehiscence	0 (0.0)	0 (0.0)	2 (33.3)	2 (10.0)
BREAST-Q				
Psychosocial well-being	83 (83–90)	83 (72–90)	81 (75–100)	83 (80–91)
Sexual well-being	84 (68–95)	70 (66–87)	66 (47–80)	70 (66–84)
Satisfaction with breasts	100 (75–100)	88 (85–100)	73 (66–91)	88 (71–100)
Physical well-being	82 (70–85)	82 (68–92)	76 (74–76)	76 (75–85)
Satisfaction with outcome	71 (59–100)	91 (70–100)	83 (73–93)	91 (67–100)
Satisfaction with care	100 (100–100)	100 (100–100)	100 (91–100)	100 (100–100)
Adjuvant treatment				
No	0 (0.0)	0 (0.0)	2 (33.3)	2 (10.0)
TZT+RT+ET	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.0)
CTX+RT	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
CTX+RT+ET	4 (80.0)	2 (22.2)	1 (16.7)	7 (35.0)
CTX+TZT+RT+ET	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
RT+HT	1 (20.0)	5 (55.6)	2 (33.3)	8 (40.0)
LICAP: Lateral intercostal artery perforator; LTAP: Lateral thoracic artery perforator; ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy; TZT: Trastuzumab; CTX: Chemotherapy; RT: Radiotherapy; ET: Endocrine therapy; HT: Hormone therapy				

Discussion and Conclusion

To our knowledge, this report represents the first national experience in Peru evaluating LICAP-based oncoplastic volume replacement techniques, and it suggests that these flaps are safe, versatile, and reproducible options for partial breast reconstruction. Furthermore, our findings suggest that LICAP-based techniques can expand the indications for BCS in a Latin American population, enabling reliable reconstruction of lateral and central defects with minimal morbidity and encouraging early oncologic outcomes comparable to those reported in international series.

Breast cancer in Peru has an incidence of 7,797 new cases annually, representing the second most frequent malignancy among women nationwide (9) and the most common in Lima, the capital of Peru (10). In this context, the need for breast surgeons trained in oncoplastic surgery emerged in 2008 with the first national cases and specialized training courses led by international experts, including Benigno Acea Nebril (Spain), Eduardo González (Argentina), Régis Resende Paulinelli, and Cicero Andrade Urban (Brazil); these developments contributed to improving understanding of the OBS philosophy at the national level. This experience subsequently led to the first

national reports by Garcés et al. (11) as well as international publications, describing level I and II oncoplastic mammoplasty techniques (12). Oncologic safety outcomes have been reported, with local recurrence rates of 2.6%, regional recurrence of 1.61%, and distant recurrence of 2.67% over a 10-year follow-up, as described by Chávez et al. (13).

The classification of OBS into volume displacement and volume replacement techniques has facilitated surgical decision-making. Volume replacement OBS represents an appropriate option for immediate partial breast reconstruction using chest wall perforator vessels, allowing BCS for patients who would otherwise be considered candidates for mastectomy (14).

The use of LICAP flaps, initially described by Hamdi et al. (4), and the modifications proposed by Meybodi et al. (2), Paulinelli et al. (5), and McCulley et al. (6), have improved aesthetic outcomes of the incision, expanded indications to include central tumors, and enhanced perfusion reliability when combined with LTAP. In our initial experience, the described variants were successfully applied, supporting the use of LICAP-based volume replacement flaps as a safe option for reconstruction of lateral and central breast quadrants. These techniques were adapted to use the bilobed LICAP flap in two cases involving the superomedial quadrant because of tumor fragmentation after chemotherapy and multifocal disease (Figure 6).

Patient selection should be performed carefully, particularly in patients without ptosis, with mild ptosis, or in those with ptosis who decline breast reduction and contralateral symmetrization (15). This allows reproducibility of the techniques, which is further facilitated by the use of Doppler ultrasound similar to that described by Ersan and Yıldız (16). In our series, Doppler ultrasound aided preservation of LICAP within the skin paddle at the base of the flap, which was dissected as needed to allow greater rotation (propeller or turnover), and aided identification of LTAP in cases where dual-perfusion flaps were planned. This approach was directly associated with a mean operative time of 134 minutes (range 90–195 minutes), comparable to that reported by other authors such as Shen et al. (17) (142 minutes) Mangialardi et al. (18) (156 minutes) and Abd El Mohsen et al. (19) (134.4).

In BCS, achieving negative margins is crucial. Some series recommend intraoperative margin assessment and the option of delaying perforator flap reconstruction to a second stage when *in situ* disease is difficult to evaluate intraoperatively (18). In our series, immediate reconstruction was performed in all patients. The rate of positive margins was 5%, which falls within the range reported for BCS in multicenter studies (13.4%) (20) as well as in series focused on LICAP-based volume replacement OBS (7.3%) (14).



Figure 6. Modified bilobed LICAP flap reconstruction for an upper inner quadrant breast tumor. A. Preoperative flap design. B. Intraoperative defect following tumor resection. C. Flap elevation with identification of the LTAP perforator to increase flap mobility. D. Clinical appearance at 6-month follow-up after adjuvant radiotherapy (frontal, oblique, and lateral views), demonstrating preserved breast contour and satisfactory aesthetic outcome

LICAP: Lateral intercoastal artery perforator

LICAP-based flaps offer the main advantage of minimal donor-site morbidity, as they preserve the muscular structure, with low complication rates, as reported by Soumian et al. (20) (7.1%), Nava et al. (21) (13%) and Burhamah et al. (22) (16.4%), including hematoma, infection, seroma, wound dehiscence, partial or total flap necrosis, and fat necrosis. In our series, the complication rate was 15%; all complications were classified as Clavien-Dindo grade I and did not delay adjuvant therapy. No cases of fat necrosis or flap-related complications after radiotherapy were observed during the available follow-up, similar to the findings reported by Pujji et al. (23), who observed rates of total and partial flap necrosis of 0.2% and 1.8%. Overall, our patients demonstrated favorable short-term outcomes without clinically evident breast deformities during follow-up.

Our results demonstrate the versatility of partial breast reconstruction using LICAP flaps and their modifications. However, this study has limitations inherent in its descriptive, retrospective design and clinical context. As this case series represents the first national experience in Peru and was performed by a single surgeon, it was limited to 20 patients who were distributed into three groups according to the surgical technique used. Consequently, the sample size was insufficient to detect statistically significant differences between groups, increasing the risk of a type II error. For this reason, formal comparative analyses between surgical technique groups were not performed, and the study was intentionally designed as a descriptive case series. Furthermore, as this is a single-surgeon, single-center experience, the generalizability of these findings to other institutions and patient populations may be limited. Larger prospective multicenter studies are warranted to validate these results. Additionally, the median follow-up was 22.5 months, precluding assessment of long-term oncologic outcomes and durability of aesthetic results.

Aesthetic outcomes were assessed through physical examination, standardized photography, and validated patient-reported outcome measures, such as the BREAST-Q. However, objective cosmetic assessment tools, such as BCCT.core (breast cancer conservative treatment: cosmetic results), which evaluates breast asymmetry, color discrepancy, scar appearance, and the position of the nipple-areola complex, were not used. This represents a limitation of the study, and future research should incorporate standardized objective cosmetic assessment tools to complement patient-reported outcomes.

The LICAP-based oncoplastic volume-replacement flap is a versatile, reproducible technique for partial breast reconstruction. Its multiple modifications enable wide excisions in the lateral and central breast quadrants while preserving thoracic and dorsal musculature and minimizing donor-site morbidity.

This approach can be performed immediately or in a delayed setting and may broaden the indications for BCS in selected patients. To our knowledge, this represents the first reported national experience, demonstrating encouraging early oncologic outcomes, postoperative complication rates, and operative times comparable to those reported in international series. These findings suggest that LICAP-based techniques represent a safe and reproducible strategy to expand BCS in evolving oncoplastic settings, with encouraging short-term oncologic and aesthetic outcomes. However, given the limited number of patients and the relatively short follow-up period, these findings should be interpreted with caution. Larger prospective multicenter studies with longer follow-up are needed to confirm long-term oncologic safety and validate these results.

Ethics

Ethics Committee Approval: The study was exempted from formal review by the Hospital Nacional Guillermo Almenara Irigoyen Ethics Committee of the Red Prestacional Almenara (ethics review no: 209, date: May 5, 2026).

Informed Consent: Patient data were strictly anonymized and handled confidentially, and standard informed consent for surgical procedures was obtained from all patients prior to treatment.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.C-D., C.C.C.L., H.N.S.P., W.M.G.O., J.F.T.A., M.d.R.C.P.; Concept: M.C-D., C.C.C.L., G.d.I.C.K., H.N.S.P., W.M.G.O., J.F.T.A., M.d.R.C.P.; Design: M.C-D., C.C.C.L., G.d.I.C.K., H.N.S.P., W.M.G.O., J.F.T.A., M.d.R.C.P.; Data Collection and/or Processing: M.C-D., C.C.C.L., G.d.I.C.K., J.F.T.A.; Analysis and/or Interpretation: M.C-D., C.C.C.L., G.d.I.C.K., H.N.S.P., W.M.G.O., J.F.T.A., M.d.R.C.P.; Literature Search: M.C-D., C.C.C.L., G.d.I.C.K., W.M.G.O., M.d.R.C.P.; Writing: M.C-D., C.C.C.L., G.d.I.C.K., H.N.S.P., W.M.G.O., J.F.T.A., M.d.R.C.P.

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A Rare Entity in Context: Breast Implant-Associated Anaplastic Large Cell Lymphoma Compared With Common Lymphoma Subtypes

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ABSTRACT

Objective: Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare CD30-positive, anaplastic lymphoma kinase (ALK)-negative peripheral T-cell lymphoma now recognized as a distinct entity in the 5th edition World Health Organization Classification of haematolymphoid tumors. Its clinicopathologic profile, treatment patterns, and outcomes, relative to those of other primary breast lymphomas, have not been characterized in large population-based comparative studies.

Materials and Methods: Using the Surveillance, Epidemiology and End Results (SEER) database (2017–2022), we identified patients with primary breast lymphoma based on ICD-O-3 site (C50.0–C50.9) and morphology codes for BIA-ALCL (9715/3), diffuse large B-cell lymphoma (DLBCL, 9680/3), extranodal marginal zone [mucosa-associated lymphoid tissue (MALT)] lymphoma (9699/3), and Burkitt lymphoma (BL, 9687/3). Baseline characteristics, treatment, overall survival (OS), and cancer-specific survival (CSS) were compared between BIA-ALCL and other mammary lymphomas.

Results: Two hundred fifty-two patients with BIA-ALCL were identified and compared with 185,019 patients with other mammary lymphomas. Patients with BIA-ALCL were younger than those with DLBCL and MALT, but older than those with BL (mean age 62.8 years, $p < 0.001$). BIA-ALCL demonstrated higher rates of surgical management and lower rates of radiotherapy compared with DLBCL and MALT. Chemotherapy utilization was intermediate among lymphoma subtypes. In unadjusted analyses, DLBCL was associated with worse OS [hazard ratio (HR) 1.46, 95% confidence interval (CI) 1.03–2.08] and CSS (HR 1.84, 95% CI 1.21–2.79) relative to BIA-ALCL; BL was associated with worse CSS (HR 2.08, 95% CI 1.37–3.16); MALT lymphoma showed better CSS (HR 0.54, 95% CI 0.35–0.81). Multivariable analysis yielded HRs that were not statistically distinguishable from those for BIA-ALCL, but estimates were imprecise (adjusted OS for DLBCL: HR 1.53, 95% CI 0.21–10.90; for BL: HR 2.66, 95% CI 0.37–19.20); these wide CIs reflect sparse events within the BIA-ALCL cohort and preclude conclusions about survival equivalence.

Conclusion: In this SEER-based analysis, breast-localized ALK-negative ALCL showed a distinct demographic and treatment profile characterized by surgical management, with favorable crude survival compared with that of DLBCL and BL. Early recognition and complete surgical excision remain central to the management of localized BIA-ALCL.

Keywords: Breast; lymphomas; breast implant-associated anaplastic large cell lymphoma; treatment; outcome

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KEY POINTS

- Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare CD30-positive, anaplastic lymphoma kinase (ALK)-negative peripheral T-cell lymphoma now recognized as a distinct entity in the 5th edition World Health Organization Classification of haematolymphoid tumors.
- Its clinicopathologic profile, treatment patterns, and outcomes relative to other primary breast lymphomas have not been characterized in large population-based comparative studies.
- In this Surveillance, Epidemiology and End Results-based analysis, breast-localized ALK-negative ALCL showed a distinct demographic and treatment profile characterized by surgical management, with a favorable crude survival compared with diffuse large B-cell lymphoma and Burkitt lymphoma.

Introduction

Primary breast lymphomas (PBLs) are rare extranodal malignancies, accounting for less than 1% of all non-Hodgkin lymphomas and a similarly small proportion of all breast cancers. Despite their rarity, they represent a clinically important entity due to their distinct biology, diagnostic challenges, and management strategies, which differ fundamentally from those of primary breast carcinomas (1, 2). Histologically, PBLs comprise a heterogeneous group of lymphoid neoplasms, most commonly diffuse large B-cell lymphoma (DLBCL), followed by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), with more aggressive subtypes such as Burkitt lymphoma (BL) occurring less frequently (3, 4). These subtypes exhibit substantial variability in clinical behavior, ranging from indolent, localized disease to rapidly progressive systemic malignancies, underscoring the need for subtype-specific diagnostic and therapeutic approaches.

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is now recognized as a distinct clinicopathologic entity in the 5th edition of the World Health Organization (WHO) Classification of haematolymphoid tumors (2022) and the International Consensus Classification, having been introduced as a provisional entity in the 2016 WHO revision. It is a mature CD30-positive, anaplastic lymphoma kinase (ALK)-negative peripheral T-cell lymphoma arising in association with breast implants (4, 5). Unlike conventional PBLs, which originate within breast parenchyma, BIA-ALCL typically develops in the peri-implant fluid or fibrous capsule and most commonly presents as a delayed seroma or capsular mass years after implantation (6). Immunophenotypically, it is characterized by uniform CD30 expression and absence of ALK rearrangement, distinguishing it from systemic forms of anaplastic large cell lymphoma (7).

The epidemiology of BIA-ALCL has evolved rapidly over the past decade, driven by increased awareness, improved diagnostic recognition, and the establishment of international registries. Accumulating evidence has identified a strong association between BIA-ALCL and textured-surface breast implants, with risk estimates varying widely but consistently demonstrating a markedly higher incidence compared with smooth implants (8, 9). Proposed pathogenic mechanisms emphasize the role

of chronic inflammation that is induced by bacterial biofilm formation on implant surfaces, leading to sustained immune activation and eventual malignant transformation of T-cell populations within the peri-implant microenvironment (10). Although the absolute risk remains low, the widespread use of breast implants globally has made BIA-ALCL an issue of growing clinical and public health significance.

BIA-ALCL tends to exhibit a more favorable clinical course than other mammary lymphomas when diagnosed at an early stage. Disease confined to the capsule or seroma is often effectively treated with complete surgical excision, including implant removal and total capsulectomy, which is associated with high rates of durable remission (11). In contrast, advanced disease with regional or systemic involvement may require multimodal therapy, including systemic chemotherapy and targeted agents such as brentuximab vedotin (12). These management strategies differ substantially from those employed in B-cell PBLs, where systemic chemoimmunotherapy and radiotherapy play a central role, reflecting fundamental differences in tumor biology.

Despite the expanding body of literature describing BIA-ALCL, most studies have focused on single-disease cohorts, case series, or registry-based incidence analyses. Direct comparative evaluations of BIA-ALCL and other primary mammary lymphomas remain limited. Such comparisons are critical for contextualizing its clinical behavior, clarifying whether its apparent survival advantage persists after accounting for confounding factors, and better defining its position within the broader spectrum of breast-associated lymphoid malignancies. Moreover, understanding similarities and differences in demographics, treatment patterns, and outcomes across lymphoma subtypes may inform risk stratification, optimize management strategies, and support evidence-based clinical decision-making.

Using the Surveillance, Epidemiology and End Results (SEER) database, we aimed to: (i) describe the demographic and clinicopathologic profile of breast-localized BIA-ALCL relative to primary breast DLBCL, MALT lymphoma, and BL; (ii) characterize first-course treatment patterns; and (iii) compare overall and cancer-specific survival (CSS) between subtypes, both before and after adjustment for measurable confounders. We did not seek to establish equivalence or non-inferiority in survival, and

we treated the BIA-ALCL cohort as code-based (ICD-O-3 9715/3, breast-localized) rather than implant-confirmed, since SEER does not capture implant exposure.

Materials and Methods

Study Design and Data Source

This retrospective population-based cohort study was conducted using data from the SEER database, a program of the National Cancer Institute that collects detailed information on cancer incidence, patient demographics, tumor characteristics, treatment, and survival outcomes across multiple U.S. registries.

Patient Selection and Cohort Definition

Patients with PBLs diagnosed between 1 January 2017 and 31 December 2022 were identified from SEER using SEER*Stat. Cases were restricted to those with the breast as the primary site (ICD-O-3 topography codes C50.0–C50.9) and to female patients. Histologic subtypes were defined by ICD-O-3 morphology codes: 9715/3 (used here as a proxy for BIA-ALCL), 9680/3 (DLBCL), 9699/3 (MALT lymphoma), and 9687/3 (BL). We acknowledge that ICD-O-3 code 9715/3 corresponds to anaplastic large cell lymphoma, ALK-negative, and is not specific to the implant-associated variant; SEER does not record implant exposure, surface texture, or capsule confinement. The 9715/3 cohort comprises breast-localized, ALK-negative ALCL cases, of which BIA-ALCL is the principal, but not the sole, contributor. Only microscopically confirmed cases were included. Patients identified solely through a death certificate or autopsy, as well as those with missing key demographic or survival data, were excluded.

Demographic variables extracted included age at diagnosis, sex, race, marital status, and median household income. Age was categorized into three groups: 18–49 years, 50–69 years, and ≥70 years. Clinical variables included laterality and sequence number, the latter categorized as single versus multiple primary malignancies. Treatment variables were defined according to SEER first-course therapy classifications and included surgery, radiotherapy, and chemotherapy, each recorded as received or not received. The SEER database does not provide details regarding the specific surgical procedure, the extent of axillary lymph node surgery, or the completeness of resection. Therefore, analyses were limited to surgery as a binary variable (performed vs. not performed).

Outcomes

The primary outcomes of interest were overall survival (OS) and CSS. OS was defined as the time from diagnosis to death from any cause or to the last follow-up. CSS was defined as the time from diagnosis to death attributable to lymphoma based on

the SEER cause-specific death classification. Survival time was measured in months.

Statistical Analysis

All statistical analyses were performed using Stata/SE version 18.5 (StataCorp, College Station, TX, USA). Descriptive statistics were used to summarize baseline characteristics. Categorical variables were reported as frequencies and percentages, while continuous variables were summarized as means with standard deviations.

Comparisons across lymphoma subtypes were conducted using Pearson's chi-squared test for categorical variables and one-way analysis of variance for continuous variables. A two-sided p -value <0.05 was considered statistically significant.

Survival outcomes were estimated using the Kaplan-Meier method, with differences between groups assessed using the log-rank test. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Within the BIA-ALCL cohort, univariate Cox regression was used to evaluate associations of demographic, clinical, and treatment variables with OS or CSS. To compare lymphoma subtypes, we fitted Cox proportional hazards models, both unadjusted and multivariable, with BIA-ALCL as the reference, and a priori adjusted for age category, race, marital status, income category, and receipt of surgery, radiotherapy, and chemotherapy. The proportional hazards assumption was assessed using scaled Schoenfeld residuals, and when it was violated, time-stratified models were fitted as sensitivity analyses. For CSS, we additionally performed competing-risks regression using the Fine-Gray subdistribution hazard model, treating death from non-lymphoma causes as the competing event. Given the small BIA-ALCL cohort relative to the comparator groups, model stability was examined by inspecting standard errors and CI widths; categorical levels with zero events were merged or excluded to avoid quasi-separation, and Firth's penalized likelihood was applied to univariable models with sparse cells. We did not perform formal equivalence or non-inferiority testing; non-significant HRs are therefore not interpreted as evidence of equivalent survival.

Results

Baseline Characteristics of the Cohort

A total of 185,271 patients were identified across the four diagnostic subgroups, including 252 with BIA-ALCL, 102,662 with DLBCL, 70,838 with MALT lymphoma, and 11,519 with BL. Baseline demographic and clinicopathologic characteristics are summarized in Table 1.

The mean age at diagnosis differed significantly across groups ($p<0.001$). Patients with BIA-ALCL had a mean age of 62.8 ± 14.5 years, comparable to DLBCL (65.3 ± 15.4 years) and MALT lymphoma (65.9 ± 13.9 years), and older than BL (50.8 ± 18.5 years). Within the BIA-ALCL cohort, most patients were aged 50–69 years (48.8%), followed by those ≥ 70 years (35.3%) and those aged 18–49 years (15.9%). In contrast, BL had the highest proportion of younger patients (49.7% aged 18–49 years).

Racial distribution differed significantly across subgroups ($p<0.001$). The majority of BIA-ALCL patients were categorized as “Other” race (71.4%), followed by White (23.4%) and Black (5.2%). A similar pattern was observed in the DLBCL, MALT lymphoma, and BL cohorts, with “Other” comprising approximately 55% of each group.

Marital status distributions were comparable among patients with BIA-ALCL (56.8% married), DLBCL (55.8% married), and

MALT lymphoma (55.4% married); by contrast, patients with BL had a higher proportion of unmarried patients (52.0%). Median household income was similar across all groups, with most patients falling within the \$40,000–120,000 range (BIA-ALCL: 88.5%; DLBCL: 87.8%; MALT lymphoma: 92.5%; BL: 90.5%). A greater proportion of BIA-ALCL patients was in the $>\$120,000$ income category (11.1%) than in other subgroups (range: 4.7–6.7%).

Laterality was unknown in the majority of cases across all groups (74.2% in BIA-ALCL). Among patients with known laterality, left-sided involvement was slightly more frequent than right-sided involvement in BIA-ALCL (13.1% vs. 12.3%). Most BIA-ALCL cases were a single primary malignancy (67.1%), while 32.9% had two or more primaries; this proportion was higher than that observed in BL (18.2%) and comparable to that observed in MALT lymphoma (35.8%).

Table 1. Demographic and clinicopathologic characteristics of BIA-ALCL v/s DLBCL v/s MALT v/s BL

Parameter		BIA-ALCL (252)	DLBCL (102,662)	MALT (70,838)	BL (11,519)	p-value
Age	Mean $\pm$ SD	62.8 $\pm$ 14.5	65.3 $\pm$ 15.4	65.9 $\pm$ 13.9	50.8 $\pm$ 18.5	<0.001
	18–49	40 (15.9)	16,626 (16.2)	8,964 (12.7)	5,720 (49.7)	<0.001
	50–69	123 (48.8)	38,517 (37.5)	30,319 (42.8)	3,511 (30.5)	
	≥ 70	89 (35.3)	47,519 (46.3)	31,555 (44.6)	2,288 (19.9)	
Race	Black	13 (5.2)	3,248 (3.2)	2,668 (3.8)	522 (4.5)	<0.001
	White	59 (23.4)	42,462 (41.4)	28,360 (40.0)	4,611 (40.0)	
	Other	180 (71.4)	56,784 (55.3)	39,370 (55.6)	6,373 (55.3)	
	Unknown	0 (0.0)	168 (0.2)	440 (0.6)	13 (0.1)	
Marital status	Married	143 (56.8)	57,286 (55.8)	39,251 (55.4)	5,118 (44.4)	<0.001
	Other	94 (37.3)	40,521 (39.5)	25,161 (35.5)	5,993 (52.0)	
	Unknown	15 (6.0)	4,855 (4.7)	6,426 (9.1)	408 (3.5)	
Median household income	<\$40,000	1 (0.4)	906 (0.9)	496 (0.7)	73 (0.6)	<0.001
	\$40,000–120,000	223 (88.5)	90,090 (87.8)	65,543 (92.5)	10,422 (90.5)	
	>\$120,000	28 (11.1)	5,599 (5.5)	4,773 (6.7)	544 (4.7)	
	Unknown	0 (0.0)	6,067 (5.9)	26 (0.0)	480 (4.2)	
Laterality	Left	33 (13.1)	6,703 (6.5)	8,951 (12.6)	370 (3.2)	<0.001
	Right	31 (12.3)	7,072 (6.9)	9,681 (13.7)	364 (3.2)	
	Bilateral	0 (0.0)	846 (0.8)	1,584 (2.2)	81 (0.7)	
	Paired side	1 (0.4)	609 (0.6)	613 (0.9)	51 (0.4)	
	Only one side, side unspecified	0 (0.0)	51 (0.1)	67 (0.1)	4 (0.0)	
	Unknown	187 (74.2)	87,381 (85.1)	49,942 (70.5)	10,649 (92.5)	
Sequence number	Only one primary	169 (67.1)	73,966 (72.1)	45,484 (64.2)	9,418 (81.8)	<0.001
	Two or more primaries	83 (32.9)	28,696 (28.0)	25,350 (35.8)	2,101 (18.2)	
	Unknown	0 (0.0)	0 (0.0)	4 (0.0)	0 (0.0)	

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; MALT: Mucosa-associated lymphoid tissue; BL: Burkitt lymphoma; SD: Standard deviation

Treatment Modalities

Treatment patterns are detailed in Table 2. Surgical intervention was performed in 31.4% of patients with BIA-ALCL, a higher rate than in patients with DLBCL (24.5%), MALT lymphoma (26.7%), and BL (24.3%) ($p < 0.001$). Radiotherapy was utilized in 12.7% of BIA-ALCL cases, compared with 20.7% in DLBCL, 23.6% in MALT lymphoma, and 10.4% in BL ($p < 0.001$). Among BIA-ALCL patients, radiotherapy was most commonly administered postoperatively (4.0%). Chemotherapy was administered to 65.9% of BIA-ALCL patients, representing an intermediate rate compared with those in DLBCL (74.6%), BL (84.2%), and MALT lymphoma (25.1%) ($p < 0.001$). Postoperative chemotherapy was more frequently observed in BIA-ALCL (16.7%) than in DLBCL (9.9%), MALT lymphoma (4.3%), and BL (10.7%).

Survival Outcomes

At the last follow-up, 80.2% of BIA-ALCL patients were alive, compared with 37.3% of DLBCL patients, 59.4% of MALT lymphoma patients, and 41.5% of BL patients ($p < 0.001$). Cancer-specific mortality occurred in 13.1% of BIA-ALCL patients, compared with 40.9% of DLBCL patients, 13.7% of MALT lymphoma patients, and 47.1% of BL patients. Mean survival time for BIA-ALCL was 71.8 ± 6.5 months. Corresponding mean survival times were 63.6 ± 78.4 months for DLBCL, 86.4 ± 70.4 months for MALT lymphoma, and 63.2 ± 82.9 months for BL ($p < 0.001$).

Univariate Analysis in BIA-ALCL

Univariate analyses of prognostic factors within the BIA-ALCL cohort are presented in Tables 3 and 4. Age ≥ 70 years was significantly associated with worse OS compared with the 18–49 year reference group (HR 8.55, 95% CI 1.13–64.77; $p = 0.038$). A similar trend was observed for CSS (HR 5.60, 95% CI 0.72–43.73; $p = 0.101$), although this did not reach statistical significance. Age 50–69 years was not significantly associated with OS or CSS. Race, marital status, laterality, and sequence number (single vs. multiple primaries) were not significantly associated with either of the survival outcomes. Among treatment variables, absence of chemotherapy was associated with worse CSS (HR 2.42, 95% CI 1.05–5.60; $p = 0.038$). Surgical treatment was not significantly associated with OS (HR 1.33; $p = 0.467$) or CSS (HR 1.47; $p = 0.419$).

Comparative Survival Analysis

Comparative survival analyses relative to BIA-ALCL are summarized in Table 4 and Figure 1. In unadjusted analyses, DLBCL was associated with worse OS compared with BIA-ALCL (HR 1.46, 95% CI 1.03–2.08; $p = 0.035$), while MALT lymphoma and BL did not show statistically significant differences in OS.

In unadjusted CSS analyses, DLBCL (HR 1.84, 95% CI 1.21–2.79; $p = 0.004$) and BL (HR 2.08, 95% CI 1.37–3.16; $p = 0.001$) were associated with worse outcomes compared with BIA-ALCL,

Table 2. Treatment modalities (surgery, chemotherapy, radiotherapy) and survival outcomes of BIA-ALCL v/s DLBCL v/s MALT v/s BL

Parameter		BIA-ALCL (252)	DLBCL (102,662)	MALT (70,838)	BL (11,519)	p-value
Surgery	Performed	79 (31.4)	25,172 (24.5)	18,926 (26.7)	2,794 (24.3)	<0.001
	Not performed	171 (67.9)	76,149 (74.2)	51,356 (72.5)	8,611 (74.8)	
	Unknown	2 (0.8)	1,341 (1.3)	556 (0.8)	114 (1.0)	
Radiotherapy	Yes	32 (12.7)	21,241 (20.7)	16,706 (23.6)	1,199 (10.4)	<0.001
	No	0 (0.0)	515 (0.5)	378 (0.5)	18 (0.2)	
	Unknown	220 (87.3)	80,906 (78.8)	53,754 (75.9)	10,302 (89.4)	
Chemotherapy	Yes	166 (65.9)	76,545 (74.6)	17,755 (25.1)	9,702 (84.2)	<0.001
	No	86 (34.1)	26,117 (25.4)	53,083 (74.9)	1,817 (15.8)	
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Cause of death	Alive	202 (80.2)	38,297 (37.3)	42,079 (59.4)	4,784 (41.5)	<0.001
	Breast cancer	33 (13.1)	41,957 (40.9)	9,700 (13.7)	5,428 (47.1)	
	Other	17 (6.7)	22,408 (21.8)	19,059 (26.9)	1,307 (11.4)	
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Survival months	Mean $\pm$ SD	71.8 ± 6.5	63.6 ± 78.4	86.4 ± 70.4	63.2 ± 82.9	<0.001
	Unknown	0 (0.0)	333 (0.3)	38 (0.1)	42 (0.4)	

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; MALT: Mucosa-associated lymphoid tissue; BL: Burkitt lymphoma; SD: Standard deviation

Table 3. Univariate analysis of demographic risk factors affecting overall survival and cancer-specific survival of BIA-ALCL

Parameter		Overall survival		Cancer-specific survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	18–49	Reference		Reference	
	50–69	5.12 (0.68–38.75)	0.114	3.75 (0.48–29.02)	0.206
	≥70	8.55 (1.13–64.77)	0.038	5.60 (0.72–43.73)	0.101
Race	Black	Reference		Reference	
	White	1.99 (0.25–16.24)	0.519	1.70 (0.20–14.14)	0.625
	Other	1.41 (0.19–10.49)	0.739	0.99 (0.13–7.51)	0.990
Marital status	Married	Reference		Reference	
	Other	0.74 (0.35–1.54)	0.415	0.76 (0.32–1.82)	0.545
Median household income	<\$40,000	Reference		Reference	
	\$40,000–120,000	2.46e+07 (–.)	.	2.47e+07 (–.)	.
	>\$120,000	2.16e+07 (–.)	.	2.08e+07 (–.)	.

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; HR: Hazard ratio; CI: Confidence interval

Table 4. Univariate analysis of clinicopathologic risk factors and treatment modalities affecting overall survival and cancer-specific survival of BIA-ALCL

Parameter		Overall survival		Cancer-specific survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Laterality	Left	Reference		Reference	
	Right	5.20 (0.61–44.57)	0.132	4.19 (0.47–37.57)	0.200
	Bilateral	. (–.)	.	. (–.)	.
	Paired side	5.59e-16 (–.)	.	3.59e-15 (–.)	.
	Only one side, side unspecified	. (–.)	.	. (–.)	.
Sequence number	Only one primary	Reference		Reference	
	Two or more primaries	1.65 (0.81–3.36)	0.172	0.84 (0.33–2.16)	0.725
Surgery	Performed	Reference		Reference	
	Not performed	1.33 (0.61–2.90)	0.467	1.47 (0.58–3.77)	0.419
Radiotherapy	Yes	Reference		Reference	
	No	. (–.)	.	. (–.)	.
Chemotherapy	Yes	Reference		Reference	
	No	1.58 (0.76–3.26)	0.217	2.42 (1.05–5.60)	0.038

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; HR: Hazard ratio; CI: Confidence interval

whereas MALT lymphoma was associated with improved CSS (HR 0.54, 95% CI 0.35–0.81; $p = 0.003$).

In multivariable models adjusted for age category, race, marital status, income, and treatment, the point estimates for OS were attenuated for DLBCL (adjusted HR 1.53, 95% CI 0.21–10.90; $p = 0.671$), MALT lymphoma (adjusted HR 0.56, 95% CI 0.08–4.00; $p = 0.564$), and BL (adjusted HR 2.66, 95% CI 0.37–19.20; $p = 0.331$). The corresponding adjusted HRs for CSS were 0.85 (95% CI 0.12–6.05; $p = 0.868$) for DLBCL, 0.15 (95% CI 0.02–1.05; $p = 0.056$) for MALT lymphoma, and 1.60 (95% CI 0.22–11.68; $p = 0.641$) for BL. CIs spanning 50- to 100-fold reflect the small number of events

within the BIA-ALCL reference cohort relative to the number of estimated parameters, and the presence of substantial sparse-data bias; these estimates are statistically unstable and should not be interpreted as evidence of equivalent survival across subtypes.

Discussion and Conclusion

In this SEER-based comparative analysis, breast-localised ALK-negative ALCL—used here as a registry proxy for BIA-ALCL—differed from primary breast DLBCL, MALT lymphoma, and BL in demographic profile, treatment composition, and crude survival. Surgery was the dominant first-course modality;

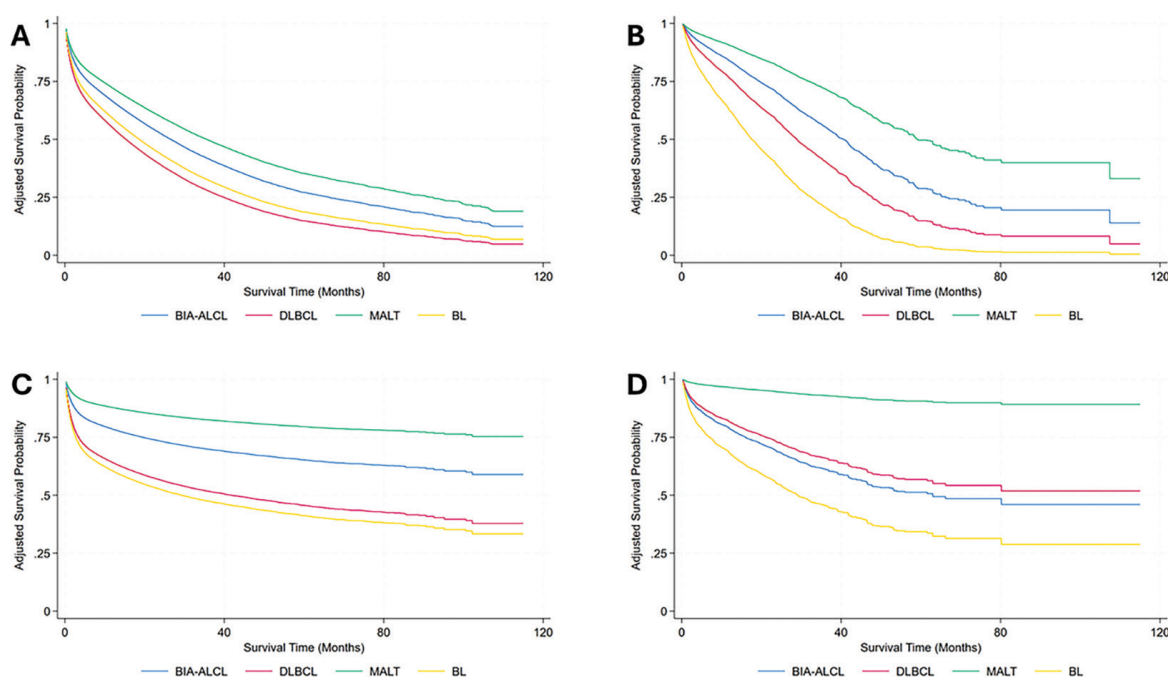


Figure 1. Comparative survival analysis of primary mammary lymphoma subtypes relative to BIA-ALCL. (A) Unadjusted Cox proportional hazards analysis comparing overall survival across lymphoma subtypes, with BIA-ALCL as the reference group. DLBCL: HR 1.46 (95% CI 1.03–2.08), $p = 0.035$; MALT lymphoma: HR 0.80 (95% CI 0.56–1.13), $p = 0.209$; BL: HR 1.29 (95% CI 0.90–1.83), $p = 0.164$. (B) Multivariable-adjusted Cox proportional hazards analysis of overall survival, with BIA-ALCL as the reference group. DLBCL: HR 1.53 (95% CI 0.21–10.90), $p = 0.671$; MALT lymphoma: HR 0.56 (95% CI 0.08–4.00), $p = 0.564$; BL: HR 2.66 (95% CI 0.37–19.20), $p = 0.331$. (C) Unadjusted Cox proportional hazards analysis of cancer-specific survival, with BIA-ALCL as the reference group. DLBCL: HR 1.84 (95% CI 1.21–2.79), $p = 0.004$; MALT lymphoma: HR 0.54 (95% CI 0.35–0.81), $p = 0.003$; BL: HR 2.08 (95% CI 1.37–3.16), $p = 0.001$. (D) Multivariable-adjusted Cox proportional hazards analysis of cancer-specific survival, with BIA-ALCL as the reference group. DLBCL: HR 0.85 (95% CI 0.12–6.05), $p = 0.868$; MALT lymphoma: HR 0.15 (95% CI 0.02–1.05), $p = 0.056$; BL: HR 1.60 (95% CI 0.22–11.68), $p = 0.641$

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; HR: Hazard ratio; CI: Confidence interval; MALT: Mucosa-associated lymphoid tissue; BL: Burkitt lymphoma

radiotherapy was used sparingly, and chemotherapy was used at an intermediate level. Crude OS and CSS estimates appeared superior in the BIA-ALCL cohort, but these differences were attenuated and were no longer statistically significant after multivariable adjustment. We caution against interpreting non-significance as biological or clinical equivalence: CIs for adjusted HRs span more than a 50-fold range in several cases, reflecting sparse events and an unstable variance structure rather than true similarity in prognosis. The four entities differ fundamentally in cell of origin, mutational landscape, treatment paradigm, and natural history; a registry that does not capture stage, implant exposure, or treatment intensity cannot adjudicate their relative prognoses.

Several population-based studies have utilized the SEER database to investigate PBLs, consistently demonstrating the rarity of this disease. Peng et al. identified 1,427 patients with PBL diagnosed

between 1975 and 2011, while other SEER-based analyses focusing on specific histological subtypes, such as primary breast DLBCL, have reported cohorts ranging from approximately 800 to 1,000 patients (13, 14). Our study builds upon these prior investigations by evaluating BIA-ALCL, DLBCL, MALT lymphoma, and BL comparatively within a contemporary SEER cohort.

The age distribution observed in this study is consistent with existing literature describing BIA-ALCL as a disease primarily affecting middle-aged and older women, typically presenting several years after breast implants. Large cohort studies and systematic reviews have reported a median age at diagnosis ranging from the fifth to sixth decades of life, with a latency period often exceeding 8–10 years following the implantation (7, 8). In contrast, BL demonstrated a younger age profile in our cohort, which aligns with its known epidemiology as an aggressive, high-grade lymphoma that more commonly affects

younger individuals and immunocompromised populations (15). DLBCL and MALT lymphomas showed older age distributions, consistent with the increasing incidence of B-cell lymphomas with advanced age (4).

The observed socioeconomic distribution, with a greater proportion of BIA-ALCL patients in higher-income brackets, likely reflects the sociodemographic composition of the population undergoing cosmetic or reconstructive breast implantation rather than indicating a direct biological association. Prior epidemiological studies have highlighted that BIA-ALCL is more frequently reported in regions with higher rates of breast implant utilization, particularly in developed countries with established cosmetic surgery practices (9). While socioeconomic status was not independently associated with survival in this study, disparities in access to specialized surgical care and early diagnosis may still influence outcomes and warrant further investigation.

Management patterns in this study reinforce the central role of surgery in BIA-ALCL. The higher rate of surgical treatment, compared with other lymphoma subtypes, is consistent with current consensus guidelines, which recommend complete surgical excision, including total capsulectomy and implant removal, as the cornerstone of therapy for localized disease. Multiple studies have demonstrated that complete surgical resection is associated with excellent long-term outcomes and may be curative in early-stage disease (11). In contrast, systemic therapy is reserved for patients with advanced disease, nodal involvement, or incomplete resection. The intermediate rate of chemotherapy use observed in this cohort likely reflects this risk-adapted approach. Notably, targeted therapies such as brentuximab vedotin have shown efficacy in relapsed or advanced CD30-positive T-cell lymphomas, including ALCL (12).

Radiotherapy utilization was lower in BIA-ALCL than in B-cell lymphomas, consistent with differences in disease biology and treatment paradigms. MALT lymphoma, in particular, is highly radiosensitive and often treated with involved-site radiotherapy in early-stage disease, achieving excellent local control rates (16, 17). In contrast, radiotherapy plays a limited role in BIA-ALCL and is generally reserved for residual or unresectable disease. These differences further underscore that BIA-ALCL requires a distinct therapeutic approach compared with other PBLs.

The higher proportion of patients alive at follow-up in the BIA-ALCL cohort likely reflects a combination of earlier clinical presentation, effective surgical management, and favorable tumor biology. BIA-ALCL most commonly presents as a delayed peri-implant seroma, prompting early clinical evaluation and facilitating diagnosis at a localized stage (7). This contrasts with other lymphoma subtypes, which may present with systemic disease or more aggressive clinical features. However, the

attenuation of survival differences after adjustment highlights the importance of confounding variables, particularly age, treatment modality, and disease extent. These findings suggest that when appropriately treated, patients with different primary mammary lymphoma subtypes may have comparable outcomes.

Within the BIA-ALCL subgroup, advanced age was associated with worse OS, consistent with broader oncologic data demonstrating poorer outcomes in older adults due to comorbidities, reduced treatment tolerance, and competing mortality risks. The association between lack of chemotherapy and worse CSS should be interpreted with caution. While it may suggest a benefit of systemic therapy in higher-risk patients, this finding is likely influenced by selection bias inherent in retrospective analyses, as patients who do not receive chemotherapy may differ significantly in disease severity or fitness for treatment.

This study has several limitations. The most consequential issue is case ascertainment: the ICD-O-3 morphology code 9715/3 captures all anaplastic large cell lymphomas of ALK-negative type, of which BIA-ALCL is the principal but not exclusive subset. SEER does not record implant exposure, implant surface (textured vs. smooth), implant manufacturer, latency from implantation, or whether the disease was confined to the peri-implant capsule. The 252-case cohort almost certainly admixes implant-associated and sporadic ALK-negative ALCL of the breast, and we cannot separate them. Independent registries such as the PROFILE registry (US) and the Australian BIA-ALCL registry, which collect implant-specific data, provide more accurate incidence and outcome estimates, and should be considered the gold-standard data sources for definitive comparisons. A second, consequential limitation is that the study window (2017–2022) straddles the July 2019 food and drug administration (FDA)-requested global recall of Allergan Biocell textured implants and the associated increase in patient and clinician awareness; both the ascertainment of incidence and treatment patterns may differ between pre- and post-recall periods. Third, SEER is subject to inherent biases, including missing data, misclassification, and limited availability of clinical variables. Several important parameters, such as implant characteristics (e.g., textured versus smooth surfaces), duration of implantation, and detailed staging information were not available for BIA-ALCL patients. This is particularly relevant given the well-established association between textured implants and increased risk of BIA-ALCL (9, 10). Additionally, information on specific treatment regimens, completeness of surgical excision, and disease recurrence was not captured, which limited the ability to perform more detailed analyses of outcomes. Despite these limitations, the population-based design provides valuable comparative insights across rare lymphoma subtypes.

Several research priorities follow from these findings. First, linkage between SEER and prospective implant-exposure registries (PROFILE, national breast implant registry, Australian BIA-ALCL registry) would allow distinguishing implant-associated from sporadic ALK-negative ALCL of the breast and enable accurate estimation of incidence stratified by latency, manufacturer, and texture. Second, the TNM-based BIA-ALCL staging system proposed by Clemens and colleagues should be uniformly applied to enable stage-adjusted survival comparisons. Third, characterization of recurrent driver mutations (JAK1, STAT3, DNMT3A, TP53) and their relationship to bacterial biofilm composition would clarify the mechanism of T-cell lymphomagenesis in the peri-implant microenvironment and identify candidates for targeted therapy beyond brentuximab vedotin. Finally, era-stratified analyses comparing periods before and after 2019 (when the FDA-requested global recall of Allergan Biocell textured implants altered both exposure and ascertainment) are essential for interpreting incidence trends and treatment patterns.

BIA-ALCL is a biologically distinct, CD30-positive, ALK-negative peripheral T-cell lymphoma, now formally recognized in the WHO-HAEM5 classification. In this population-based analysis, the breast-localized ALK-negative ALCL cohort (used as a SEER proxy for BIA-ALCL) showed a demographic and treatment profile dominated by surgical management, with an apparently favorable crude survival relative to primary breast DLBCL and BL. Adjusted comparisons were inconclusive: CIs were too wide to support claims of superiority or equivalence, and lack of statistical significance should not be interpreted as evidence that survival outcomes are similar across these biologically distinct entities. Complete surgical excision with total capsulectomy remains the cornerstone of management for capsule-confined disease, and brentuximab vedotin-based regimens have an established role in advanced disease. The most pressing methodological gap is the absence of implant-specific variables in SEER; definitive comparative outcome studies will require linkage between cancer registries and prospective implant-exposure registries such as PROFILE and the national breast implant registry.

Ethics

Ethics Committee Approval: The study used the anonymized data from the Surveillance, Epidemiology, and End Results (SEER) Program. Since no identifiable patient information is accessed, ethics committee approval are not required. The corresponding author signed a data-use agreement with the SEER (no: SEER-ID: 17257-Nov2018, date: October 24, 2019).

Informed Consent: Not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.T., O.T., M.M.A., R.B., S.A.A., G.R.B., S.V.; Concept: O.T., G.R.B., S.V.; Design: D.T., O.T., G.R.B., S.V.; Data Collection or Processing: D.T., O.T., G.R.B., S.V.; Analysis or Interpretation: D.T., O.T., M.M.A., R.B., S.A.A., G.R.B., S.V.; Literature Search: D.T., O.T., G.R.B., S.V.; Writing: D.T., O.T., G.R.B., S.V.

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Endoscopic and Robotic Minimally Invasive Breast Surgery (MIBS) for Benign Breast Lesions: Our Experience of 80 Cases and Descriptive Comparison

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ABSTRACT

Objective: Minimally invasive breast surgery (MIBS) via an extramammary approach offers an alternative to conventional open lumpectomy, eliminating breast scarring and improving psychological outcomes in patients with benign breast lesions. While endoscopic MIBS (EMIBS) has been described, data on robotic MIBS (RMIBS) are sparse. We analyzed the clinical and cosmetic outcomes of EMIBS and RMIBS.

Materials and Methods: Eighty patients undergoing MIBS for benign breast lumps were divided into endoscopic ($n = 40$) and robotic ($n = 40$) groups. Primary endpoints included cosmetic outcomes [evaluated via Patient and Observer Scar Assessment Scale (POSAS) and BREAST-Q], total operative and docking times, and complications, which were statistically analysed (IBM SPSS Statistics version 30).

Results: Groups were comparable in age ($p = 0.325$), lesion size (median 2.0 vs. 2.75 cm; $p = 0.247$), and number of lumps (median 1 in both groups; $p = 0.165$). Operative time analysis showed that operative time was significantly longer in the robotic group (median 150 vs. 95 minutes; $p < 0.001$). Complications were minor, self-resolving, and comparable across both groups (Fisher's exact $p = 0.647$). Cosmetic outcomes (at 1 month) were comparable between the two groups: median POSAS score 2 and median BREAST-Q score 88 (breast-conserving therapy module, satisfaction with breasts subscale). A subjective reduction in physical strain on the surgeon was noted in the robotic group; no objective ergonomic measurements were performed.

Conclusion: We demonstrate the feasibility and safety of both approaches for benign breast lesions, with comparable and favorable cosmetic outcomes, and with the robotic platform offering subjective improvement in ergonomic strain, especially in difficult-to-access medial quadrants. These findings are hypothesis-generating and require validation using instruments such as NASA-TLX or the Borg CR-10 scale in larger studies.

Keywords: Benign breast lumps; breast surgery; endoscopic breast surgery; minimally invasive breast surgery; robotic breast surgery

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KEY POINTS

- Our series of 80 patients provides insight into minimally invasive breast surgery (MIBS) and compares the two modalities—endoscopic and robotic—in the context of benign breast lesions.
- Both modalities offer comparable aesthetic outcomes and have similar complication profiles.
- Robotic MIBS is safe and feasible; despite having longer operating times, it offers relative subjective reductions in ergonomic strain.
- Robotic surgery provides wristed articulation, enabling dissection of difficult-to-access medial-quadrant lesions with relative ease.

Introduction

Benign breast lumps, including fibroadenomas, epithelial proliferation, and fibrocystic changes, are the most common breast pathologies in young women, with incidence peaking between the ages of 25 and 40. In India, 82% of premenopausal and 38% of postmenopausal women with breast lumps have benign breast disease (1). The 2025 American Society of Breast Surgeons (ASBrS) guidelines recommend excision for lesions exhibiting discordant imaging, substantive growth, a size >4–6 cm, or suspicion of phyllodes tumor (PT), and for symptomatic relief or patient preference.

Historically, open lumpectomy has been the standard of care, involving anterior access via periareolar, radial, or circular incisions and division of the breast parenchyma; although effective, this approach causes visible scarring, prolongs recovery, and results in patient dissatisfaction with cosmetic outcomes. A small subset will also have resultant breast asymmetry, especially when lumps are >5 cm (2, 3). Poorer aesthetic outcomes following traditional surgery for benign breast disease often lead to a desire for subsequent reconstructive surgery (3-5). Minimally invasive breast surgery (MIBS) employing endoscopic and robotic techniques has emerged as a potential alternative for addressing these limitations. MIBS was first described in 1995 (6), and developed in East Asia for the removal of benign and malignant tumors (7-10). Studies have reported excellent cosmetic outcomes and quality of life on subsequent follow-up, with minimal complications.

Despite the excellent cosmesis offered by MIBS, working within the confined retromammary space is technically challenging, because standard endoscopic instruments lack articulation, and 2D visualization limits depth perception, leading to suboptimal ergonomics and increased physical strain for the operator. The advent of robotic surgery offers potential solutions to these limitations via 3D high-definition visualization, tremor filtration, and instruments with seven degrees of freedom.

Studies comparing endoscopic and robotic approaches have predominantly discussed nipple-sparing mastectomy (NSM) (11, 12). Limited data exist on robotic breast lumpectomy for benign disease, and comparisons between endoscopic MIBS (EMIBS) and robotic MIBS (RMIBS) are sparse. This study aims to evaluate patients undergoing EMIBS and RMIBS, analyze cosmetic

efficacy, perioperative safety, and operative times, and detail our experience with surgeon ergonomics across the 2 modalities.

Materials and Methods

A comparative study analyzed 80 female patients who underwent MIBS for benign breast lesions. The cohort was divided into two groups: endoscopic ($n = 40$) and robotic ($n = 40$). Allocation was done temporarily: we performed EMIBS exclusively until the acquisition of a surgical robot; thereafter, we performed only RMIBS. Group assignment was not determined by randomization, patient preference, surgeon case selection, or lesion size. The study was approved by the Institutional Ethics Committee of St John's Medical College Hospital (IEC no: IEC/1/1246/2025; IEC study ref no: 175/2025; date: 10 September 2025) and written informed consent was obtained from the patients.

Patients aged 18 years and above who underwent MIBS in the department of surgical oncology at our institute for benign breast lumps (confirmed by ultrasound and fine-needle aspiration cytology) were included in the study. Patients undergoing MIBS for malignant etiologies, including robotic NSM, and patients under 18 years were excluded, as were cases of minimally invasive Hadfield's procedure. Inclusion criteria were aligned with 2025 ASBrS guidelines for benign fibroepithelial lesion (FEL) excision (13).

All procedures were performed under general anesthesia by a single surgeon (R.S.R.). Our technique involved a 4-cm axillary incision parallel to the midaxillary line and the creation of working space after identification of the lateral borders of the latissimus dorsi and the pectoralis major, which serve as major landmarks for appropriate placement of the access port to ensure ergonomic placement (Figure 1b). The GelPoint Advanced Access Platform (Applied Medical, Inc., Rancho Santa Margarita, CA, USA) was inserted to facilitate single-incision endoscopic surgery. Lumpectomy was performed after development of the prepectoral plane, either endoscopically or robotically. We used the Stryker 1588 platform (Stryker Corp., Kalamazoo, MI, USA) for EMIBS, along with a 30-degree, 10-mm camera, a laparoscopic monopolar spatula, and a grasper. RMIBS was performed using the DaVinci X platform (Intuitive Surgical, Sunnyvale, CA, USA), and we used monopolar hot shears, fenestrated bipolar, and a 0-degree endoscope (Figures 1c, 1d). Indocyanine green (ICG)

was administered, and the FireFly mode on the DaVinci platform was used to visualize the lesion boundaries. Specimen extraction was followed by hemostasis, lavage, and layered wound closure (Figure 1e). A sterile pressure dressing was applied and was changed on postoperative day 2.

Primary endpoints included cosmetic outcomes at 1 month, operative time, blood loss, and complications. Operative time was measured in minutes from skin incision to closure. For RMIBS, total operative time was subdivided into the docking time and console time. Cosmetic outcomes were evaluated at 1 month postoperatively using the Patient and Observer Scar Assessment Scale (POSAS) for scar quality and the BREAST-Q questionnaire (breast conservation therapy module, satisfaction with breast subscale) for breast satisfaction. Observer POSAS scoring was not blinded with respect to surgical modality, as blinding was not feasible in this single-surgeon, single-centre retrospective setting. Only the satisfaction with breast subscale was administered, because it most directly captured our aesthetic endpoint of interest, satisfaction with breasts after MIBS. Follow-up was recorded for 6 months postoperatively; patients who had not yet reached the 6-month follow-up were treated as censored observations. Subjective assessment of physical strain on the surgeon and ergonomic difficulty were recorded.

Statistical Analysis

Data were entered into an Microsoft Excel file and statistically analyzed using IBM SPSS Statistics version 30 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and described in terms of range; mean $\pm$ standard deviation, median (interquartile range), frequencies (number of cases) and relative frequencies (percentages) as appropriate. Quantitative variables were compared using the Student's *t*-test for independent samples for parametric data and the Mann-Whitney *U* test for independent samples for non-parametric data, respectively, along with 95% confidence intervals (CIs) (Hodges-Lehman estimator for non-parametric and Welch correction for parametric comparisons). Categorical variables (complications) were compared with Fisher's exact test. Operative time was compared only between unilateral procedures ($n = 38$ endoscopic, $n = 36$ robotic) because bilateral cases involve two separate lesion excisions and are not directly comparable. Bilateral cases ($n = 6$; 2 endoscopic, 4 robotic) were retained in the overall cohort and reported descriptively. To address potential confounding by lesion size and to mitigate the possibility of bias (especially since the surgeon gains considerable experience with endoscopic technique before beginning the robotic cases), multivariable linear regression was performed for unilateral cases, with a 1:1 nearest-neighbour propensity-score-matched analysis for confirmation. Because allocation was strictly temporal, surgeon experience was structurally collinear with modality and could not be entered

as an independent covariate; matching and regression therefore addressed confounding by lesion size rather than temporal drift and were interpreted as sensitivity analyses. Follow-up was analysed using Kaplan-Meier estimation and the log-rank test, accounting for ongoing follow-up in the more recently operated robotic cohort. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Eighty patients were included ($n = 40$ endoscopic; $n = 40$ robotic). Age (mean 36.00 ± 9.47 vs. 38.28 ± 11.03 years; $p = 0.325$; 95% CI -6.85 to $+2.30$), lesion size (median 2.0 vs. 2.75 cm; $p = 0.247$), and number of lumps (median 1 in both groups; $p = 0.165$) were comparable across both groups. A total of 6 bilateral procedures were performed (2 endoscopic, 4 robotic) and excluded from the operative-time comparison. Among unilateral cases ($n = 38$ endoscopic, $n = 36$ robotic), operative times were significantly longer in the robotic group (median 150 vs. 95 minutes; $p < 0.001$, 95% CI -65 to -35 min). After adjusting for lesion size, RMIBS remained independently associated with longer operative time ($+42.8$ min; 95% CI, 26.1–59.5; $p < 0.001$); lesion size was not significant ($p = 0.379$). A propensity-matched analysis was concordant, showing a mean difference of $+43.9$ min (95% CI 25.9–62.0; $p < 0.001$). In the robotic group, mean docking time was 11.60 ± 4.18 minutes ($n = 40$, range 5–20). Systematic recording of console time commenced from the 14th case and was captured in 21 of the subsequent 27 procedures; the recorded values therefore derive disproportionately from later cases and averaged 80.29 ± 42.96 minutes (range 23–170) (Table 1). Comparison of operative times between the first and last 19 unilateral endoscopic cases and the first and last 18 robotic unilateral consecutive cases showed no significant difference (endoscopic median 95 vs. 95 min; $p = 0.735$; robotic median 152 vs. 150 minutes; $p = 0.27$). Estimated blood loss was less than 30 mL in all cases, and no conversions to open surgery occurred.

Cosmetic outcomes at 1 month were comparable between groups: POSAS observer score median 2 in both groups (mean 1.80 ± 0.69 vs. 1.70 ± 0.61 ; $p = 0.548$); BREAST-Q satisfaction with breast score median 88 in both groups (mean 88.50 ± 6.29 vs. 90.50 ± 5.97 ; $p = 0.100$) (Table 1, Figures 1a, 1f–3).

Overall, 42.5% of patients in the endoscopic group ($n = 17$) and 35% of patients in the robotic group ($n = 14$) experienced at least one complication (Fisher's exact $p = 0.647$) (Table 2). Minor complications included transient peri-incisional numbness (endoscopic $n = 3$, 7.5%; robotic $n = 4$, 10%), mild bruising (endoscopic $n = 5$, 12.5%; robotic $n = 5$, 12.5%), and subcutaneous emphysema (endoscopic $n = 7$, 17.5%; robotic $n = 6$, 15%), all resolving spontaneously (Clavien-Dindo I). In the endoscopic subgroup, One patient each developed a skin burn of the breast,

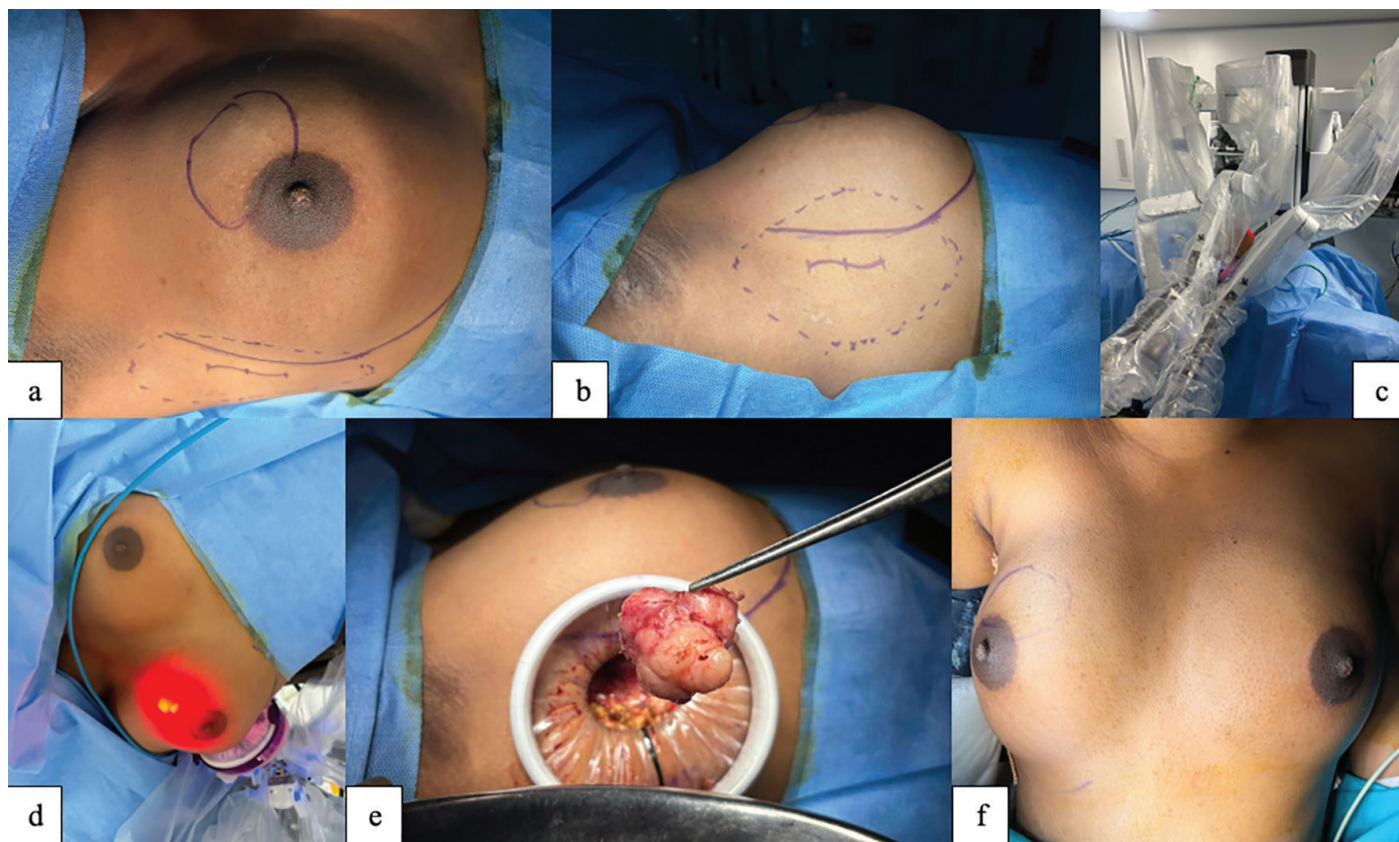


Figure 1. a) Preoperative photograph before RMIBS. b) Incision and markings for RMIBS. c) Robotic docking setup for RMIBS. d) Intraoperative photograph of dissection via GelPoint Access port in RMIBS. e) Lumpectomy with specimen retrieval via GelPoint Access port during RMIBS. f) Immediate postoperative outcome after RMIBS

RMIBS: Robotic minimally invasive breast surgery



Figure 2. One month postoperative appearance after RMIBS

RMIBS: Robotic minimally invasive breast surgery



Figure 3. Six month postoperative appearance after EMIBS

EMIBS: Endoscopic minimally invasive breast surgery

Table 1. Patient, lesion characteristics, operative time and cosmetic outcomes data

Variable	Endoscopic (<i>n</i> = 40)	Robotic (<i>n</i> = 40)	<i>p</i>	Effect size (95% CI)
Age (years), mean ± SD	36.00±9.47	38.28±11.03	0.325	Mean diff −2.28 (−6.85 to +2.30)
Lesion size (cm), median (IQR)	2.0 (2.0–3.0)	2.75 (2.0–3.5)	0.247	—
Number of lumps, median (range)	1 (1–3)	1 (1–3)	0.165	—
Laterality, <i>n</i> (%)			0.457	
Right	22 (55.0)	17 (42.5)		
Left	16 (40.0)	19 (47.5)		
Bilateral	2 (5.0)	4 (10.0)		
Operative time (min) in unilateral cases ^a	<i>n</i> = 38 Mean: 103.42±35.55 Median: 95 (IQR 80–115)	<i>n</i> = 36 Mean: 147.78±34.59 Median: 150 (IQR 130–169)	<0.001	(−65 to −35 min)
Operative time (min), adjusted for lesion size	—	—	<0.001	+42.8 min (26.1 to 59.5)
Operative time (min), full cohort ^b	<i>n</i> = 40 109.25±45.96	<i>n</i> = 40 157.88±46.49	—	—
Docking time (min), mean ± SD	—	<i>n</i> = 40 11.60±4.18 range 5–20	—	—
Console time (min), mean ± SD ^c	—	<i>n</i> = 21 80.29±42.96 range 23–170	—	—
POSAS observer score	Mean: 1.80±0.69 Median: 2 (IQR 1–2)	Mean: 1.70±0.61 Median: 2 (IQR 1–2)	0.548	−0.19 to +0.39
BREAST-Q score	Mean: 88.50±6.29 Median: 88 (IQR 88–88)	Mean: 90.50±5.97 Median: 88 (IQR 88–97)	0.100	−4.72 to 0.72

SD: Standard deviation; IQR: Interquartile range; CI: Confidence interval; POSAS: Patient and Observer Scar Assessment Scale. Groups were comparable with respect to all baseline patient and lesion characteristics. Bilateral cases excluded from operative-time comparison (*n* = 2 endoscopic, *n* = 4 robotic). ^a: The adjusted difference from a multivariable linear regression (operative time modelled on modality and lesion size) in unilateral cases (*n* = 74) showed that lesion size was not a significant predictor (*p* = 0.379). A 1:1 nearest-neighbour propensity-score-matched analysis yielded concordant results (+43.9 min; 95% CI 25.9 to 62.0; *p* < 0.001); ^b: Descriptive only; no statistical comparison performed on the full cohort given the inclusion of bilateral cases; ^c: Console time was systematically recorded for 21 of 40 robotic cases

Table 2. Complications (Clavien-Dindo Grade I)

Complication	Endoscopic <i>n</i> (%)	Robotic <i>n</i> (%)	Fisher's exact <i>p</i>
Peri-incisional numbness	3 (7.5)	4 (10.0)	1.00
Bruising	5 (12.5)	5 (12.5)	1.00
Subcutaneous emphysema	7 (17.5)	6 (15.0)	1.00
Seroma	1 (2.5)	0 (0.0)	1.00
Skin Burn	1 (2.5)	0 (0.0)	1.00
Neuropraxia	1 (2.5)	0 (0.0)	1.00
Hematoma	0 (0.0)	0 (0.0)	—
Infection	0 (0.0)	0 (0.0)	—
Any complication, per patient	17 (42.5)	14 (35.0)	0.647

a seroma after 3 months, and immediate neuropraxia of the ipsilateral upper limb. There were no significant differences between groups for any individual complication type (*p* ≥ 1.00, all types). No infections or hematomas occurred.

Kaplan-Meier estimate of follow-up duration showed a mean follow-up of 6.00 months (95% CI, 6.00–6.00) in the endoscopic group and 5.70 months (95% CI, 5.36–6.04) in the robotic group, with the difference reflecting censored observations among recently operated robotic patients. (log-rank comparison *p* = 0.397).

The final histopathologic analysis showed benign pathology in all patients, with comparable profiles across both groups (Fisher-Freeman-Halton *p* = 0.985). Fibroadenoma (simple or with associated fibrocystic changes) was the most common histopathologic diagnosis (endoscopic group: 77.5%, *n* = 31; robotic group: 72.5%, *n* = 29). Benign phyllodes tumour was present in 5 patients (endoscopic group-5%, *n* = 2; robotic group-7.5%, *n* = 3) (Table 3).

Table 3. Histopathology distribution

Histopathology	Endoscopic <i>n</i> (%)	Robotic <i>n</i> (%)	Total <i>n</i> (%)
Fibroadenoma	26 (65.0)	24 (60.0)	50 (62.5)
Fibroadenoma with fibrocystic changes/ adenosis	5 (12.5)	5 (12.5)	10 (12.5)
Fibrocystic disease	5 (12.5)	5 (12.5)	10 (12.5)
Other benign ¹	2 (5.0)	3 (7.5)	5 (6.3)
Phyllodes tumour (benign/ borderline)	2 (5.0)	3 (7.5)	5 (6.3)
Total	40 (100)	40 (100)	80 (100)

¹: Other benign lesions include pleomorphic adenoma, intraductal papilloma (with fibrocystic change), granulation/inflammation, fibrosis with calcification, and fibroadenoma with foci of usual ductal hyperplasia. All 80 patients had benign disease on final histopathology

Discussion and Conclusion

The 2025 ASBrS and the Society of Breast Imaging guidelines for management of benign FELs (13) include the following indications for fibroadenoma excision: 1) discordant imaging, 2) patient preference or symptoms, 3) concern for a PT, 4) size >4 to 6-cm, and 5) substantive growth over time. Lesions called FEL on core biopsy, with histologic or clinical suspicion for PT, should be excised without transection but do not require a negative surgical margin. They suggest that surgical planning for all breast lesions should consider aesthetics, future breastfeeding, sensory implications, and the consequences of potential final pathology. Conventional open lumpectomy techniques cause scarring over the breast, leading to cosmetic deformities, asymmetry, and even a desire for subsequent reconstruction.

The evolution of breast surgery is increasingly defined by the dual imperatives of oncologic safety and aesthetic preservation; moving the incision to extramammary sites changes the patient's psychological paradigm (8, 14). Eaves first reported endoscopic breast augmentation with excellent cosmesis (6). Kitamura et al. (8, 15) reported the first endoscopic surgery for benign breast lumps using 3 small mid-axillary line incisions, balloon dissection, CO₂ insufflation and tumor extirpation. Similar approaches for breast cancer and benign breast tumors have been reported, with good cosmetic results and concealed scars in the axilla (9, 14). Cheng et al. (10) described a periareolar endoscopic approach for giant juvenile fibroadenomas (5–10 cm) that involved a single incision, dissection of the tumor from the parenchyma, specimen retrieval in a bag (intact or morcellated) tumor removal. Oncoplastic techniques have been applied to juvenile giant fibroadenoma to limit contour deformity after excision of large lesions (16), underscoring that aesthetic consequences of open excision recur across lesion size. The extramammary approach addresses the same concerns by

a different route. In the Indian context, Bipte et al. (17) recently established feasibility and safety in 5 cases (6 breasts) for endoscopic and robotic NSM, citing the need for further larger studies with a longer duration.

Although the study lacked a comparative open lumpectomy group, the rationale for MIBS compared with conventional lumpectomy is discussed in the literature. Open lumpectomy is effective but produces a visible scar on the breast, carries a risk of contour deformity and asymmetry, especially for lesions >5 cm, and is associated with measurable dissatisfaction with the cosmetic outcome, sometimes prompting reconstruction (2-5). Extramammary approaches place incisions in the axilla, and series using endoscopic techniques have reported favorable cosmesis and quality-of-life outcomes (6-10). Shorter operative times for open lumpectomies (44.1 min–70.28 mins) (18-20) should be weighed against the cosmetic and psychological benefits of avoiding a scar on the breast itself, which is the main rationale for adoption of either modality of MIBS. This value increased as we transitioned to EMIBS (95 mins) and RMIBS (150 mins). RMIBS in our study is characterized by extended operative time owing to additional time for docking, instrument changes, and camera cleaning caused by fogging from inadequate smoke evacuation. The actual console operating time (dissection and enucleation) was efficient, though it was not sufficiently fast to offset the initial docking duration. Temporal allocation raised the possibility of bias, especially since the surgeon had already gained experience with the endoscopic technique; regression analyses and propensity score matching were performed. Despite this transferred experience, The higher robotic times reflect the statistical significance of the operative time finding. However, a contribution of prior experience to other outcomes cannot be excluded. In high-volume surgical practices, time is a critical resource, and the addition of 15–20 minutes for setup and docking cannot be ignored. Longer operative time has practical implications, including increased turnover time due to docking, undocking, and moving the robot away, and it affects operating room efficiency and scheduling, potentially reducing the number of cases per list. Breast-specific differs from docking for abdominal or pelvic surgeries. However, docking times decrease as the surgeon, assistants, and staff gain experience and familiarity with the procedure. Our mean console time was 80.29±42.96 minutes. Lian et al. (21) and Hung et al. (22) have reported a learning curve of 17 cases for endoscopic transaxillary approach, and significant reduction in operative time as surgical experience increases. In our statistical analysis, a learning-curve effect was not observed in either the endoscopic or the robotic series. Yet, larger volumes may reveal one over a longer timeframe. In our experience, EMIBS was associated with greater subjective physical strain, instrument damage, and gas leaks due to frequent manipulation; these complications were absent in robotic series, which benefited from the relative ease

of dissection in medial quadrants with wristed instrumentation and ergonomic seating of the surgeon, as well as from reduced access port damage owing to diminished manipulation and instrument torque.

In our experience in EMIBS, the benefit of tactile feedback from palpation was negated by reduced working space, gas leaks, reduced visualization due to inadequate smoke evacuation, and reduced skin-to-cautery distance. In RMIBS dissection, ICG guidance facilitated the dissection and reduced palpation, preserving the working space. Learning to operate without palpatory guidance, relying solely on 3D visualization, formed the principal part of our robotic learning curve. Once it was overcome, medial quadrant dissection was performed with relative ease.

While both techniques safely achieved complete lesion removal, in our experience the robotic platform facilitated meticulous dissection through magnified 3D-visualization and wristed articulation in the narrow, dome-like retromammary space which restricts rigid, straight endoscopic instruments, as shown by Branco et al. (23) The robotic cohort demonstrated the feasibility of performing larger lumpectomies with relative ease, as lesion size was not significant in the regression analysis; increased operating time is intrinsic to the platform and the workflow, not a function of lesion size. Endoscopic breast surgery is ergonomically difficult, forcing the surgeon to operate with elevated arms and rotated wrists in non-neutral positions, particularly in medial quadrant lesions; these positions may contribute to strain and fatigue. The robotic console enabled the surgeon to operate in a seated, optimized posture, with tremor filtration and motion scaling, which were perceived to reduce the effort of fine dissection in a constrained space. Thus, reduced musculoskeletal fatigue and subjective physical strain were reported by the surgeon. However, this observation reflects the experience of a single surgeon and requires formal validation using the NASA-TLX or the Borg CR-10 scale before firm conclusions about ergonomic benefits can be drawn.

Minor complications were similar across both modalities. The modality does not affect complications; thus, any potential benefits of RMIBS do not come at the expense of patient outcomes. Our experience mirrors the trial by Toesca et al. (24) where complications (nipple-areolar complex or skin perfusion problems, tactile impairment, seroma, hematoma, reoperations, and infections) were comparable between robotic and conventional NSM.

Our cohort demonstrated good cosmetic outcomes at 1 month in both groups (POSAS observer score median 2; BREAST-Q score median 88, range 78–100; $p = 0.100$), primarily due to the complete absence of scars on the breast mound. The axillary

incision healed well in all patients and remained completely concealed when the arm was at rest. Breast symmetry and nipple-areolar complex orientation were preserved uniformly across the 80 cases. These findings corroborate recent literature validating the cosmetically favorable results of extramammary approaches. Good cosmesis with an extramammary approach using the ABNSW grading method [breast asymmetry (A), breast shape (B), nipple shape (N), skin condition (S), and wound scars (W)] has been reported (9). Our experience confirms that the robotic platform does not require larger or more obtrusive access points than its endoscopic counterpart. At the same time, endoscopic surgery can be adopted in resource-constrained settings without access to a robot. Cosmetic satisfaction is achieved regardless of the technology used.

As in any healthcare innovation, barriers to adoption of RMIBS are influenced by resource allocation and cost (25). The use of robotic technology for benign pathologies warrants discussion of costs and requires justification. Robotic surgery entails substantial acquisition, maintenance, and consumable costs, as well as longer operative time, which should be weighed against potential benefits to surgeon ergonomics and patient-related outcomes. In resource-constrained settings, EMIBS, which achieves comparable outcomes without a surgical robot, may be a more pragmatic option. Robotic procedures in this series were performed on weekends in a dedicated operating room, reflecting local scheduling practice rather than a strategy evaluated for efficiency. Operating room throughput, turnover, case-per-list capacity, and therefore no conclusions regarding operating room efficiency or cost-effectiveness can be drawn from these data. Formal economic and workflow analyses are required before the additional operative time associated with RMIBS can be weighed against any proposed benefit.

Study Limitations

The study has several limitations: it is a retrospective, single-surgeon, single-center series, and the findings may not be generalizable. We lacked a concurrent open-surgery cohort, and the cosmetic advantage was inferred from the literature rather than directly demonstrated; we did not explicitly analyze the statistical superiority of MIBS over open surgery. Group allocation was strictly sequential; thus, surgeon experience is, by design, inseparable from modality. Regression and matching adjust for lesion characteristics but cannot account for temporal drift in operator proficiency, and therefore surgeon experience could not be modelled as a covariate. The operative-time difference is interpretable in one direction only: as the robotic group followed accumulated endoscopic experience, the longer robotic times are unlikely to reflect inexperience. For all other outcomes, a contribution from accumulated experience cannot be excluded. Bilateral cases ($n = 6$) were excluded from the

operative time comparison. Console time was not recorded for the first 13 robotic procedures; therefore, the reported values derive from later cases and the missingness is non-random, so console time should not be read as representative of the whole series. The ergonomic assessment was subjective and should be regarded as a preliminary observation; future studies using objective ergonomic assessment tools, such as NASA-TLX or similar instruments, are required. Formal analysis is also needed to ascertain the superiority of RMIBS in difficult-to-access medial-quadrant lesions. Relatively short follow-up periods (6 months) necessitate further studies to evaluate long-term cosmetic outcomes and patient-reported outcomes. Further studies are required to obtain a more comprehensive analysis of aesthetic outcomes, as only scar and breast satisfaction were analyzed, and the instruments used did not assess symmetry, contour, and volume. Cosmetic assessment was not blinded: observer POSAS scores were assigned by the authors, who were aware of the operative modality, and observer bias in favour of the newer technique cannot be excluded. The two groups did not differ on either cosmetic measure, which limits the practical consequences of this bias. Blinded or independent photographic assessments are warranted in future studies. Neither procedural cost nor operating room efficiency were formally measured in this study, both of which are required to justify RMIBS in the context of benign lumps. These limitations mean the study should be interpreted as exploratory and hypothesis-generating, rather than establishing superiority of either modality

Our study, which is among the larger series on the minimally invasive approach to benign breast lumpectomy, demonstrates the safety and feasibility of EMIBS and RMIBS for benign breast lumps in the Indian context. A descriptive comparison reveals comparable and satisfactory cosmetic results. EMIBS was associated with significantly shorter operative times than RMIBS. The robotic platform reduced subjective strain during assessment, especially in difficult-to-access medial quadrants, highlighting the need for further large-scale, prospective, multicenter studies comparing the two modalities to confirm the ergonomic advantages of robotic surgery using NASA-TLX or similar instruments and to include a cost-effectiveness analysis.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of St John's Medical College Hospital (IEC no: IEC/1/1246/2025; IEC study ref no: 175/2025; date: 10 September 2025).

Informed Consent: Written informed consent was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.S.R., N.D., G.S., M.S., V.L.V.V., S.A., N.K.; Concept: R.S.R., N.D.; Design: R.S.R., N.D.; Data Collection and/or Processing: R.S.R., N.D., G.S., S.A., N.K.; Analysis and/or Interpretation: R.S.R., N.D., G.S.; Literature Search: R.S.R., N.D., G.S.; Writing: R.S.R., N.D., G.S., M.S., V.L.V.V.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Predictive Value of CT-Derived Skeletal Muscle Metrics for Pathologic Complete Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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ABSTRACT

Objective: To investigate the predictive value of computed tomography (CT)-derived body composition parameters for pathological complete response (pCR) in breast cancer patients receiving neoadjuvant chemotherapy (NAC).

Materials and Methods: Female patients who received NAC between January 2010 and December 2022 were retrospectively evaluated. Skeletal muscle index (SMI) and muscle density [mean Hounsfield unit (HU)] were measured at the L3 vertebral level on pretreatment CT. Clinicopathological variables, including molecular subtype, histological grade, and clinical stage, were recorded. Treatment response was categorized as pCR or non-pCR. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of pCR. Receiver operating characteristic (ROC) analysis was used to assess the predictive performance of SMI and HU.

Results: A total of 365 patients (mean age, 50.2±11.79 years) were included, and pCR was achieved in 27.9% of cases. Molecular subtype was the strongest independent predictor of treatment response, with the highest pCR rates observed in HER2-positive tumors and the lowest in luminal tumors. Histological grade was associated with pCR in univariate analysis but lost significance in multivariate analysis. Neither SMI nor HU independently predicted pCR. Additional analyses according to molecular subtype demonstrated no significant associations between SMI, HU, and treatment response in luminal, HER2-positive, or triple-negative breast cancer subgroups. ROC analyses showed poor discriminatory performance of both parameters in the overall cohort and subtype-specific analyses (area under the curve range, 0.477–0.565).

Conclusion: Molecular subtype remains the primary predictor of treatment response following NAC. In contrast, CT-derived SMI and muscle density showed no predictive value for pCR in either the overall cohort or molecular subtype-specific analyses, suggesting that tumor biology plays a more dominant role than body composition in determining treatment response.

Keywords: Breast carcinoma; neoadjuvant chemotherapy; computed tomography; skeletal muscle index; body composition

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KEY POINTS

- Computed tomography (CT)-derived skeletal muscle index and muscle density did not predict pathological complete response, either in the overall cohort or within individual molecular subtypes.
- CT-derived body composition parameters, including skeletal muscle index and muscle density, are not associated with treatment response.
- Body mass index and skeletal muscle index may reflect similar biological characteristics, while muscle density reflects muscle quality as a distinct parameter.

Introduction

Breast cancer is the most common malignancy among women worldwide and remains one of the leading causes of cancer-related morbidity and mortality (1, 2). Neoadjuvant chemotherapy (NAC) is widely used, particularly in locally advanced and selected early-stage breast cancers, to reduce tumor size, facilitate breast-conserving surgery, and evaluate treatment response (3, 4). Pathological complete response (pCR) achieved after NAC is an important prognostic marker and has been strongly associated with long-term survival in selected patient groups (5-7).

Identifying factors that can predict treatment response is of great importance for patient selection and the development of personalized treatment strategies. Among the predictive factors, molecular subtypes reflecting tumor biology are known to play a fundamental role in determining response to NAC. Higher pCR rates have been reported particularly in HER2-positive and triple-negative subtypes, whereas response rates are lower in luminal subtypes (7-10). In addition, not only tumor-related characteristics but also factors such as age, tumor grade, clinical stage, and Ki-67 are thought to influence treatment response (11-14).

Computed tomography (CT)-based measurements, including skeletal muscle index (SMI) and mean muscle density [Hounsfield unit, (HU)], provide objective information regarding muscle quantity and quality (15). Sarcopenia and low muscle density have been associated with poor prognosis, increased toxicity, and decreased survival in various cancer types (16). However, studies investigating the effect of these parameters on response to NAC in breast cancer have reported inconsistent results (17-24).

Particularly regarding pCR, the contribution of body composition remains unclear. Therefore, the role of CT-based muscle parameters in predicting treatment response compared with molecular and clinical factors should be evaluated in greater detail.

The aim of this study was to investigate the factors affecting pCR in breast cancer patients receiving NAC and, in particular, to evaluate the predictive value of CT-based body composition parameters, including SMI and muscle density, in this process.

Materials and Methods

Ethics

This retrospective study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (approval no. 2024/010.99/9/12, date: 25.10.2024), and the requirement for informed consent was waived.

Study Population

Female patients diagnosed with invasive breast cancer and treated with NAC between January 2010 and December 2022 were retrospectively evaluated. A total of 519 consecutive patients were initially identified. Patients were excluded if they were male ($n = 3$), had no pretreatment positron emission tomography (PET)/CT examination ($n = 57$), had CT images with artifacts precluding accurate body composition measurements ($n = 10$), had metastatic disease at diagnosis ($n = 32$), or had incomplete clinicopathological or pathological response data ($n = 52$). The final study population consisted of 365 female patients.

Clinical Data

Patient data including age, weight, height, body mass index (BMI), menopausal status, histological subtype, molecular subtype, treatment protocol, and pathological treatment response were retrieved from hospital records. Estrogen (ER) and progesterone (PR) positivity were defined as nuclear staining in $\geq 1\%$ of tumor cells according to American Society of Clinical Oncology/ College of American Pathologists recommendations. HER2 status was determined by immunohistochemistry (IHC), and cases with an equivocal (2+) IHC result were further evaluated by fluorescence *in situ* hybridization (FISH). HER2 positivity was defined as IHC 3+ or IHC 2+ with *HER2* gene amplification on FISH. Molecular subtype was classified into three groups according to institutional clinical practice: triple-negative breast cancer (ER-/PR-/HER2-), HER2-positive breast cancer (HER2-positive irrespective of hormone receptor status), and luminal breast cancer (hormone receptor-positive/HER2-negative). Ki-67 expression was classified as low ($<20\%$) or high ($\geq 20\%$). ER Standard anthracycline- and taxane-based NAC regimens were administered. HER2-positive patients additionally received anti-HER2 targeted therapy according to institutional protocols, while selected triple-negative patients received carboplatin.

Adjuvant endocrine therapy was administered to hormone receptor-positive patients when indicated. Patients with clinical stage I disease received NAC when they had biologically aggressive tumors, including HER2-positive or triple-negative breast cancer, according to multidisciplinary team recommendations.

pCR was defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes (ypT0/is ypN0), according to the College of American Pathologists classification. Residual cancer burden was not evaluated (25). Clinical nodal stage was categorized as N0 and N1–3 for statistical analysis. Missing data were not imputed. Analyses were performed using available data, and the valid number of observations is reported for each variable in the tables.

For statistical analyses, patients were categorized into pCR and non-pCR groups.

CT Analysis

Non-contrast CT images obtained from PET/CT examinations performed for pretreatment staging were used for analysis (General Electric Healthcare, Discovery IQ-5Ring). Imaging parameters were as follows: tube voltage 120 kVp, mAs 23, slice thickness 2.5 mm, and slice gap 2 mm.

Measurements were performed using Infinitt PACS software (Healthcare IT, Seoul, South Korea) on axial CT images at the L3 vertebral level, which is the most widely validated anatomical landmark for CT-based body composition assessment and correlates strongly with whole-body skeletal muscle mass. Skeletal muscle was identified using a HU threshold of -29 to $+150$ HU. The psoas, erector spinae, quadratus lumborum, and abdominal wall muscles were manually segmented by two radiologists with 9 and 6 years of experience, respectively. Before the measurements, the two radiologists jointly reviewed the measurement protocol and agreed on a standardized methodology. Each patient was subsequently evaluated independently by one of the two radiologists. Interobserver agreement was assessed using the intraclass correlation coefficient (ICC). Skeletal muscle area (SMA) and HU were recorded. SMI was calculated as SMA divided by height squared (cm^2/m^2) and analyzed as a continuous variable without applying a predefined sarcopenia cut-off.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean $\pm$ standard deviation or median (minimum-maximum), while categorical variables were expressed as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test.

Comparisons between two groups were performed using the independent samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Correlations between continuous variables were evaluated using Spearman correlation analysis.

Binary logistic regression analysis was performed to identify factors associated with treatment response. A multivariable model including variables significant in the univariable analyses was used to identify independent clinicopathological predictors. A second hypothesis-driven model including age, clinical stage, molecular subtype, Ki-67, SMI, and HU evaluated the independent predictive value of CT-derived skeletal muscle parameters. SMI and HU were retained regardless of univariable significance because they were the primary variables of interest. Receiver operating characteristic (ROC) curve analysis assessed the discriminative performance of SMI and HU for predicting pCR. A p -value <0.05 was considered statistically significant.

Results

A total of 365 patients with a mean age of 50.2 ± 11.79 years were included in the study. pCR was achieved in 27.95% of the patients, whereas 72.05% did not achieve pCR. The majority of the patients were overweight or obese (78.9%), and the most common tumor type was invasive ductal carcinoma (92.3%). Most tumors were grade 2–3 (94.3%). Regarding molecular subtype distribution, luminal subtype (48.8%) was the most common, followed by HER2-positive (39.7%) and triple-negative (11.5%) subtypes (Table 1). Among the 145 HER2-positive tumors, 93 (64.1%) were hormone receptor-positive and 52 (35.9%) were hormone receptor-negative. Interobserver agreement was good for SMI [ICC = 0.883, 95% confidence interval (CI): 0.753–0.944] and excellent for HU (ICC = 0.998, 95% CI: 0.996–0.999).

Comparisons according to treatment response demonstrated statistically significant associations between pCR and histological diagnosis, histological grade, and molecular subtype (Table 2). pCR rates were higher in HER2-positive tumors and lower in luminal subtypes. No significant associations were observed between pCR and age, clinical stage, Ki-67, SMI, or HU values.

In multivariate analysis including histological factors, only molecular subtype remained statistically significant, whereas histological grade lost its independent significance (Table 3).

In the final multivariate model, molecular subtype was identified as the only independent predictor of treatment response (Table 4). Using the triple-negative subtype as the reference category, the risk of non-pCR was higher in the luminal subtype [odds

ratio (OR): 4.241; 95% CI: 1.780–10.106; $p = 0.001$] and lower in the HER2-positive subtype (OR: 0.393; 95% CI: 0.180–0.859; $p = 0.019$). SMI ($p = 0.217$) and HU ($p = 0.331$) were not found to have independent effects on treatment response. Age, clinical stage, and Ki-67 were also not significant in multivariate analysis.

Table 1. Descriptive characteristics of the patients	
	Statistics
Treatment response	
pCR	102 (27.95%)
Non-pCR	263 (72.05%)
Age	50.2±11.79
Menopausal	
Premenopausal	191 (52.33%)
Postmenopausal	174 (47.67%)
Family history	
No	315 (86.30%)
Yes	46 (12.60%)
Unknown	4 (1.10%)
ECOG performance	
0-1	313 (85.75 %)
≥2	50 (13.70 %)
Unknown	2 (0.55 %)
BMI	
Normal/underweight	77 (21.10%)
Overweight	118 (32.32%)
Obese	170 (46.58%)
Histological type	
Invasive ductal carcinoma	337 (92.33 %)
Invasive lobular carcinoma	17 (4.66 %)
Other	11 (3.01%)
Inflammatory breast cancer	
Yes	11 (3.02%)
No	364 (96.98%)
Histological grade	
Grade 1	20 (5.47%)
Grade 2	218 (59.73%)
Grade 3	113 (30.96%)
Unknown	14 (3.84%)
ER	
Negative	96 (26.30%)
Positive	269 (73.70%)

Table 1. Continued	
	Statistics
PR	
Negative	137 (37.53%)
Positive	228 (62.47%)
Cerb-B2	
Negative	220 (60.27%)
Positive	145 (39.73%)
Molecular subtype	
TN	42 (11.50%)
Her2	145 (39.73%)
Luminal	178 (48.77%)
Ki-67	
Low	54 (14.79%)
High	276 (75.62%)
Unknown	35 (9.59%)
Clinical T stage	
T1	99 (27.12%)
T2	222 (60.82%)
T3/4	37 (10.14%)
Unknown	7 (1.92%)
Clinical N stage	
N0	24 (6.58%)
N1-3	337 (92.32%)
Unknown	4 (1.10%)
Clinical stage	
Stage 1	43 (11.78%)
Stage 2	213 (58.36%)
Stage 3	105 (28.77%)
Unknown	4 (1.09%)
NAC regimen	
Anthracycline and taxane	343 (93.97%)
Other	22 (6.03%)
Surgical treatment	
BCS	155 (42.47%)
Mastectomy	210 (57.53%)
SMI	55.59 (29.22–97.24)
HU	26.3 (1.17–46.87)
n: Number of patients; pCR: Pathological complete response; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group, ER: Estrogen; PR: Progesterone; TN: Triple-negative; NAC: Neoadjuvant chemotherapy; BCS: Breast conserving surgery; SMI: Skeletal muscle index; HU: Hounsfield unit; %: Column percentage; continuous variables are presented as mean ± standard deviation or median (min-max)	

Table 2. Comparison of variables according to treatment response

	Treatment response		Test statistics	p-value
	pCR (n = 102)	Non-pCR (n = 263)		
Age	49.52±10.6	50.47±12.23	0.465	0.642
Histological type			9.222	0.010
Invasive ductal carcinoma	101 (99.0%)	236 (89.7%)		
Invasive lobular carcinoma	0 (0.0%)	17 (6.5%)		
Other	1 (1.0%)	10 (3.8%)		
Histological grade			14.488	0.001
Grade 1	2 (2%)	18 (6.8%)		
Grade 2	51 (50.0%)	167 (63.5%)		
Grade 3	46 (45.1%)	67 (25.5%)		
Unknown	3 (2.9%)	11 (4.2%)		
Molecular subtype			64.040	0.001
TN	13 (12.7%)	29 (11.0%)		
Her2	72 (70.6%)	73 (27.8%)		
Luminal	17 (16.7%)	161 (61.2%)		
Ki-67			4.347	0.114
Low	9 (8.8%)	45 (17.1%)		
High	84 (82.4%)	192 (73.0%)		
Unknown	9 (8.8%)	26 (9.9%)		
Clinical stage			0.374	0.829
Stage 1	10 (9.8%)	33 (12.5%)		
Stage 2	59 (57.8%)	154 (58.6%)		
Stage 3	29 (28.4%)	76 (28.9%)		
Unknown	4 (4%)	0 (0.0%)		
SMI	55.62 (38.14–97.24)	55.59 (29.22–93.34)	0.053	0.958
HU	26.77 (6.73–46.87)	26.26 (1.17–41.92)	0.534	0.593

n: Number of patients; pCR: Pathological complete response; TN: Triple negative; SMI: Skeletal muscle index; HU: Hounsfield unit; %: Column percentage; continuous variables are presented as mean ± standard deviation or median (min-max)

Table 3. Multivariable logistic regression model including variables significant in univariable analysis

	β	Standard error	Wald	p	OR	95% CI for OR	
						Lower limit	Upper limit
Constant	1.572	0.851	3.411	0.065	4.817		
Grade 1			5.765	0.056			
Grade 2	-0.367	0.807	0.206	0.650	0.693	0.142	3.374
Grade 3	-1.018	0.816	1.555	0.212	0.361	0.073	1.789
TN			46.099	0.001			
Her2	-0.949	0.401	5.595	0.018	0.387	0.176	0.850
Luminal	1.182	0.453	6.803	0.009	3.260	1.341	7.922

Variables entered in step 1: histological grade, and molecular subtype. Outcome variable: non-pCR (reference category: pCR). Reference categories: Grade 1 and triple-negative subtype. β: Regression coefficient; CI: Confidence interval; TN: Triple negative; OR: Odds ratio; pCR: Pathological complete response

Table 4. Final multivariable logistic regression model evaluating the independent predictive value of CT-derived skeletal muscle parameters for treatment response

	β	Standard error	Wald	p	OR	95% CI for OR	
						Lower limit	Upper limit
Constant	3.224	1.400	5.304	0.021	25.132		
Age	0.001	0.013	0.000	0.995	1.000	0.975	1.026
Stage 1			3.578	0.167			
Stage 2	-0.801	0.432	3.432	0.064	0.449	0.193	1.048
Stage 3	-0.792	0.473	2.804	0.094	0.453	0.179	1.144
TN			5.980	0.001			
Her2	-0.933	0.399	5.483	0.019	0.393	0.180	0.859
Luminal	1.445	0.443	10.637	0.001	4.241	1.780	10.106
Ki-67-low			1.923	0.382			
Ki-67-high	-0.421	0.457	0.847	0.357	0.656	0.268	1.609
Ki-67-unknown	0.124	0.619	0.040	0.841	1.132	0.336	3.813
SMI	-0.014	0.012	1.526	0.217	0.986	0.964	1.008
HU	-0.017	0.018	0.943	0.331	0.983	0.949	1.018

Variables entered in step 1: age, clinical stage, molecular subtype, Ki-67, SMI, and HU mean. Outcome variable: non-pCR (reference category: pCR). Reference categories: Stage 1, triple-negative subtype, and low Ki-67. β : Regression coefficient; CI: Confidence interval; TN: Triple negative; SMI: Skeletal muscle index; HU: Hounsfield unit; OR: Odds ratio; pCR: Pathological complete response; CT: Computed tomography

Correlation analyses between SMI, BMI, and HU demonstrated a moderate positive correlation between BMI and SMI ($r = 0.446$; $p < 0.001$), a weak-to-moderate negative correlation between BMI and HU ($r = -0.337$; $p < 0.001$), and a weak negative correlation between SMI and HU ($r = -0.210$; $p < 0.001$).

The discriminative performance of SMI and HU for predicting pCR was evaluated using ROC analysis. The area under the curve value was 0.498 for SMI ($p = 0.958$) and 0.518 for HU ($p = 0.574$) (Figure 1).

Exploratory subgroup analyses were performed according to molecular subtype (luminal, HER2-positive, and triple-negative breast cancer). No statistically significant associations were observed between SMI, HU, and pCR within any molecular subtype. Similarly, subtype-specific logistic regression and ROC analyses did not demonstrate meaningful predictive performance of either parameter (Table 5).

Discussion and Conclusion

In this study, factors predicting pCR to NAC in breast cancer patients were evaluated. Our results demonstrated that molecular subtype was the strongest and independent predictor of treatment response, whereas CT-based body composition parameters, including SMI and HU, did not have independent predictive value for pCR.

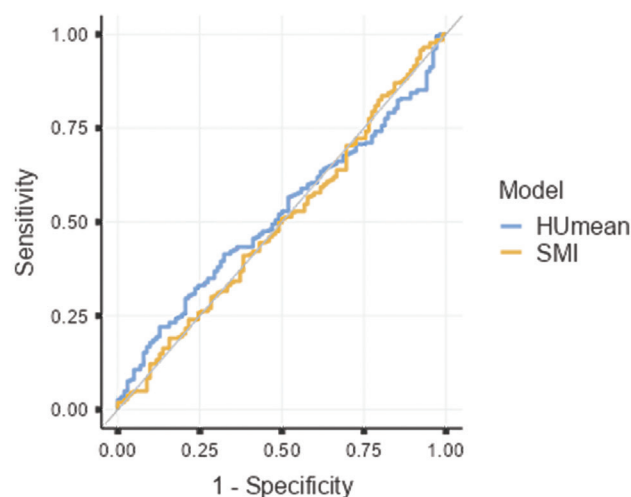


Figure 1. ROC analysis of SMI and HU for predicting pathological complete response

ROC: Receiver operating characteristic; SMI: Skeletal muscle index; HU: Hounsfield unit

The determining role of molecular subtype on treatment response is consistent with the literature. Several studies have shown higher pCR rates in HER2-positive tumors and lower response rates in luminal subtypes (26-29). This finding supports the dominant effect of tumor biology on treatment sensitivity. Similarly, in our study, the probability of achieving pCR was significantly higher in HER2-positive patients, whereas it was lower in the luminal subtype.

Table 5. Receiver operating characteristic analysis of SMI and mean muscle attenuation for predicting pathological complete response								
Variables	Cut-off	AUC	Std. error	p	Asymptotic 95% CI		Sensitivity	Specificity
					Lower bound	Upper bound		
SMI	≤79.91	0.498	0.0339	0.958	0.432	0.565	95.82	7.84
HU	≤18.20	0.518	0.0320	0.574	0.455	0.581	22.05	87.25

AUC: Area under the curve; SMI: Skeletal muscle index; HU: Hounsfield unit; CI: Confidence interval; Std.: Standard

Although histological grade was significant in univariate analysis, it lost its independent significance in multivariate analysis. This finding may be related to the biological association between histological grade and molecular subtype. Since HER2-positive and triple-negative tumors are generally high-grade tumors, the independent contribution of grade may have disappeared under the dominant effect of molecular subtype in the multivariate model. Consistent with our findings, previous studies have shown that although high grade is associated with pCR, it is not an independent predictive factor by itself (28, 30, 31).

In the present study, SMI and HU were not identified as independent factors for predicting treatment response. Previous studies investigating the relationship between body composition and treatment response have reported inconsistent results. Some studies demonstrated that low SMI values were associated with lower pCR rates, although SMI was not identified as an independent predictive factor (16, 22, 23). In contrast, other studies found no significant association between SMI and pCR (18, 21, 24). Similarly, Isiklar et al. (17) did not find a significant association between BMI and pCR, consistent with our results. In a meta-analysis by Zhang et al. (19), a weak negative association between BMI and pCR was reported. The heterogeneous findings among studies evaluating body composition and NAC response may be related to differences in measurement techniques, patient selection criteria, and analytical approaches. In particular, evaluating body composition as categorical variables versus continuous variables may lead to different results. In the study by Butler et al. (21), although SMI was not an independent factor for treatment response, it was associated with long-term survival outcomes. This finding suggests that SMI may be more closely related to the patient’s general condition and prognosis rather than direct tumor response. In addition, SMI and HU are dynamic parameters that may change during NAC due to treatment-related toxicity, nutritional status, systemic inflammation, and changes in physical activity (32-34). Therefore, a single pre-treatment measurement may not reflect the dynamic changes associated with treatment response. Another possible explanation for the lack of association between skeletal muscle parameters and pCR is the relatively homogeneous body composition of our cohort, as approximately 79% of the patients were overweight or obese.

This may have reduced the variability of SMI and limited our ability to detect modest associations. In addition, sarcopenic obesity may partly explain why muscle quantity alone was not associated with treatment response. Future studies including more heterogeneous populations are warranted.

Exploratory subgroup analyses according to molecular subtype yielded findings consistent with the overall cohort. However, these analyses, particularly in the triple negative subgroup, should be interpreted cautiously because of the limited sample size and statistical power. Larger multicenter studies are needed to validate these findings.

In our study, no significant association was observed between HU and pCR. However, Mun et al. (20) demonstrated a possible association between HU and treatment response in a study including only triple-negative breast cancer patients receiving immunotherapy-containing treatment regimens. These findings indicate that treatment response may be strongly influenced not only by patient-related factors but also by tumor biology and treatment type. In our cohort, which included a heterogeneous patient population with different molecular subtypes receiving standard NAC, no independent association was observed between SMI, HU, and pCR.

In addition, the moderate correlation between BMI and SMI in our study suggests that these two parameters partly reflect similar biological characteristics. In contrast, the weak negative correlations involving HU suggest that muscle quality may reflect different biological properties compared with muscle quantity. These findings support the idea that functional and metabolic characteristics of body composition may be more important than quantitative measurements alone.

The poor discriminative performance of SMI and HU in ROC analysis further suggests that these parameters have limited clinical utility in predicting pCR. These findings also suggest that body composition parameters may be more closely associated with treatment tolerance, treatment-related complications, or long-term outcomes rather than direct treatment response.

This study has several limitations. First, its retrospective design may have introduced selection bias. In addition, the majority of the study population was overweight or obese, which may have limited the variability of body composition parameters. Furthermore, other body composition parameters, including adipose tissue measurements, as well as functional muscle assessments and metabolic biomarkers, were not included in the analysis. Muscle attenuation measurements were obtained from the low-dose CT component of PET/CT, which may have affected HU measurements. Finally, the relatively long study period may have introduced temporal heterogeneity despite the use of the same PET/CT system and generally consistent NAC regimens throughout the study period.

In conclusion, pretreatment CT-derived skeletal muscle parameters did not provide additional predictive value for pCR beyond molecular subtype in this relatively large single-center cohort. These findings add to the existing evidence suggesting that pretreatment body composition alone has limited utility for predicting treatment response. Larger prospective multicenter studies are warranted.

Ethics

Ethics Committee Approval: This retrospective study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (approval no. 2024/010.99/9/12, date: 25.10.2024).

Informed Consent: The requirement for informed consent was waived.

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For transparency, the authors note that an artificial intelligence assisted language model (ChatGPT, OpenAI) was utilized to support language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.R., A.Ö.S., S.Y., H.O., Ş.K.; Concept: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.; Design: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.; Data Collection and/or Processing: G.R., A.Ö.S., S.Y., Ş.K.; Analysis and/or Interpretation: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.; Literature Search: G.R., A.Ö.S.; Writing: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.

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Quality of Life After Breast Cancer Surgery in Patients Receiving Adjuvant Radiotherapy: A Cross-Sectional Analysis

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ABSTRACT

Objective: As breast cancer survivorship improves, quality of life (QoL) has become a key determinant in treatment decision-making. While breast-conserving approaches are widely adopted, variations in surgical extent persist across clinical settings. This study aimed to compare patient-reported QoL scores between women undergoing breast-conserving surgery and those undergoing modified radical mastectomy in the context of adjuvant radiotherapy.

Materials and Methods: This single-center, cross-sectional, observational study included 98 women who were treated at a tertiary hospital between January 2021 and January 2024. Of 200 potentially eligible patients contacted, 98 consented and completed the European Organisation for Research and Treatment of Cancer core quality of life questionnaire (QLQ-C30) and the breast cancer-specific module (QLQ-BR23) after radiotherapy. Fifty-eight patients underwent breast-conserving surgery, and 40 underwent modified radical mastectomy. Scores were transformed to a 0-100 scale; functional and global health scales were interpreted conventionally, and symptom summaries were oriented so that higher scores reflected lower symptom burden. Unadjusted group comparisons were performed using the Mann-Whitney U test, and exploratory correlations were assessed using Spearman correlation coefficients.

Results: Patients treated with breast-conserving surgery reported higher QLQ-C30 functional scores than those treated with modified radical mastectomy (median 60.00 vs. 46.66; $p = 0.005$) and higher global health status scores (66.66 vs. 37.50; $p < 0.001$). Symptom summary scores also favored breast conservation (67.94 vs. 58.97; $p = 0.001$). On the QLQ-BR23, the breast-conserving group reported higher functional scores (57.77 vs. 44.44; $p = 0.008$) and higher symptom summary scores (87.50 vs. 84.38; $p = 0.045$). These values represent unadjusted between-group differences and should be interpreted in light of the observational design and the unavailability of clinical covariates.

Conclusion: In patients receiving adjuvant radiotherapy, less extensive breast surgery was associated with more favorable patient-reported quality of life outcomes. These findings highlight the importance of incorporating survivorship outcomes into shared decision-making in breast cancer care.

Keywords: Breast cancer; breast surgery; breast conserving surgery; modified radical mastectomy; radiotherapy; patient reported outcomes; quality of life; EORTC QLQ-C30; EORTC QLQ-BR23; STROBE

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KEY POINTS

- Breast-conserving surgery was associated with better patient-reported quality of life than modified radical mastectomy in patients receiving adjuvant radiotherapy.
- Patients treated with breast-conserving surgery reported higher European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 functional scores and global health status scores.
- Breast cancer-specific EORTC QLQ-BR23 functional outcomes also favored breast-conserving surgery.
- Less extensive breast surgery may contribute to lower symptom burden and better survivorship experience after radiotherapy.
- Quality of life outcomes should be incorporated into shared decision-making when breast-conserving surgery is oncologically feasible.

Introduction

Breast cancer remains the most commonly diagnosed malignancy in women worldwide, and growing survivorship has shifted attention from oncologic control alone to long-term functional and psychosocial outcomes (1). For women with operable disease, the choice between breast conserving surgery (BCS) and mastectomy is therefore not purely technical. It is also a quality of life decision that can shape body image, daily activities, symptom burden, treatment satisfaction, and social recovery after therapy.

Long-term randomized trials established that, in appropriately selected patients, BCS followed by radiotherapy (RT) provides survival outcomes comparable to mastectomy (2, 3). Once this oncologic equivalence is accepted, patient-reported outcomes become highly relevant. The extent of breast removal may influence how patients perceive physical recovery, femininity, intimacy, and overall health after treatment. These dimensions are important in contemporary shared decision-making, particularly when more than one local treatment strategy is feasible.

Health-related quality of life after breast cancer surgery is multidimensional and may be affected by age, tumor burden, adjuvant systemic therapy, RT-related effects, complications, and psychosocial context. The European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and breast-specific module (QLQ-BR23) are among the best validated instruments for capturing these outcomes in a standardized way (4, 5). Their combined use allows assessment of both global cancer-related functioning and breast-cancer-specific concerns, such as body image and treatment-related symptoms.

Existing observational literature generally suggests that breast conservation is associated with better body image and more favorable psychosocial outcomes than mastectomy, although the magnitude of this advantage varies across populations and treatment pathways (6-8). Engel et al. (6), Arndt et al. (7), and later comparative studies and meta-analyses showed that quality of life differences may persist beyond the acute postoperative phase. However, many cohorts mix patients with and without

RT, include heterogeneous reconstructive pathways, or reflect healthcare environments that differ from routine tertiary practice in our region.

Because reporting of observational data should be methodologically transparent, the present study was structured in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies (9). We compared patient-reported quality of life in women who underwent BCS or modified radical mastectomy (MRM), all of whom completed postoperative RT at a tertiary referral center. We hypothesized that less extensive surgical approaches would be associated with more favorable patient-reported outcomes in this post-RT cohort.

While surgical practice has evolved toward breast conservation in many high-income settings, substantial variation persists globally, particularly in heterogeneous and resource-variable healthcare environments. Therefore, comparing patient-reported outcomes across surgical approaches remains clinically relevant, especially in the context of adjuvant RT, which may influence long-term survivorship experiences.

Materials and Methods

Study Design and Setting

This single-center, cross-sectional, observational study was conducted at the general surgery clinic of a tertiary training and research hospital. The study period extended from January 2021 through January 2024. Reporting was aligned with the STROBE statement for cross-sectional studies. The primary objective was to compare quality of life outcomes between women treated with BCS and those treated with MRM after completion of postoperative RT. Secondary exploratory objectives were to examine correlations between selected treatment intensity variables and quality of life summary scores.

Participants

Women aged 18 years or older with histologically confirmed breast cancer who had undergone definitive breast surgery and completed postoperative RT were eligible. Potentially eligible patients were identified from institutional follow-up records

and contacted to participate. Of 200 women approached, 98 consented to and completed the study procedures: 58 in the BCS group and 40 in the MRM group. Patients were excluded if they had not completed RT, had active recurrent disease at the time of survey administration, or had been unable to complete the questionnaires reliably. Because chemotherapy-related variables were included in exploratory analyses, prior systemic therapy was not considered an exclusion criterion.

Data Collection and Variables

Quality of life was assessed after completion of RT in the outpatient oncology setting using the EORTC QLQ-C30 and QLQ-BR23. Questionnaires were administered either as supervised self-report or through direct interview. The QLQ-C30 evaluates physical, role, emotional, cognitive, and social functioning, global health status, and symptom burden. The QLQ-BR23 complements this with breast-cancer-specific domains including body image, sexual functioning, future perspective, and treatment-related symptoms. Scores were transformed to a 0–100 scale. Functional domains and global health status were interpreted conventionally, with higher scores indicating better status. To maintain intuitive consistency across summary analyses, symptom summary scores were oriented so that higher values reflected a lower symptom burden, which differs from the conventional presentation of raw EORTC symptom scales and was stated explicitly to avoid misinterpretation.

Additional variables abstracted from clinical records included age, chemotherapy cycles, RT cycles, chemotherapy duration, and RT duration. These variables were used only for exploratory association analyses. The source dataset did not contain sufficiently complete and standardized patient-level data on tumor and nodal stage, pathological characteristics, receptor or molecular subtype, systemic treatment categories, axillary surgery, reconstruction, menopausal status, body mass index, RT technique and target volumes, or intervals from surgery and RT completion to questionnaire administration. These variables, therefore, could not be reported by treatment group or included in adjusted analyses.

Bias and Study Size

Several sources of bias were considered. First, treatment allocation was non-random and determined by clinical indications and patient-physician decision-making, introducing confounding by indication and potential selection bias. Second, 98 of the 200 women contacted participated (49.0%); characteristics of non-participants were unavailable for comparison, and, therefore, non-response bias cannot be excluded. Third, quality of life was measured at a single post-RT time point, and the interval between treatment completion and questionnaire administration was not available. These issues were addressed by presenting participant

flow transparently, avoiding causal language, and interpreting the findings as unadjusted associations. The sample size was pragmatic and reflected the number of eligible and consenting patients during the study period; no formal a priori sample size calculation was performed.

Ethics

The study protocol was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Scientific Research Ethics Committee (approval no: 83, date: March 28, 2024). All participants provided informed consent before questionnaire administration. Data were analyzed anonymously, and the study was conducted in accordance with the Declaration of Helsinki and institutional requirements for observational human research.

Statistical Analysis

Continuous data were summarized using medians and ranges. Between-group comparisons of QLQ-C30 and QLQ-BR23 summary scores were performed using the Mann-Whitney U test. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Exploratory correlations among age, treatment intensity measures, and quality of life summaries were examined using Spearman coefficients. No adjustment for multiple comparisons was applied because these analyses were exploratory; the reported p -values are therefore unadjusted. Multivariable regression and propensity-based adjustment were not performed because the principal clinical covariates required to address confounding by indication were unavailable. A model restricted to the few recorded variables would not have adequately controlled for the major expected differences between the surgical groups. Effect sizes and 95% confidence intervals could not be calculated reliably because patient-level data and complete Mann-Whitney U test outputs were unavailable in the archived analytic dataset. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Participant selection is summarized in Figure 1.

Results

A total of 98 women were included in the final analysis: 58 treated with BCS and 40 treated with MRM. The median age of the cohort was 53 years (range 35–70 years). Of the 200 potentially eligible women contacted, 102 did not participate, yielding a participation rate of 49.0%. Participant flow from contact through final analysis is shown in Figure 1, and the cohort characteristics from the source dataset are summarized in Table 1. Detailed clinicopathological comparability between the surgical groups could not be assessed.

On the EORTC QLQ-C30, all reported summary domains favored breast conservation (Table 2). The median functional score

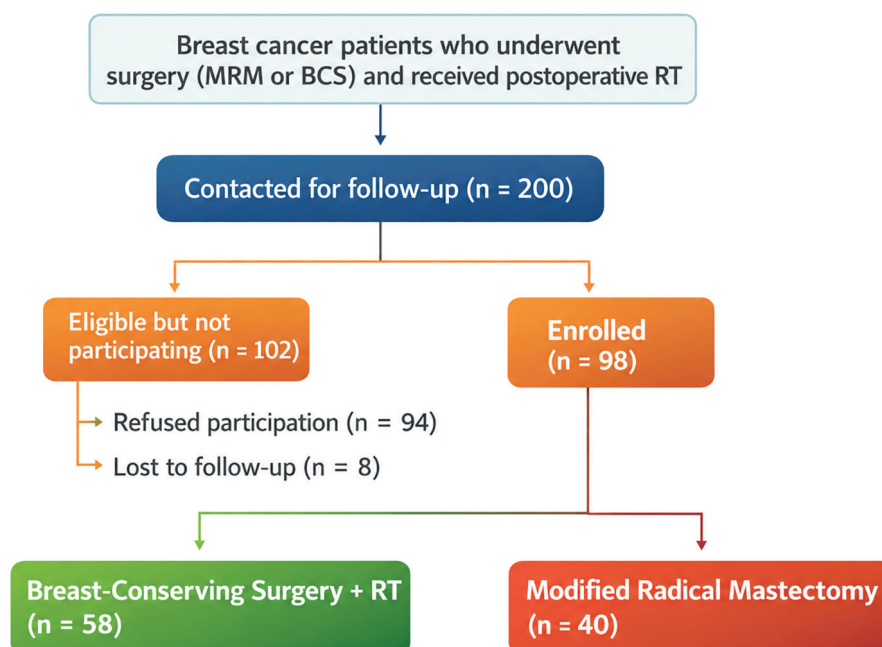


Figure 1. Participant flow diagram compatible with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Flow diagram showing patient identification, participation, and final allocation to the BCS + RT and MRM + RT analytical groups

BCS: Breast conserving surgery; RT: Radiotherapy; MRM: Modified radical mastectomy

Table 1. Cohort characteristics and design features available from the source dataset

Variable	Overall cohort	Comment
Total analyzed participants	98	58 BCS + RT; 40 MRM + RT
Potentially eligible women contacted	200	102 did not participate
Participation rate	49.0%	Characteristics of non-participants were unavailable
Age	Median 53 years (range 35–70)	Group-specific descriptive data unavailable
Study design	Cross-sectional observational	Single-center tertiary hospital cohort

BCS: Breast conserving surgery; RT: Radiotherapy; MRM: Modified radical mastectomy

Table 2. Comparison of EORTC QLQ-C30 summary scores according to surgical approach

Domain	BCS + RT (n = 58)	MRM + RT (n = 40)	p-value
Functional score, median (min-max)	60.00 (11.11–93.33)	46.66 (6.67–91.11)	0.005
Symptom summary score*, median (min-max)	67.94 (28.21–97.44)	58.97 (33.33–89.74)	0.001
Global health status, median (min-max)	66.66 (0–100)	37.50 (1–75)	<0.001

*: Symptom summary scores were oriented so that higher values indicate lower symptom burden; BCS: Breast conserving surgery; RT: Radiotherapy; MRM: Modified radical mastectomy; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30

was higher in the BCS group than in the MRM group (60.00 vs. 46.66; $p = 0.005$). Global health status showed the largest absolute between-group difference (66.66 vs. 37.50; $p < 0.001$). The symptom summary score—oriented so that higher values represent lower symptom burden—was also higher in the BCS group (67.94 vs. 58.97; $p = 0.001$). These are unadjusted

comparisons and likely reflect more favorable patient-reported scores in the BCS group, rather than indicating an independent effect of the surgical procedure.

Breast-cancer-specific quality of life findings followed the same pattern (Table 3). The BCS group reported higher functional

Table 3. Comparison of EORTC QLQ-BR23 summary scores according to surgical approach

Domain	BCS + RT (n = 58)	MRM + RT (n = 40)	p-value
Functional score, median (min-max)	57.77 (15.56–93.33)	44.44 (6.67–84.44)	0.008
Symptom summary score*, median (min-max)	87.50 (67.19–100)	84.38 (71.88–95.31)	0.045

*: Symptom summary scores were oriented so that higher values indicate lower symptom burden; BCS: Breast conserving surgery; RT: Radiotherapy; MRM: Modified radical mastectomy; EORTC: European Organisation for Research and Treatment of Cancer

scores than the MRM group on the QLQ-BR23 (57.77 vs. 44.44; $p = 0.008$). The BR23 symptom summary score was also higher in the BCS group (87.50 vs. 84.38; $p = 0.045$). The absolute difference in the symptom summary score was modest, and its clinical importance cannot be determined from the available summary data.

Exploratory correlations, which were not part of the primary between-group comparisons, are provided in Supplementary Table 1.

Discussion and Conclusion

In this cross-sectional observational study of women who completed postoperative RT after breast cancer surgery, BCS was associated with more favorable patient-reported quality of life scores than MRM across the general and breast-specific summary measures examined. The largest absolute difference was observed in QLQ-C30 global health status, while the direction of the unadjusted differences was consistent across functional and symptom summaries. Because baseline clinical comparability and the timing of questionnaire administration could not be assessed, these findings should not be interpreted as evidence that the surgical procedure itself caused the observed differences.

The observed differences are potentially relevant to counseling because the decision between BCS and mastectomy may be preference-sensitive when both approaches are oncologically appropriate. Patients may consider daily functioning, body image, symptoms, and perceived health alongside recurrence risk and margin-related outcomes. Accordingly, patient-reported survivorship outcomes merit consideration during shared decision-making, while the unadjusted nature of our comparisons should be made explicit.

The median QLQ-C30 global health status score differed by 29.16 points between groups. Although this numerical separation appears substantial, clinical importance cannot be established with confidence without adjusted analyses, domain-level results, and standardized information on the timing of assessment. The findings should also be interpreted within evolving surgical and radiation oncology practice, including changes in RT volumes and techniques (10, 11), wider use of oncoplastic breast conservation (12), immediate reconstruction, and de-escalated axillary

surgery. These developments may limit the generalizability of a comparison restricted to BCS and MRM.

The current findings are broadly concordant with the long-term randomized and observational evidence that reshaped modern breast surgery. Fisher et al. (2) and Veronesi et al. (3) showed that BCS plus RT provides survival comparable to mastectomy in appropriately selected patients. In this context, quality of life is an important additional outcome. The present study provides institutional data showing that, among respondents who had received RT, patient-reported summary scores were more favorable in the BCS group; however, the study cannot isolate the effect of surgical extent from differences in patient selection and treatment.

Engel et al. (6) reported better long-term quality of life outcomes in selected domains after breast conserving therapy, and Arndt et al. (7) showed that quality of life differences may persist over years of survivorship. Ganz et al. (13) likewise emphasized that psychosocial concerns remain central long after acute treatment. Our results fit within this broader framework. Nevertheless, the differences observed in our cohort may reflect surgical extent, baseline disease burden, treatment intensity, reconstructive pathways, patient preference, or other unmeasured factors. The meta-analysis by Ng et al. (8) similarly found that BCS was associated with better body image and several quality of life domains than mastectomy.

Postmastectomy quality of life is heterogeneous rather than uniformly poor. Howes et al. (14), Hanson et al. (15), and Zehra et al. (16) showed that reconstruction may narrow some quality of life differences between mastectomy and breast conservation. Reconstruction status was not available in our dataset, so the MRM group could not be characterized as reconstructed or non-reconstructed. This prevents direct comparison of our findings with contemporary reconstruction-based mastectomy pathways and limits their generalizability.

Recent longitudinal data continue to support the importance of breast preservation where feasible. Gulis et al. (17) reported favorable health related quality of life outcomes after partial and oncoplastic partial mastectomy, while cross cultural studies by Kamińska et al. (18) similarly suggested better outcomes after breast-conserving treatment than after mastectomy in several domains. Deepa et al. (19), however, reported more comparable

long-term outcomes in another setting, underscoring that culture, timing of assessment, reconstructive access, and adjuvant treatment patterns can modify observed differences. Emiroğlu et al. (12) also emphasized that oncoplastic techniques can expand breast conservation while supporting oncologic and aesthetic goals. For this reason, institution-specific data remain valuable for counseling patients in the healthcare environment where the decision is made.

The similar direction of the QLQ-C30 and QLQ-BR23 summary findings supports their internal coherence; however, it does not overcome residual confounding or establish clinical significance.

The clinical implication of our study is not that MRM should be avoided when oncologically indicated. Potential differences in patient-reported outcomes should be discussed when BCS and mastectomy are both reasonable options. Surgical planning should consider oncologic safety, patient preferences, and anticipated survivorship outcomes.

Shared decision-making in breast surgery often emphasizes local control, margin management, risk of re-excision, and adjuvant therapy. These are essential topics, but they do not fully address how patients will live with the consequences of treatment.

In this post-RT cohort, breast preservation was associated with more favorable functioning scores and perceived health scores; however, the independent contributions of surgery, RT, and patient selection could not be separated.

The between-group difference in global health status also supports discussion of overall well-being rather than focusing only on isolated symptoms. A multidisciplinary counseling model may involve breast surgeons, radiation oncologists, nursing teams, and psycho-oncology support when available. Patients should be informed not only about oncologic eligibility for BCS but also about how different local treatment pathways may be associated with recovery, body image, arm symptoms, and daily life.

These findings illustrate that patient-reported treatment burden extends beyond oncologic outcomes, although the independent contribution of surgical extent to this burden could not be determined.

Study Limitations

This study has several strengths. It used two internationally validated instruments that together capture generic and breast-specific aspects of survivorship. It also restricted the analysis to women who completed postoperative RT, thereby reducing one broad source of treatment heterogeneity. The consistent direction of the QLQ-C30 and QLQ-BR23 summary findings supports their internal coherence, but does not overcome the limitations of the unadjusted observational comparison.

Nevertheless, the limitations are substantial and should inform the interpretation of the findings. First, the cross-sectional design cannot establish causality or temporal changes. Baseline quality of life was not measured, and the intervals from surgery completion and RT completion to questionnaire administration were unavailable. Second, the modest single-center cohort limits statistical power and external generalizability. Because no *a priori* sample size calculation was performed, non-significant findings cannot be assumed to demonstrate equivalence. Third, treatment allocation was not randomized and was likely influenced by tumor extent, nodal involvement, multifocality, clinical indication, and patient preference. These characteristics were not available for group-level comparison or adjustment. Confounding by indication and residual confounding are, therefore, major limitations.

Fourth, only 98 (49.0%) of the 200 women contacted participated, and characteristics of non-participants were unavailable; therefore, the direction and magnitude of non-response bias cannot be assessed. Fifth, information on receptor and molecular subtype, neoadjuvant and adjuvant systemic treatments, endocrine and HER2-directed therapy, axillary surgery, reconstruction, menopausal status, body mass index, complications, and lymphedema was unavailable. Sixth, RT technique, target volumes, regional nodal irradiation, boost use, dose, and fractionation were not captured in a standardized, patient-level form. This is important because RT volumes have been associated with late cosmetic and quality of life outcomes after BCS (10), and contemporary RT approaches may alter toxicity profiles (11). Seventh, domain-level EORTC results, including body image, emotional and sexual functioning, future perspective, breast and arm symptoms, were unavailable. This limits assessment of both the source and the clinical importance of the differences in summary scores. Finally, symptom summaries were reverse-scored so that higher scores indicated lower symptom burden; this scoring direction is documented in the Methods and in the table footnotes.

Accordingly, the results should be regarded as exploratory, unadjusted associations that require confirmation in clinically characterized longitudinal cohorts.

Future studies should adopt prospective longitudinal designs with preoperative baselines and repeated postoperative measurements. They should distinguish among BCS plus RT, mastectomy alone, mastectomy with immediate reconstruction, and mastectomy with delayed reconstruction, while accounting for clinicopathological characteristics, axillary surgery, RT parameters, systemic therapy, complications, and socioeconomic context. Propensity-based comparative analyses may be useful when randomized trials are impractical. Incorporating validated patient-reported outcome measures into routine follow-up could also improve survivorship counseling.

In this post-RT cohort, women in the BCS group reported more favorable quality of life summary scores than women in the MRM group. These unadjusted associations do not establish an independent effect of surgical approach, but support the inclusion of patient-reported survivorship outcomes in shared surgical decision-making.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Scientific Research Ethics Committee (approval no: 83, date: March 28, 2024).

Informed Consent: All participants provided informed consent before questionnaire administration.

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For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support text editing and language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.Ö., H.K., K.T., F.B., F.E.; Concept: H.K.T., H.K., K.T., F.B., F.E.; Design: H.K.T., H.K., K.T., F.B., F.E.; Data Collection and/or Processing: S.A., H.K., M.K., P.A., C.K., B.G., F.E.Y.; Analysis and/or Interpretation: S.A., H.K., M.K., P.A., C.K., B.G., F.E.Y.; Literature Search: H.K.T., Ş.Ö., H.K., M.K., P.A., C.K., B.G., F.E.Y., K.T., F.B., F.E.; Writing: H.K.T., Ş.Ö., H.K., F.E.

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Supplementary Material Table 1: <https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/6d34b63e-49c7-49fb-bbd8-6c15ee4ef76.pdf>

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Male Mammary Myofibroblastoma Masquerading as Malignancy

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ABSTRACT

We report a case of myofibroblastoma (MFB) of the breast in a 58-year-old man who presented with a large painless lump in the left breast. Radiologic breast imaging showed a well-circumscribed mass with no microcalcifications. Microscopic examination revealed fascicles of spindle cell neoplasm with intervening thick bundles of hyalinized collagen and interspersed vessels. Pertinent immunohistochemistry markers showed positivity for CD34, estrogen receptor, progesterone receptor and androgen receptor. A diagnosis of MFB of the breast was rendered. It is crucial to differentiate MFB from other entities in the breast like fibroadenoma, phyllodes tumor, gynecomastia, carcinoma and sarcoma for its appropriate management.

Keywords: Myofibroblastoma; male breast; immunohistochemistry; benign; mesenchymal tumor

KEY POINTS

- Myofibroblastoma
- Male breast
- Immunohistochemistry
- Benign
- Mesenchymal tumor

Introduction

Myofibroblastoma (MFB) is an uncommon mesenchymal neoplasm seen chiefly in the breast. It is commonly reported in the middle aged and elderly of both sexes. The differential diagnosis for a male breast mass includes gynecomastia, infection, lipoma, metastatic disease, and schwannoma, which are more likely than MFB due to its rarity. A hormonal etiology for MFB is suggested because of the expression of sex steroid hormone receptors by tumor cells. An association with pseudoangiomatous stromal hyperplasia (PASH) and

gynecomastia has also been suggested. We discuss the pertinent clinical, radiological and histopathological characteristics of MFB in a 58-year-old man with a large lump in the left breast. Clinical and radiological correlation and biopsy evaluation with appropriate immunohistochemical markers to confirm diagnosis is essential for an appropriate treatment approach (1, 2).

Case Presentation

A 58-year-old man visited the surgical oncology department because of the presence of a large lump in the left breast for two

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months. The lump was painless and not associated with nipple discharge. He had no significant past history or family history. He was a chronic tobacco chewer. On examination of the left breast, a well-defined, firm mass of 10x8 cm was noted which was freely movable, non-tender and not fixed to the chest wall or overlying skin. No skin ulceration or secondary skin changes were seen. No axillary lymphadenopathy was noted.

Diagnostic bilateral mammography (Figure 1) revealed a well-circumscribed oval 10x6 cm high-density mass lesion of suspicious appearance in the central quadrant of the left breast with fat halo sign, and assessment with the Breast Imaging-Reporting Data System (BIRADS) resulted in a grading of 4B (BIRADS 4B). Ultrasound (USG) correlation of left breast confirmed a well-circumscribed hypoechoic solid 95x55 mm mass lesion with some internal vascularity in the central quadrant with well-defined margins. Microcalcifications and axillary lymphadenopathy were not noted. The right breast showed round grouped microcalcifications in the upper inner quadrant adjacent to skin with no significant abnormality detected on USG (BIRADS 2).

Subsequent to the mammography, a tru-cut biopsy was performed. Microscopy of hematoxylin and eosin (H&E) sections showed a spindle cell lesion with intervening bands of hyalinized collagen. No necrosis, mitosis or significant cytologic atypia was seen. On immunohistochemistry (IHC), positivity for CD34 and progesterone receptor (PgR) was seen. A provisional diagnosis of MFB was rendered.

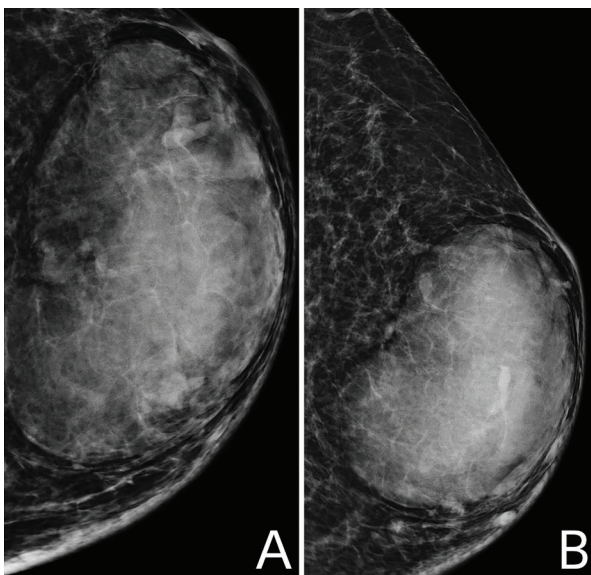


Figure 1. Mammography images (A) Craniocaudal, (B) Mediolateral oblique views. A large oval circumscribed high density mass lesion measuring 10x6 cm is seen in the retro-areolar region with a fat halo sign, suggestive of a Breast Imaging-Reporting Data System 4B mass lesion

A simple mastectomy of the left breast was performed in view of the above diagnosis. Wide local excision is generally the preferred approach for small, well-localized mammary MFBs that occupy a limited portion of the breast, as it provides complete removal with adequate margins while preserving breast tissue. In our case, however, the patient presented with a large, well-circumscribed mass measuring 10 cm in greatest dimension, involving almost the entire breast parenchyma. Under such circumstances, achieving adequate margins through wide local excision would not have been possible without significant breast deformity. Therefore, a simple mastectomy was performed to ensure complete excision. Gross examination (Figure 2) revealed a circumscribed, reddish-brown mass in the central quadrant which was not infiltrating the adjoining mammary tissue. Microscopy of H&E sections showed a non-encapsulated, benign spindle cell neoplasm composed of multiple nodules divided by fibrous septae of variable thickness. Multiple slit-like and a few ectatic congested vessels were seen. The tumor showed fascicular arrangement, storiform pattern and whorls of elongated to oval cells exhibiting mild nuclear pleomorphism, vesicular chromatin, occasional tiny nucleoli, and moderate amounts of well-defined cytoplasm (Figure 3). Extracellular thick bands of collagen, edema, interspersed mast cells and foci of perivascular lymphocytic inflammation were seen. Mitosis was sparse. No necrosis, calcification, *in situ* component or malignant epithelial component was noted. No entrapped mammary ducts or lobules were seen. Histopathological examination confirmed clear surgical margins, and the postoperative course was uneventful. On IHC, tumor cells expressed positivity for CD34, desmin, estrogen receptor (ER) and PgR. The Ki-67 labeling index was 2% (Figure 4a-d). IHC for pan-cytokeratin, p63, alpha smooth muscle actin (SMA) and S100 protein were negative. Based on the microscopic



Figure 2. Gross image showing a large circumscribed reddish-brown mass

evaluation and IHC, a final diagnosis of MFB was confirmed. As mammary MFB is a benign spindle cell neoplasm with no reported risk of recurrence or metastasis following complete excision, no adjuvant therapy was administered. The patient

has been kept under regular follow-up and remains disease-free to date. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion and Conclusion

Soft tissue tumors in the breast are quite uncommon in comparison to malignant neoplasms in the breast, including carcinomas. Hence, a wide range of differential diagnosis are considered. Benign soft tissue neoplasms are uncommon, with lipoma being more common among this group and spindle cell hemangioma the rarest among them. MFB is an uncommon mesenchymal neoplasm. It was initially reported in the mammary region with purported origin from mammary stromal cells. Extramammary regional involvement has been reported, including head and neck, popliteal fossa, inguinal and para-testicular region, gluteal region and vulva (3). Hormonal etiology, gynecomastia and PASH have been implicated in its etiopathogenesis (4).

MFB usually presents as a unilateral, painless and mobile breast mass. Rarely, bilaterality and multicentricity may be seen. It affects elderly men and women equally. However, due to regular breast screening in women, the detection of these masses is much earlier and easier. Mammographic and USG

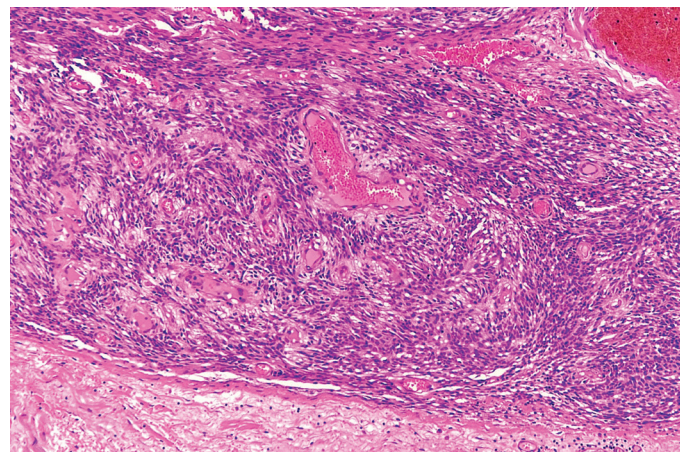


Figure 3. Hematoxylin and eosin stain, 100X, A non-encapsulated, benign spindle cell neoplasm with multiple slit-like to ectatic congested vessels. Fascicular arrangement, storiform pattern and whorls of elongated to oval cells with mild nuclear pleomorphism, vesicular chromatin, occasional tiny nucleoli, and moderate amounts of well-defined cytoplasm. Extracellular thick bands of collagen are evident

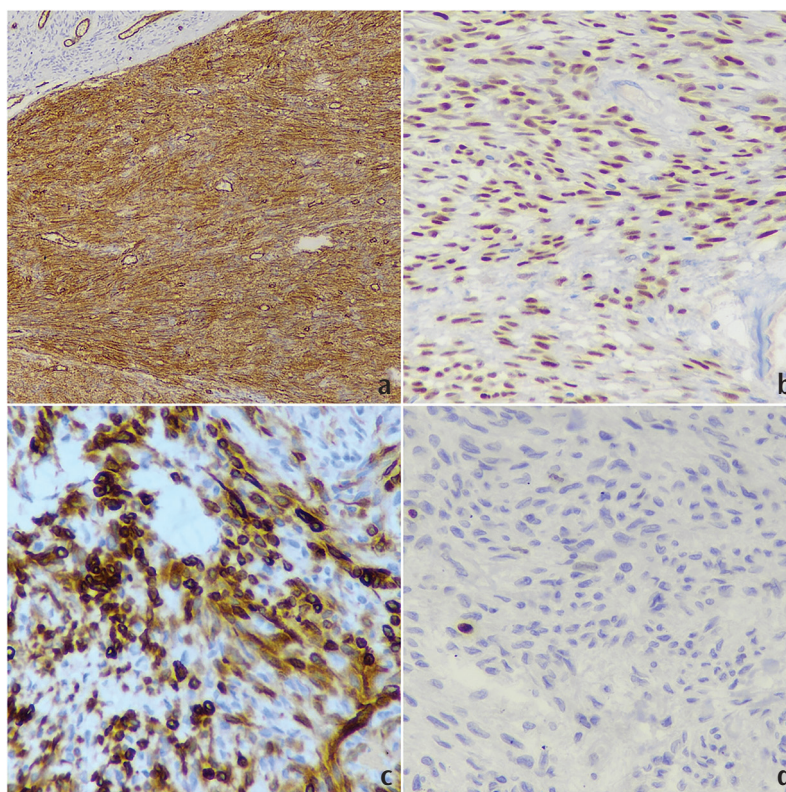


Figure 4. Immunohistochemistry, 100X. (a) CD34, (b) estrogen receptor, (c) desmin, and (d) Ki-67

imaging show a well-circumscribed, lobulated and homogenous mass with no evidence of microcalcifications. However, on USG imaging, differentiation from fibroadenoma may be difficult (5-7). Owing to its rarity, MFB can mimic several benign and malignant neoplasms of the breast, both clinically and radiologically. A careful assessment based on gross, microscopic and IHC correlation is essential to arrive at a correct diagnosis for appropriate management. Fine needle aspiration cytology has a limited role due to high chances for misdiagnosis. Thus, a core biopsy with IHC plays a pivotal diagnostic role (1, 4).

Grossly, MFB is a well-circumscribed, unencapsulated tumor with a rubbery to gelatinous white to yellow cut surface which shows no infiltration into the adjacent parenchyma. Usually, secondary degenerative changes are absent. On microscopy, the tumor shows spindle cells in fascicular pattern with intervening bundles of collagen. Small to medium-sized blood vessels are seen. Entrapped ducts and breast lobules are not seen. Interspersed adipose tissue lobules and mast cells may be present. A few morphological variants have been described besides classical type, including epithelioid, decudoid, cellular, collagenized, lipomatous, myxoid and infiltrative. The differentials of MFB of the breast include fibromatosis, nodular fasciitis, PASH, solitary fibrous tumor, schwannoma, low grade sarcoma, invasive lobular carcinoma and metaplastic spindle cell carcinoma. To resolve this diagnostic quandary, IHC is essential. On IHC, the tumor cells show positivity for CD34 along with vimentin and desmin. IHC positivity for alpha SMA, CD10, ER, PgR and androgen receptor may also be noted. Cytokeratin, p63, EMA, CD117 and S100 protein are negative on IHC. The Ki-67 proliferation index tends to be low (4, 8).

Cytogenetic studies by fluorescent *in situ* hybridization have shown 13q14 deletion, loss of *RB1* and *FOXO-1* loci in MFB. This molecular profile has also been seen in spindle cell lipoma and few other entities, implying a close association between these lesions (2). In a case of MFB of left breast in a 70-year-old man, abrupt transition from MFB to an area with cellular atypia and increased mitosis, resembling sarcomatous transformation, has been recently described, highlighting the necessity for thorough evaluation and careful follow-up (9).

The appropriate treatment comprises of wide local excision without sentinel lymph node biopsy. Simple mastectomy is performed for larger masses, in masses with associated gynecomastia and in women. Follow-up of cases over 15–20 years has shown no distant metastasis. Following adequate excision of the tumor with clear margins obviates the need for any additional therapy, thus conferring a good long-term prognosis (10).

In conclusion, a diagnosis of MFB, though rare, should be considered with careful evaluation of the clinical and radiological features and confirmed by histopathological examination with

relevant IHC markers. A possibility of malignancy should be excluded in a unilateral male breast mass. However, due to the benign nature of MFB and a good long-term prognosis, arriving at the correct diagnosis is crucial to avoid over-treatment, as surgical excision is curative in these cases.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.R.P.; Concept: V.N.G., P.A.E., B.T., T.Y., D.R.P.; Design: V.N.G., P.A.E.; Data Collection or Processing: V.N.G., P.A.E., B.T., T.Y., D.R.P.; Analysis or Interpretation: V.N.G., P.A.E., B.T., T.Y., D.R.P.; Literature Search: V.N.G., P.A.E.; Writing: V.N.G., P.A.E., B.T., T.Y., D.R.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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Primary Merkel Cell Carcinoma of the Breast - A Report of an Extremely Rare Case

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ABSTRACT

Neuroendocrine carcinoma of the breast is a very rare malignancy, and when it presents with characteristics similar to Merkel cell carcinoma (MCC), it is even more uncommon. This report discusses a case of small cell carcinoma exhibiting Merkel cell-like features in an 80-year-old woman who had a history of rheumatoid arthritis under treatment with immunosuppressive drugs. Microscopic analysis showed tissue fragments with areas of necrosis, as well as focal regions containing neoplastic cells. These cells were small to medium in size, with poorly defined borders, scant cytoplasm, and hyperchromatic, atypical nuclei. Immunohistochemical staining revealed perinuclear (dot-like) positivity for cytokeratin 18/8 and strong positivity for cytokeratin 20 and cluster of differentiation 56. The cell proliferation marker Ki-67 was positive in over 80% of the cells. What is extremely rare in this case is the presentation of MCC of the breast as a retro areolar lesion, located behind the areola and associated with nipple discharge, without evidence of a primary cutaneous lesion.

Keywords: Avelumab; CD56 marker, CK20 positivity; HER2 negative, Ki-67; merkel cell carcinoma; merkel cell carcinoma of the breast; neuroendocrine carcinoma of the breast

KEY POINTS

- Merkel cell carcinoma of the breast is extremely rare.
- Diagnosis is challenging due to its similarity to other neuroendocrine tumors.
- Early recognition and multidisciplinary approach are crucial for optimal management.

Introduction

Merkel cells are found in the epidermis and function as touch receptors. They help transmit sensory information related to touch, including texture and pressure, to the brain. These cells also produce certain hormones, which is why they are sometimes

considered neuroendocrine cells (1). Merkel cell carcinoma (MCC) is an unusual primary neuroendocrine carcinoma that mainly appears on the skin (2). Primary neuroendocrine carcinoma of the breast (NECB) is extremely uncommon, accounting for less than 0.1% of all breast cancers (3). MCC is an even rarer and more aggressive subtype of NECB, often seen in immunocompromised

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and elderly patients (4). Here, we present a case of MCC of the breast (MCCB). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Case Presentation

An 80-year-old female with no personal or family history of breast cancer presented with a palpable mass in the right breast without any other significant findings in the breast morphology. The patient was given antibiotic treatment due to a diagnosis of possible mastitis after visiting another breast center with no symptom resolution. This patient has a history of rheumatoid arthritis, under treatment with immunosuppressive drugs, and liver cirrhosis. After visiting our clinical center physical examination of the right breast revealed a retro areolar mass in the right breast, with lymph nodes in the corresponding axillary region without any significant edema of the nipple of the right breast. A breast ultrasound was performed, which revealed, as the initial evaluation, a right peri areolar isoechoic lesion at the 6 o'clock position with increased vascularity and dimensions of 2.37x1.5 cm, displacing but not invading adjacent structures and associated with mild subcutaneous edema. After that visit to our center, the patient decided to abstain for a period of two months without any other visits in the interim. After those two months, the patient reappeared with a worsening of her clinical condition, a worsening of the alteration in the morphology of the nipple, initial ulceration, and a discharge from the nipple.

At this stage, after visiting our unit, the patient underwent digital mammography, which revealed a large, radiodense, retro areolar mass of the right breast causing skin and interstitial thickening with a diameter of 5.5 mm and partial obscuration of its borders, and a recommendation was made for further evaluation with a biopsy. The imaging was evaluated according to Breast Imaging Reporting and Data System (BI-RADS) and was categorized as BI-RADS 5 (Figures 1, 2).

From the magnetic resonance imaging (MRI) of the breast, a large, ovoid-oval, space-occupying lesion was detected in the retro areolar region of the right breast with maximum transverse, anteroposterior, and craniocaudal diameters of 41.2 mm, 39.1 mm, and 59.9 mm, respectively. The imaging findings were highly suggestive of malignancy. A second lesion of smaller dimensions, with a maximum diameter of 36.7 mm, was detected on the posterior surface of the central region of the same breast, 12.7 cm from the nipple. Based on its identical morphological and kinetic enhancement characteristics compared to the retro areolar mass, this posterior lesion was interpreted as a second malignant focus within the same breast, consistent with multifocal disease rather than artifact. Simultaneously, the right breast showed diffuse skin thickening and diffuse interstitial edema (Figures 3, 4).

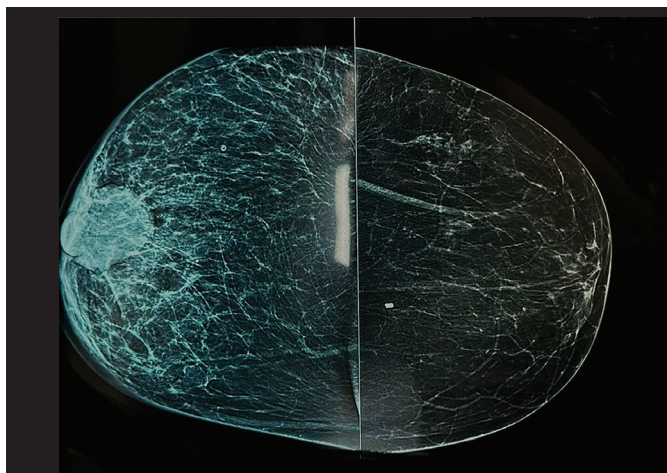


Figure 1. Digital mammography of the right breast revealing a retroareolar, radiodense mass with partially obscured borders and associated skin and interstitial thickening. The lesion measures approximately 5.5 cm in greatest dimension and was classified as Breast Imaging Reporting and Data System 5, indicating high suspicion for malignancy. A posterior density with similar morphology is also visible in the right breast, corresponding to a second malignant focus on magnetic resonance imaging (multifocal disease). Dense artifacts are visible only in the caudal subcutaneous area of the left breast mediolateral oblique projection, related to acquisition technique, without affecting diagnostic interpretation

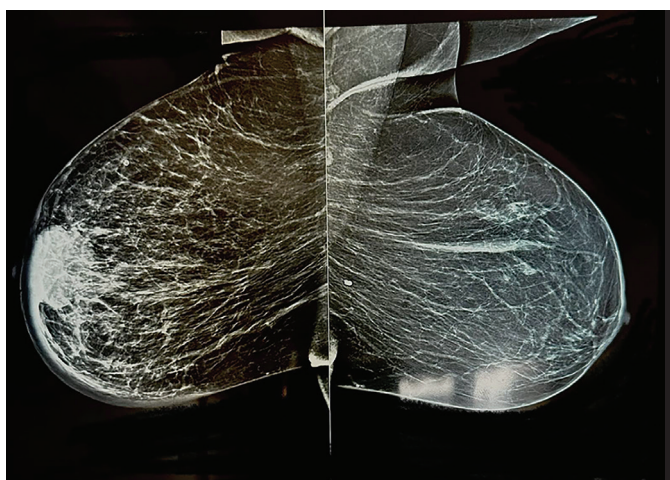


Figure 2. Mediolateral oblique view from digital mammography of the right breast, showing a dense retroareolar mass with architectural distortion and skin thickening. The lesion is radiodense with irregular borders, compatible with a Breast Imaging Reporting and Data System 5 classification. Dense artifacts are visible in the caudal subcutaneous area of the left breast, attributable to compression folds during acquisition, and do not interfere with interpretation



Figure 3. Contrast-enhanced breast magnetic resonance imaging (multiplanar views) showing a large ovoid-oval retroareolar mass with heterogeneous enhancement. A second lesion is visible posteriorly, located 12.7 cm from the nipple. Diffuse skin thickening and interstitial edema are also evident

After the above imaging exams, the patient underwent a percutaneous breast biopsy under ultrasound guidance, and the sample was sent for histopathological examination.

During the microscopic examination, fragments with areas of necrosis were evident, along with focal presence of neoplastic tissue consisting of small and medium-sized cells with indistinct cell borders, minimal cytoplasm, and hyperchromatic nuclei with atypia (Figures 5-8).

The immunohistochemical investigation revealed features, including perinuclear (dot-like) positivity on immunostaining for cytokeratin 18/8 and strong positivity on immunostaining for cytokeratin 20 (CK20) (Figure 9) and cluster of differentiation 56 (CD56) (Figure 10). The cell proliferation marker Ki-67 was positive in more than 80% of the cells (Figure 11). The immunostaining for GATA binding protein 3, estrogen receptor (ER), progesterone receptor, human epidermal growth factor receptor 2 (HER2), and E-cadherin were negative.

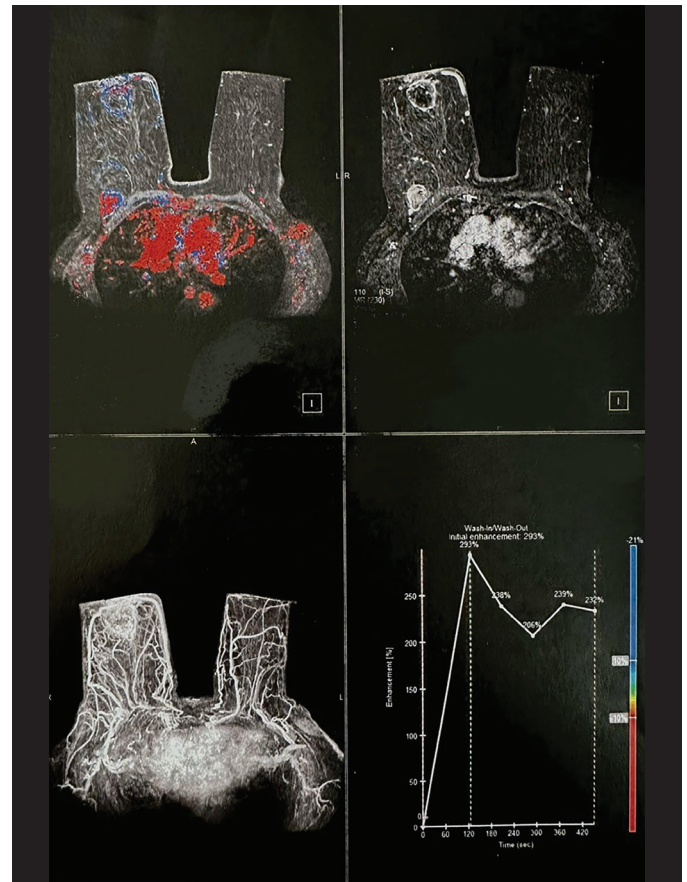


Figure 4. Dynamic contrast-enhanced magnetic resonance imaging of the right breast demonstrating a type III kinetic curve, characterized by rapid initial enhancement, subsequent washout, and a late plateau phase. This enhancement pattern supports the diagnosis of an aggressive malignancy

The conclusion of the Histological Examination was reported as: "Morphological and immunohistochemical features are consistent with the presence of a high-grade carcinoma, primarily of small cell morphology with neuroendocrine characteristics.

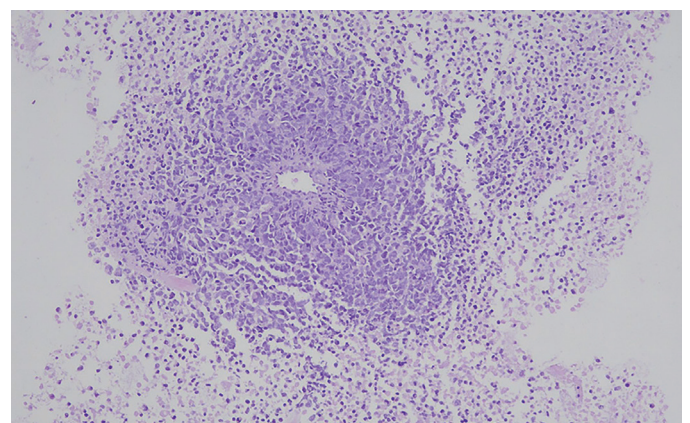


Figure 5. Hematoxylin and eosin stain x200, high-grade nuclear features

Based on the immunophenotype, with CK20 perinuclear dot-like positivity, CD56 expression, and a high Ki-67 proliferation index (>80%), the findings are diagnostic of MCC of the breast”.

To further clarify the diagnosis, the paraffin-embedded tumor tissue was sent to an external certified molecular diagnostic laboratory. Virological analysis was performed using real-time

polymerase chain reaction (RT-PCR, TaqMan method) targeting the Large T Antigen region of the Merkel cell polyomavirus (MCV) genome. Total DNA was extracted from the sample, quality-checked spectrophotometrically, and amplified in the presence of positive and negative controls, as well as an internal amplification control to exclude PCR inhibition. The RT-PCR

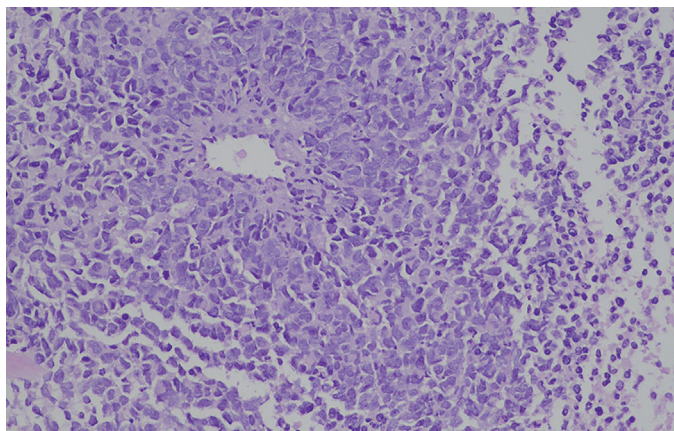


Figure 6. Hematoxylin and eosin stain x400, high-grade nuclear features

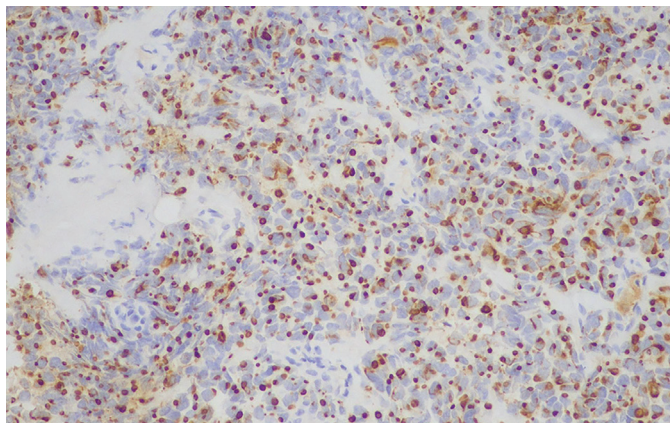


Figure 9. Cytokeratin 20 dot-like immunohistochemical positivity

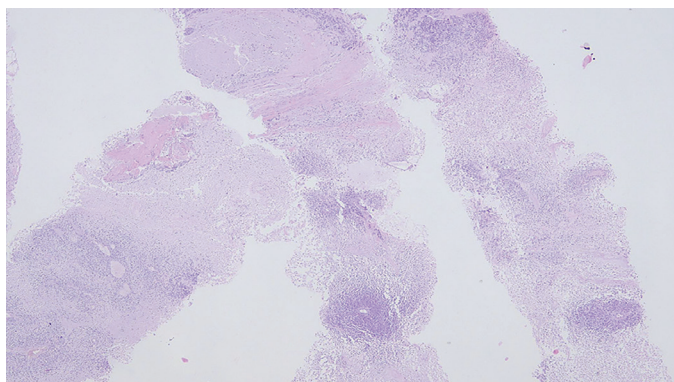


Figure 7. Hematoxylin and eosin stain showing extensive necrosis

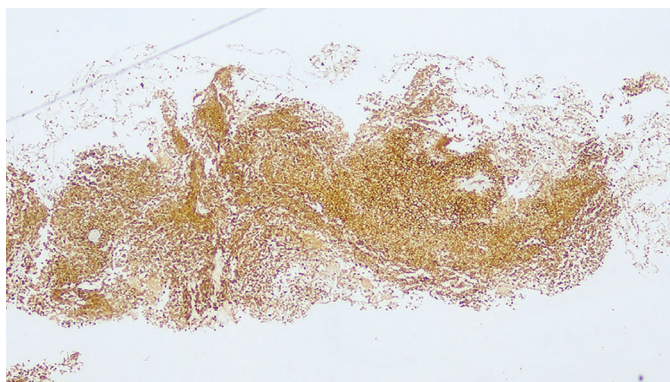


Figure 10. Cluster of differentiation 56 immunohistochemical positivity

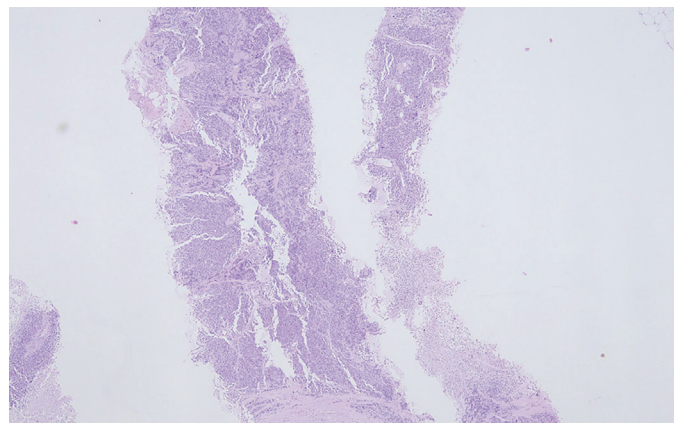


Figure 8. Hematoxylin and eosin stain x40

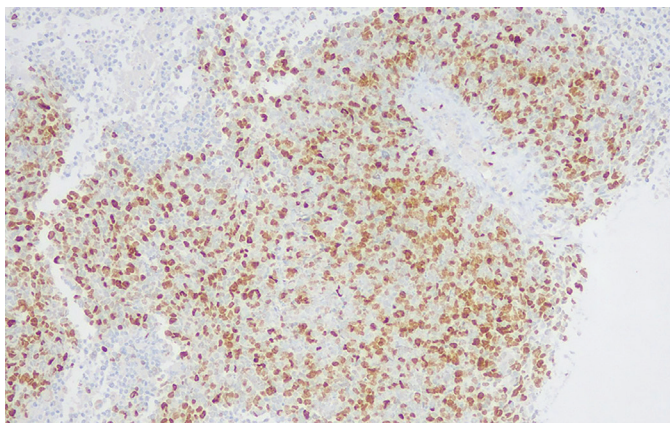


Figure 11. Ki-67 immunohistochemical positivity

result was positive (+) for MCV DNA, confirming viral detection in the tumor tissue. The assay's analytical sensitivity was 50 viral copies per reaction.

The patient, following the diagnosis, was placed on a therapeutic regimen with Avelumab 800 mg Q2W with clinical improvement in the appearance of nipple deformity, after consultation with a specialist oncologist.

Discussion and Conclusion

NECB with Merkel cell characteristics is a rare variant, representing less than 0.1% of all breast cancer cases, with few reports published. The limited literature suggests that this neoplasm primarily affects patients between 60 and 70 years old and does not present with specific clinical features (4-6). It is important to note that the patient was under long-term immunosuppressive treatment for rheumatoid arthritis, which has been recognized, among others, as a risk factor for the development of MCC (5).

On imaging, the lesions of this type of carcinoma are predominantly oval or irregular in shape on mammography, ultrasound, and MRI (7). When the presented case underwent MRI of the breast, a large, ovoid-oval, space-occupying lesion was reported. However, a second posterior lesion was identified on breast MRI. The posterior lesion demonstrated the same imaging morphology and enhancement kinetics as the primary retro areolar tumor, strongly suggesting that it represented a second malignant focus within the same breast. These findings support the diagnosis of multifocal MCCB, rather than artifact or a separate primary tumor. In the present case, the overlying breast skin was intact at initial clinical presentation, and the only finding was a palpable retro areolar mass. The skin and nipple changes observed later on MRI were most consistent with secondary tumor-associated edema and outward extension from the underlying breast parenchyma, rather than primary cutaneous involvement. Histological correlation was not available, and therefore the absence of ductal carcinoma *in situ* in the surrounding tissue could not be confirmed. The posterior lesion was not visible on mammography or during the initial ultrasound examination. It was first identified by MRI of the breast, which highlighted its similar morphological and kinetic features to the primary, retro areolar lesion.

The differential diagnosis includes mainly: i) invasive ductal carcinoma; or ii) malignant phyllodes tumor. Patients with MCCB generally present with larger tumors and are more likely to have positive lymph nodes when compared to other types of invasive breast cancer (4). This contrasts with our case, in which axillary lymph nodes were palpable on clinical examination but imaging studies showed no radiological evidence or pathological lymph node involvement.

The diffuse interstitial changes and skin thickening observed on MRI were most consistent with tumor-associated edema, in line with the dermal involvement of the retro areolar mass. Although lymphangiosis carcinomatosa cannot be entirely ruled out, no evidence of posterior lymph node obstruction was found.

Immunohistochemical analysis is essential for identifying the expression of neuroendocrine markers in tumor cells. The most sensitive and specific markers include chromogranin A, chromogranin B, and synaptophysin. Hormone receptor expression in neuroendocrine breast cancer varies, with reports showing ER positivity in the range 54-90%. The ER immunostaining was negative in the presented case. MCCs typically display a distinctive dot-like immunoreactivity around the nucleus for CK20, which represents the clustering of CK20 intermediate filaments (8). Perinuclear positivity for CK20 immunostaining was also observed in our case. NECB is often positive for hormone receptors, whereas HER2 is almost always negative, although there are also reports of HER2-positive NECB (9). HER2-positive breast carcinomas tend to have a more aggressive behavior and show higher cytological and histological grade compared to HER2-negative breast carcinomas (10). The HER-2 immunostaining was negative in our case.

CK20 is a low-molecular-weight keratin (CK) that is predominantly expressed in the gastrointestinal epithelium, urothelium, and Merkel cells. In a study, 34 individuals with MCC were investigated, and 33 were positive for CK20. That strongly suggests that CK20 positivity in a small cell carcinoma of unknown origin indicates MCC when most tumor cells are positive. A negative CK20 result can effectively exclude the diagnosis of MCC as long as proper antigen retrieval methods are employed and satisfactory staining is achieved with other cytokeratin antibodies (11).

Although our case initially demonstrated the characteristic CK20 perinuclear dot-like positivity, further molecular testing was performed to clarify the diagnosis. The patient's paraffin-embedded tumor block was sent for virological analysis using RT-PCR targeting the *Large T Antigen* region of the MCV genome. The analysis confirmed the presence of MCV DNA within the tumor tissue, providing molecular confirmation of MCCB. Therefore, the final diagnosis was established based on the combined morphologic, immunohistochemical, and molecular findings, definitively identifying this tumor as a MCCB.

Avelumab is a monoclonal antibody and immune checkpoint inhibitor that targets the programmed death-ligand 1 (PD-L1) receptor on tumor cells. By blocking the interaction between PD-L1 and PD-1, Avelumab reactivates T-cell-mediated immune responses against the tumor. It has been approved in several countries for the treatment of metastatic or advanced MCC and has shown significant clinical benefit in this patient population.

To summarize, MCCB is an exceptionally rare and more aggressive form of neuroendocrine carcinoma, sharing clinical and imaging characteristics with other, more common breast cancers. To accurately diagnose MCC and distinguish it from other NECBs, obtaining tissue samples and performing immunohistochemical staining, particularly for CK8/18 and CK20, is essential. Correctly identifying MCC is crucial, as it is often associated with a poorer prognosis for the patient. In the present case, the diagnosis was further confirmed by molecular testing confirming the presence of MCV DNA in the tumor tissue. This molecular confirmation strengthens the diagnosis of MCCB and highlights the importance of incorporating molecular virological analysis in diagnostically challenging and exceptionally rare cases. What was extremely rare and important to highlight in this case report was that the MCCB did not appear on the skin of the breast at initial presentation. On the contrary, it was located behind the areola and was associated with nipple discharge, which has not been mentioned in other case reports referring to this very rare and unusual tumor.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., A.Bou., I.G.; Concept: A.S., I.G.; Design: A.Si., T.A.T.; Data Collection or Processing: A.Si.; Analysis or Interpretation: A.Si.; Literature Search: A.Si., T.A.T.; Writing: A.Si.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Early-Onset Radiation-Induced Angiosarcoma of the Breast: A Case Report and Literature Review

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ABSTRACT

Secondary breast angiosarcomas are rare tumors, and more likely to occur after breast-conserving surgery. They are commonly a late adverse event of radiation therapy that typically presents after ten years of treatment. We report a case of radiation-induced breast angiosarcoma presenting as early as 30 months following the completion of postoperative radiotherapy for breast cancer. Angiosarcoma has a potentially significant risk for local and metastatic recurrence despite total mastectomy. Therefore, a low threshold for suspicion is essential for prompt diagnosis and appropriate treatment.

Keywords: Radiation-induced angiosarcoma; breast-conserving surgery; breast cancer, radiation therapy, secondary malignancy

KEY POINTS

- Reporting an early onset of radiation-induced angiosarcoma after breast-conserving surgery.
- To raise the awareness among breast clinicians and promote early detection of radiation-induced breast angiosarcoma (RIAS).
- To emphasize the importance of early diagnosis and treatment of RAIS.

Introduction

Angiosarcoma is a rare type of cancer that has a considerable impact on patients' prognosis. It is an aggressive malignant tumor of the vascular endothelium. It accounts for less than 1% of all soft tissue breast tumors and tends to be aggressive with a high risk of local recurrence and distant metastases (1). The most common distant metastasis is to the lungs. However, multiple studies have shown metastasis to the cecum, tonsils, buttocks, oropharynx, and heart (1). While the first case of breast angiosarcoma was presented in 1907 by Borrmann, the rarity of the disease has limited the assessment of prognostic factors and

treatment methods (2). Multiple studies have linked histological features and growth patterns to outcomes.

Breast angiosarcoma is categorized into primary and secondary types. Primary angiosarcoma of the breast occurs de novo with no identifiable predisposing factors. It typically presents as a rapidly growing palpable mass with or without skin changes. It usually affects women between the ages of 30 and 50 years (2).

On the other hand, secondary angiosarcoma is mostly seen in elderly patients between the ages of 60 and 70 years, presenting as painless ecchymotic skin lesions with or without ulceration (1, 3).

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Secondary angiosarcoma develops secondary to underlying risk factors, most commonly, after exposure of the breast to ionizing radiation. Radiation-induced angiosarcoma (RIAS) usually develops 7–10 years following radiation therapy to the breast and/or chest wall (1, 2). It frequently appears at the edge of radiation fields where doses and tumor necrosis may be heterogeneous (1). Secondary angiosarcoma may also develop secondary to chronic lymphedema, usually after breast surgery and lymph node dissection. This condition is known as Stewart-Treves syndrome (1). There is a higher incidence of secondary angiosarcoma than primary angiosarcoma because of the availability of early detection of breast cancer and the increased use of breast conservation therapy and adjuvant radiotherapy in the past 30 years. Other predisposing factors for secondary breast angiosarcoma include pathogenic mutations, e.g., *cellular-mycelomatosis oncogene (c-MYC)* amplification, which is directly associated with secondary breast angiosarcoma but to a lesser extent with primary angiosarcoma (4). Also, alterations in FLT4, HRAS, KMT2D, and CRKL are seen in RIAS (4).

Diagnosis can be established by core needle biopsy (CNB), as imaging is often equivocal. Excessive bleeding after CNB could indicate the presence of a highly vascular tumor (2). It is also recommended to perform a skin punch or incisional biopsy in case of secondary angiosarcoma (5). Histopathological analysis of the lesions shows irregular vascular formations with hyperchromatic and irregular nuclei (2). The diagnosis can be confirmed with immunohistological staining markers like CD31, VIII, Fli1, and CD34 (2).



Figure 1. Left breast showing multiple purplish skin lesions (angiosarcoma)

The purpose of reporting this rare case of early-onset RIAS of the breast is to raise the awareness among breast surgeons and oncologists, promote early detection, and discuss the latest guidelines for managing secondary angiosarcoma of the breast.

Case Presentation

Our patient is a 72-year-old female with multiple medical comorbidities and a past medical history of left breast cancer, that was treated with wide local excision and axillary lymph node dissection followed by adjuvant whole breast irradiation. Radiotherapy was in the form of 40.05 Gy in 15 fractions encompassing the whole left breast and regional lymphatics with deep inspiration breath hold technique. It was delivered between February and March 2021. The patient was placed on aromatase inhibition therapy thereafter.

In September 2023, the patient attended the breast surgical oncology clinic with a complaint of left breast skin changes. The left breast examination (Figure 1) revealed a healed radial lumpectomy scar at 3:00 position with no underlying palpable masses. Skin hyperpigmentation was observed at 9:00, associated with multiple cherry-like, small, purple skin nodules around the areola, with no underlying masses. There was no axillary or supraclavicular lymphadenopathy. There was no evidence of breast or upper limb lymphedema. The rest of the examination was unremarkable.

Diagnostic Work Up

Bilateral Breast Mammogram

Mammography revealed bilateral nipple retraction. Left breast showed skin thickening. A lesion with lucent center was identified in the left breast upper outer quadrant (UOQ). Left retro-areolar suspicious calcifications were of note. There was no suspicious axillary lymphadenopathy. The left breast was labelled as Breast Imaging Reporting and Data System (BIRADS 4) (Figure 2).

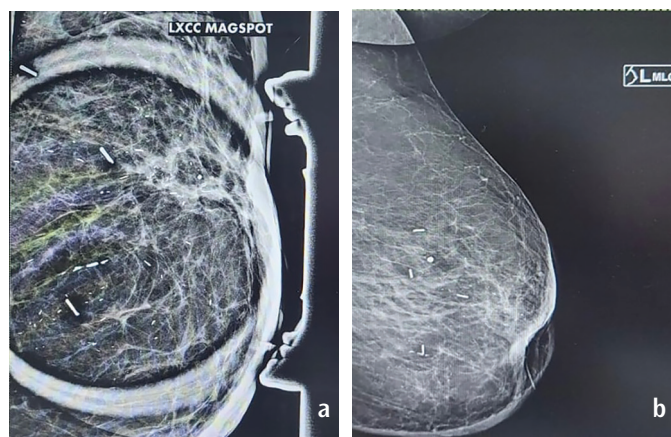


Figure 2. Mammogram of the left breast craniocaudal magnification view (a) showing central microcalcifications, and mediolateral oblique view (b) showing skin thickening

Bilateral Breast Ultrasound

The ultrasound showed evidence of left skin thickening and mild subcutaneous edema, more prominent in the area of skin nodules. A thick wall, poorly defined area of fat necrosis measuring about 17x14 mm was observed in the UOQ, corresponding to the mammographic finding. No significantly enlarged axillary lymph nodes were noted. The left breast was reported as BIRADS 4.

Breast Biopsy

The temporary unavailability of the stereotactic mammogram biopsy at that time precluded the ability to biopsy the left breast BIRADS 4 microcalcification. However, a skin biopsy was determined appropriate to obtain a histological assessment of those skin lesions. Left breast multiple skin punch biopsy showed infiltrative vasoformative nodular growth with focal vasoformative differentiation and solid spindle cell irregular nodules with nuclear atypia and frequent mitosis. The immunohistochemical (IHC) stains showed strong CD34, CD31, and VIMENTIN positivity. In addition, SMA was positive in focal areas. The Ki-67 was 40%. The other IHC stains were all negative, including Caldesmon, Pankeratine Desmin, Calponin, EMA, S100, and CK AE1/AE3. The histopathological examination confirmed the diagnosis of angiosarcoma (Figure 3).

Metastatic Work Up

PET-CT scan was performed to rule out nodal or distal metastasis. It showed fluorodeoxyglucose avid skin enhancement of the

medial aspect of the left breast, with no underlying parenchymal enhancement. There was no evidence of nodal or distal metastasis (Figure 4).

Course of Management

The case was discussed in both breast and sarcoma multidisciplinary tumor boards as a radiation-induced secondary angiosarcoma of the breast with no evidence of distal metastasis and no evidence of breast cancer recurrence. Genetic testing was recommended due to the very early onset of disease occurrence. The tumor boards recommended mastectomy as the primary treatment. Axillary surgery was not recommended due to the lack of clinical evidence of nodal metastasis and the previous history of axillary dissection for breast cancer. In the absence of distal metastasis, National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology guidelines recommend adjuvant chemotherapy if the final pathological size of the tumor is more than 5 cm (6, 7). The patient underwent simple skin-reducing mastectomy, with no reconstruction, in an attempt to excise most of the radiated skin and reduce the risk of recurrence.

The final pathology examination reported post-radiation angiosarcoma involving the skin, 4 cm in maximum dimension, intermediate grade (stage 2A). No necrosis was identified. All surgical margins were negative for tumor cells. Histological examination of the breast tissue showed post-surgical scarring, with no evidence of mammary invasive carcinoma, ductal carcinoma *in situ*, or atypia.

Based on the final diagnosis, no adjuvant treatment was offered for the sarcoma. The patient continued receiving adjuvant aromatase inhibitor for the breast cancer.

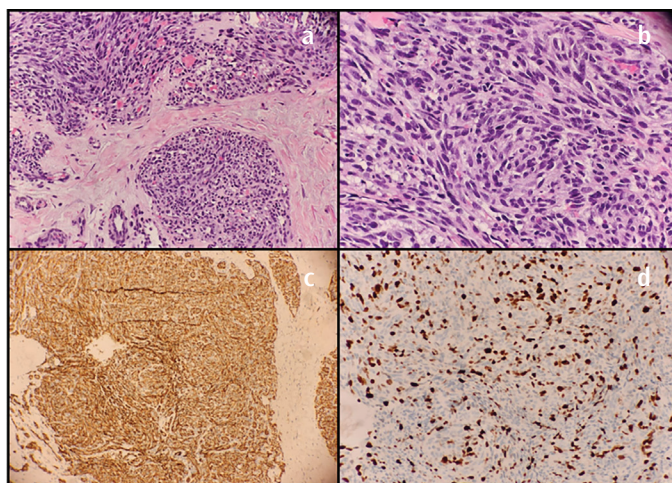


Figure 3. Post-radiation angiosarcoma; intermediate grade. (a) Hematoxylin and eosin shows infiltrating vasoformative spindle cell growth in the deep dermis, (b) High power field shows intermediate-grade solid areas of spindle cell growth, (c) Immunohistochemistry shows diffusely positive CD31. (d) High proliferative activity confirmed through high Ki-67 staining

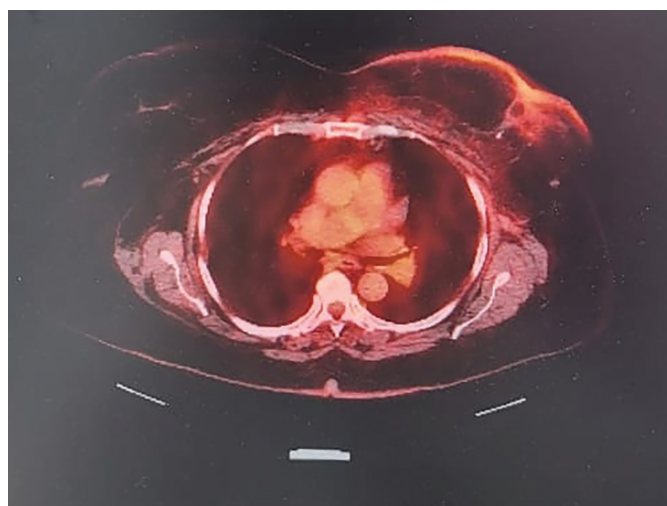


Figure 4. Positron emission tomography-computed tomography of left breast showing fluorodeoxyglucose-avid skin enhancement of the medial aspect of the left breast

Follow-Up

The patient is under surveillance and she remains disease free of both RIAS and breast cancer to date.

Genetic Testing

A hereditary cancer comprehensive panel of 158 genes test was performed for this patient. It showed no pathogenic variants that may explain the clinical phenotype.

Ethical Considerations

A written informed consent was obtained from the patient for publication of this case report and any accompanying images. This was done in accordance with institutional guidelines, the patient’s information/identity was kept anonymized and confidential to ensure privacy.

Discussion and Conclusion

In this case, we report the earliest onset of radiation-induced secondary angiosarcoma of the breast described in the literature, occurring approximately 2.5 years after adjuvant whole-breast radiotherapy. To our knowledge, the shortest latency period previously reported was three years following radiation, with a median latency period of 6.5 years (5).

We conducted a literature review in MEDLINE and PubMed to identify papers published in English over the past 10 years (between 2015 to 2025), about radiation- induced secondary angiosarcoma of the breast, which are summarized in Table 1 (1, 3, 8-15). In all reported series, similar to our case, RIAS developed after whole-breast radiation therapy. Most patients were postmenopausal and diagnosed with RIAS between 50

Table 1. Previously reported RIAS									
Study	Age (Y)	Breast cancer surgery	Radiation therapy	Radiation type	Onset of RIAS (years)*	RIAS grade	Surgical treatments	Systemic treatments	Prognosis
Wyer et al. (12) (2025)	56	BCS	WBR	CFRT	5	NA	Mastectomy+extensive skin resection+portions of pectoralis major muscle+SLNB	None	NA
Parisi et al. (10) (2024)	57	BCS	WBR	CFRT	5	Intermediate	Mastectomy	None	Recurrence at 18 months; received chemotherapy+ radiation. Died 6 months later
Kawata et al. (13) (2024)	70	BCS	WBR	HFRT	6	NA	Skin tumor resection	Chemotherapy	No recurrence
Caterino et al. (1) (2023)	58	BCS	WBR	CFRT	7	High	Mastectomy and ipsilateral node sampling	None	Recurrence after 2 years; underwent excision +adjuvant chemotherapy
Yoshino et al. (3) (2023)	70	BCS	WBR	CFRT	10	Intermediate	Mastectomy	Chemotherapy	NA
Rhoul et al. (9) (2023)	52	BCS	WBR	CFRT	3	NA	Mastectomy	Chemotherapy	No recurrence
Retter et al. (11) (2022)	67	BCS	WBR	CFRT	10	High	Mastectomy	None	No recurrence
Layton et al. (15) (2022)	68	BCS	WBR	HFRT	3	NA	Mastectomy	Radiotherapy	NA
Kacen et al. (14) (2021)	60	BCS	WBR	HFRT	4	NA	Mastectomy	Chemotherapy	NA
Shiraki et al. (8) (2020)	72	BCS	WBR	CFRT	5	High	Mastectomy+extensive skin resection+skin graft	None	Recurrence after 1 year; underwent excision +chemotherapy. Died 32 months after surgery
N: Number of cases reported; RIAS: Radiation-induced angiosarcoma; BCS: Breast conserving surgery; RT: Radiotherapy; WBR: Whole breast radiation; HFRT: Hypofractionated radiotherapy; CFRT: Conventionally fractionated radiation therapy; SLNB: Sentinel lymph node biopsy; N/A: Not available; *: Since radiotherapy									

and 70 years of age, a similar age group to our patient. The typical latency period ranges from 3 to 10 years after irradiation. Our patient had the shortest latency period of 2.5 years, compared to reported cases. Mastectomy was the treatment of choice in almost all reported cases, as well as in our case, to achieve a wide surgical margin. In the studies that reported follow-up, recurrence of angiosarcoma was observed within 2 years of surgery and was associated with a poor outcome. After 30 months of follow up, our patient remains disease-free despite not receiving adjuvant chemotherapy or radiation therapy. This could be attributed to detection at an early stage, when the lesion was small in size and of low grade.

There have been multiple suggested theories regarding the mechanism of radiation-induced angiosarcoma. Some studies suggest that ionizing radiation alters DNA structure, damaging the genome and leading to instability and cancer-related gene mutations, thereby promoting tumorigenesis (16). Multiple studies have reported many genetic alterations associated with angiosarcoma, including amplification of the chromosome 8q24 mapping, *TP53* gene expression, *MYC* oncogene inactivation, and alteration in *POT1*, *RAS*, *ATM*, *APC*, and many more (16). The *MYC* oncogene is subdivided into *c-MYC*, *L-MYC*, and *N-MYC* (16). They are essential in regulating cell growth, maturation, and cell death (16). Many studies have shown that *MYC* amplification is more likely to be present in secondary angiosarcoma than primary angiosarcoma (16). This may aid in distinguishing the primary cause of angiosarcoma. In our case, the patient's genetic test showed no pathogenic variants that may explain the clinical phenotype.

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant disorder that affects the *TP53* (17). It was reported in 1969 by Li and Fraumeni as a remarkable cancer predisposition syndrome (17). It is known to highly predispose patients to leukemia, breast cancer, soft tissue sarcoma, brain tumors, and adrenocortical cancer (17). RIAS risk increases by 16-fold in patients with LFS, through radiogenetic mutations. The *p53* gene is crucial in DNA repair, cell differentiation, apoptosis, and cell cycle arrest (17). Moreover, it was noted that prominent expression of *p53* and *MDM-2* proteins correlates with increased vascular endothelial growth factor (VEGF) expression, which is observed in approximately 80% of angiosarcomas. Alterations in the VEGF receptors, either by mutation or amplification, can lead to the development of angiosarcoma and is associated with worse overall survival (16). *CHEK2* gene mutation has also been reported in LFS (16). Therefore, for patients with LFS who develop breast cancer, many physicians recommend mastectomy over breast conservative surgery to avoid radiation exposure and risk of secondary malignancies such as angiosarcoma.

The diagnosis of breast angiosarcoma can be challenging as imaging is deemed to be nonspecific. It has been reported that 33% of mammary angiosarcomas present with normal mammograms (18). On magnetic resonance imaging, angiosarcoma appears as a low T1 signal and prominently high T2 signal lesion, and the dynamic phase shows early staining followed by persistent staining. Approximately 37% of FNA and CNB results can be false-negative (18). Tumor histological grade is classified into three groups: a) low-grade, vascular channels that anastomose to invade the surrounding breast tissue; b) intermediate-grade, characterized by increased mitotic rate and solid neoplastic vascular growth; c) high-grade lesions that are composed of necrosis, sarcomatous areas, infarction, and hemorrhage (18). The tumor in our patient did not demonstrate any necrosis or infarction, and was labeled as intermediate grade. Certain immunohistochemistry markers may be used to confirm the diagnosis, such as CD31, VIII, Fli1, and CD34, or to differentiate between primary and secondary angiosarcoma in the absence of known risk factors. For example, *MYC* amplification can be identified in 55% of primary angiosarcoma and up to 100% in secondary angiosarcoma. The loss of H3K27me3, an epigenomic chemical marker, has been reported as a valuable tool in the diagnoses of secondary angiosarcoma (3). In this case report, the IHC stains were strong for CD34, CD31, and VIMENTIN positivity, which confirmed the diagnosis of RIAS.

There is no standard staging or grading system for angiosarcoma, due to the different subtypes, locations and organs of origin. The American Joint Committee on Cancer (AJCC) Staging Manual uses a complex system that includes tumor size (T), regional lymph node involvement (N), distant metastasis (M), and histological grade (G), then further divides the primary tumor according to the tumor depth in relation to deep fascia; “a” for superficial tumors and “b” for deep tumors, then categorizes it into anatomic stage or prognostic group. The AJCC TNM system is difficult to apply in staging soft tissue angiosarcoma, because of the different subtypes and the dispersed anatomical locations. The Fédération Nationale des Centres de Lutte Contre le Cancer is a French grading system that looks into tumor differentiation score, mitotic score, and necrosis score (19). Based on the French system, the sarcoma stage in our patient was 2A.

There are no specific guidelines for the management of breast angiosarcoma. However, there are two management guidelines for other soft-tissue sarcomas that are published by the European Society for Medical Oncology and the NCCN (6, 7). Both guidelines for soft tissue sarcoma are comparably similar, and categorize the recommendations based on the AJCC stage.

The mainstay of treatment of breast angiosarcoma is surgical resection. It is essential to ensure a negative margin of at least 2–4 cm (5). Residual tumors after resection may reduce survival.

Our patient underwent a simple mastectomy to enable wide margin excision at the skin level. However, a 54–92% recurrence rate has been reported after negative-margin resection (5). Lymph node metastasis is rare. As a result, axillary surgery is not necessary (2). A prospective study showed that high-grade tumors less than 5 cm have a low recurrence rate with surgery alone (7). This finding supports the NCCN guideline recommendation to omit chemotherapy in tumors <5 cm if widely respected (7). Therefore, our patient did not receive adjuvant chemotherapy. The role of adjuvant treatment in breast angiosarcoma is not well established. It is, however, reported that chemotherapy may play a role in high-grade tumors and metastatic tumors (14). The most commonly used chemotherapies are paclitaxel, docetaxel, and doxorubicin. Paclitaxel is usually recommended in unresectable and metastatic angiosarcoma, as studies have shown good outcomes with its use (8). Also, bevacizumab (anti-VEGF antibody) and pazopanib (tyrosine kinase inhibitor) are used as second-line therapies (8).

The prognosis of RIAS is generally poor. Angiosarcoma, in general, shows a five-year recurrence-free survival rate of only 33% and the median survival is usually two years (16). Multiple factors contribute to the poor prognosis of angiosarcoma, such as tumor size (>5 cm), older age (>60 years), histological grade of the tumor, positive surgical margins, multiple skin lesions, and distant metastasis (5). The early recognition of the disease in our patient ensured the diagnosis at an early stage and favorable disease characteristics that are likely to improve her prognosis.

Radiation-induced secondary angiosarcoma of the breast is a rare malignant tumor with a very poor prognosis. This case study showed that the disease can onset as early as within the first three years after radiotherapy. Therefore, physicians should have a low suspicion index for skin lesions in women with a prior history of radiotherapy, as prompt diagnosis at earlier stage may improve prognosis.

Ethics

Informed Consent: A written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., K.A., F.A., A.D., J.A.; Concept: S.A., J.A.; Design: S.A., J.A.; Data Collection or Processing: S.A., J.A.; Analysis or Interpretation: S.A., K.A., F.A., A.D., J.A.; Literature Search: S.A., J.A.; Writing: S.A., K.A., F.A., A.D., J.A.

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Eur J Breast Health 2026;22(4):518-519

Comment on “Sentinel Lymph Node Biopsy for Breast Cancer in North Africa: A Retrospective Analysis of Feasibility, Safety, and Morbidity Reduction in a Real-World Setting”

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University of Health Sciences (Youcef El Khatib), Algiers, Algeria

Keywords: Breast cancer; sentinel lymph node biopsy; sentinel lymph nodes

Dear Editor,

We read with great interest the article by Belkhodja et al. (1) evaluating the implementation of sentinel lymph node biopsy (SLNB) for early-stage breast cancer at the Maternity Center of Bizerte, Tunisia. This retrospective study of 64 patients compared SLNB with axillary lymph node dissection (ALND) and reported an 89% SLN detection rate using a dual-tracer technique (technetium-99m and methylene blue). The study demonstrates reduced postoperative morbidity in patients undergoing SLNB, including lower incidence of lymphedema, less hemoglobin loss, shorter hospital stay, less pain, and fewer limitations in arm mobility.

The study provides valuable insights, particularly through its detailed description of the SLNB technique and intraoperative procedures; comprehensive data collection from patient records, pathology reports, surgical logs, and follow-up; and its contribution of evidence from a previously underrepresented population.

However, several limitations should be noted. Providing additional details on patient characteristics, including age distribution and menopausal status, would not only help

contextualize the observed outcomes but also allow a more precise comparison with international guidelines and facilitate interpretation of SLNB applicability across different patient subgroups (2).

Additionally, limited details regarding tumor grade and hormone receptor/human epidermal growth factor receptor 2 status restrict precise assessment of patient risk and consideration of omitting ALND or SLNB. Existing evidence highlights the importance of these parameters for informed patient selection and for guiding adjuvant therapy (3).

Furthermore, the study includes N1 patients; what criteria were used to decide whether to perform ALND after a positive SLNB? How do these criteria align with current guidelines that recommend omission in patients with one or two positive SLNs under defined conditions (4)? Additionally, could a longer follow-up period provide a more complete assessment of late recurrences, particularly among luminal subtypes? In patients receiving neoadjuvant chemotherapy (NAC), the absence of reported clipping of the target node may underestimate residual nodal disease, raising the possibility of false-negative SLNB results (5).

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This study demonstrates the feasibility of SLNB and its benefits in reducing morbidity in a Tunisian setting, and highlights key aspects of its implementation.

Recent consensus suggests that SLNB may be safely omitted in select postmenopausal patients with favorable tumor characteristics, serving primarily as a staging tool rather than determining systemic therapy (2). Notably, the reported 11% SLNB failure rate appears to largely reflect cases with extensively involved nodes rather than procedural limitations.

Although the study is limited by its retrospective, single-center design and relatively small cohort, it nonetheless provides valuable real-world data. Careful patient selection, incorporation of targeted node clipping for NAC, and extended follow-up could further strengthen the safe application of axillary de-escalation strategies in similar settings, ultimately supporting evidence-based, individualized surgical management.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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One-Stop Contrast-Enhanced Mammography-Guided Breast Biopsy: A Practical Workflow from a Tertiary Referral Center

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Dear Editor,

Contrast-enhanced mammography (CEM) improves the visualization of tumor neovascularity through intravenous administration of iodinated contrast medium. Using a dual-energy digital mammography technique, CEM produces low-energy images alongside iodine-specific recombined images that clearly delineate contrast-enhancing lesions within the breast parenchyma (1).

Established clinical indications for CEM include clarification of suspicious screening findings, locoregional staging of breast cancer, and assessment of treatment response, with recent evidence further supporting its role as a supplemental screening tool in women with dense breasts (1, 2). CEM is particularly valuable in the management of enhancing mass and/or non-mass lesions detected on magnetic resonance imaging (MRI) or CEM that lack a sonographic correlate. In such cases, CEM-guided biopsy offers a critical diagnostic pathway for lesions occult on ultrasound (US) (3-5).

Our breast clinic is a tertiary referral center serving a large regional population. Diagnostic and interventional breast procedures are therefore routinely performed within a one-stop clinic model, often on the same day, with the aim of minimizing diagnostic delays, reducing repeated hospital visits, and alleviating overall

patient burden. The majority of patients referred for CEM-guided biopsy present with suspicious lesions detected exclusively on breast MRI. At many institutions, diagnostic CEM and biopsy are performed on separate days; alternatively, some centers repeat iodinated contrast several hours later to enable same-day biopsy (3). Both approaches may result in repeated contrast exposure and a less efficient workflow.

Proposed Workflow

All patients referred to our center with MRI-only enhancing lesions first undergo a targeted US examination performed by a dedicated breast radiologist. In the absence of a sonographic correlate, CEM is scheduled to localize the occult lesion. As lesion localization has already been established on prior MRI, patients are counseled regarding the possibility of same-day biopsy before imaging begins.

Intravenous administration of non-ionic iodinated contrast medium (1.5 mL/kg) is initiated. Approximately 2 minutes after the start of contrast injection, the breast is positioned on the biopsy table with appropriate compression. Subsequently, a contrast-enhanced full-field diagnostic acquisition is performed in the craniocaudal projection. Once adequate lesion conspicuity is confirmed, the stereotactic biopsy unit is mounted immediately, and CEM-guided biopsy is performed without

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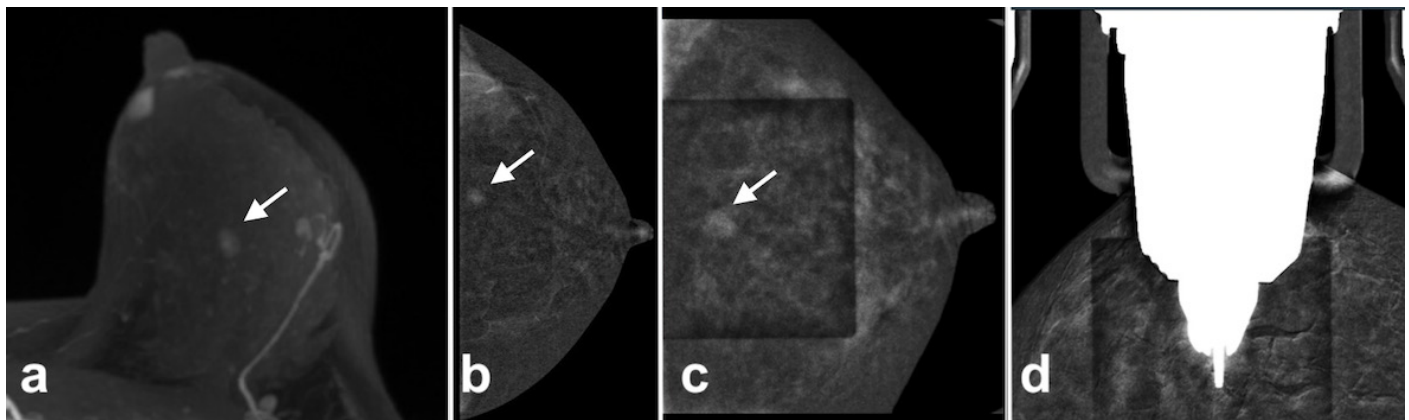


Figure 1. CEM-guided biopsy of an MRI-only enhancing lesion using a single contrast administration. (a) Follow-up breast MRI demonstrates a newly detected 6.5-mm lobulated mass with circumscribed margins and a heterogeneous enhancement pattern in the upper central quadrant of the left breast (arrow). (b) A unilateral craniocaudal CEM recombined image confirms lesion conspicuity (arrow). (c) Planning image acquired following stereotactic unit mounting demonstrates persistent lesion enhancement (arrow). (d) Pre-fire image obtained using a vertical approach confirms accurate needle targeting. Histopathological analysis of the 14-gauge core needle biopsy specimen reported columnar cell changes with apical snouts

CEM: Contrast-enhanced mammography; MRI: Magnetic resonance imaging

additional contrast administration (Figure 1), in accordance with previously described technical principles (3-5). If lesion localization remains uncertain, the examination is limited to diagnostic imaging alone, the mediolateral oblique view is completed, and biopsy is deferred to a subsequent session.

Practical Advantages

This workflow offers several clinically meaningful advantages:

- Avoidance of repeated iodinated contrast administration, either within the same day or across separate visits.
- Completion of diagnostic confirmation and biopsy within a single visit, in accordance with one-stop clinic principles.
- Improved patient satisfaction by consolidating diagnostic and interventional procedures during a single session.

Prior studies have demonstrated that radiation doses associated with CEM-guided biopsy remain within accepted safety thresholds and are comparable to those of conventional stereotactic biopsy techniques, supporting the routine integration of CEM guidance into interventional breast practice (6).

Timing Considerations, Limitations and Future Perspective

In our institutional experience, lesions identified on diagnostic CEM generally remain conspicuous beyond the initial 10-minute post-contrast window, with persistent enhancement providing sufficient time to safely complete the biopsy procedure (3). Conspicuity-related issues due to increased background

parenchymal enhancement and a theoretical risk of diminished enhancement over time remain potential pitfalls that should be acknowledged when adopting this technique (3).

Current evidence supports the use of single-contrast protocols and targeted diagnostic confirmations to optimize interventional CEM workflows (3-5). In our workflow, skin surface measurements and markings are applied prior to CEM acquisition as a supportive step for procedural planning (4). These markings serve as a practical guide to determine the most appropriate patient positioning (either upright or lateral decubitus) on the biopsy table. We additionally perform an initial full-field diagnostic CEM acquisition before mounting the stereotactic unit, which provides an essential baseline for confirming lesion conspicuity and facilitates a more confident procedural start, particularly during the early stages of adopting this technique when clinical experience may be limited.

Should a loss of conspicuity occur following lesion localization, alternative strategies remain available, including rescheduling the procedure for a separate day or repeating contrast administration several hours later. In cases where the lesion cannot be visualized under CEM guidance, MRI-guided biopsy remains a viable and established alternative.

A single-contrast, one-stop CEM-guided biopsy protocol appears to be a practical, time-efficient, and patient-centered approach for the management of MRI-only enhancing breast lesions, particularly in high-volume tertiary referral centers. This strategy has the potential to reduce cumulative contrast exposure

while streamlining the diagnostic and interventional pathway, without compromising procedural feasibility or diagnostic yield. Multicenter prospective studies are warranted to test the feasibility of this approach and to establish standardized protocols for broader clinical implementation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ö., U.A.P.; Concept: H.Ö., H.Ö.A.; Design: H.Ö., H.Ö.A.; Analysis and/or Interpretation: H.Ö., H.Ö.A.; Literature Search: H.Ö., U.A.P.; Writing: H.Ö., U.A.P., H.Ö.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Methodological Considerations on Tomosynthesis-Guided Vacuum-Assisted Excision for B3 Breast Lesions

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Keywords: B3 lesions; breast biopsy; surgical de-escalation; upgrade risk; vacuum-assisted-excision

Dear Editor,

The article by Valkovic Zujic et al. (1) addresses whether vacuum-assisted excision (VAE) can safely reduce surgical overtreatment of B3 lesions diagnosed by tomosynthesis-guided vacuum-assisted biopsy (VAB). The study is commendable for its focus on multidisciplinary de-escalation in a field where practice remains heterogeneous (2).

Several methodological aspects, however, deserve attention when interpreting the conclusion that VAE represents a safe alternative to surgical excision (SE) for B3 lesions (1). The comparison between VAE and SE is intrinsically shaped by allocation decisions made by the multidisciplinary team: lesions considered radiologic-pathologic concordant and lower risk were directed toward VAE, whereas lesions with greater concern for underestimation were preferentially referred for surgery (1). This allocation is clinically appropriate, but has important methodological implications: the VAE and SE cohorts are enriched for different baseline oncologic risk profiles and do not represent equivalent treatment arms; the 30.8% upgrade rate observed in the SE group is a direct consequence of this selection strategy (1, 3).

Second, the absence of malignant upgrades in the VAE group should be interpreted with caution, given the limited number of VAE-treated lesions and the shorter mean follow-up compared with that of the surgical cohort (1). In published retrospective series, upgrade after VAE or VAB is uncommon but not negligible, and is consistently influenced by histologic subtype, particularly by the presence of atypia (3, 4). Recent single-centre data on 366 screen-detected B3 microcalcifications further confirm non-zero upgrade rates despite vacuum-assisted sampling (4).

A zero-upgrade rate in a small, highly selected series is therefore reassuring, yet is better viewed as hypothesis-generating than as definitive proof of long-term oncologic safety (1, 3). This interpretation aligns with current guideline-based stratification. The 2024 European recommendations (European Society of Breast Cancer Specialists/European Society of Breast Imaging/European Society of Pathology/European Society of Surgical Oncology) support VAE or surveillance for selected B3a lesions when there is radiologic-pathologic concordance, while recommending surgery for ADH/AIDEP and lobular carcinoma *in situ*/lobular intraepithelial neoplasia grade 2, whose upgrade rates remain higher (2, 4). In the present study, ADH/AIDEP accounted for most surgical upgrades, reinforcing that VAE's

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strength lies in selective use rather than in broad substitution for surgery (1). Prior ultrasound-guided 8-gauge VAE experience with BI-RADS 3–4 masses points in the same direction, with lesion size and imaging features emerging as key determinants of complete excision (5). Although ultrasound-guided and tomosynthesis-guided settings are not directly superimposable, both approaches converge on the same practical message: minimally invasive excision is most reliable when grounded in strict radiologic-pathologic concordance and subtype-specific risk assessment (1, 2, 5).

These observations contextualise rather than diminish the authors' contribution. The study supports multidisciplinary team-guided de-escalation, but underscores the need for larger prospective registries, standardized subtype-specific reporting, and longer follow-up before equivalence with surgery can be claimed (3). In this evolving field, the challenge is not simply to replace surgery with minimally invasive excision, but to match the intensity of intervention to the biological and radiologic risk of each B3 lesion, so that de-escalation becomes a matter of precision rather than simplification.

Footnotes

Authorship Contributions

Concept: E.A., T.P.; Design: E.A., T.P.; Data Collection and/or Processing: E.A.; Analysis and/or Interpretation: E.A., T.P.; Literature Search: E.A., T.P.; Writing: E.A., T.P.

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Following the publication of the article “Burhamah W, Shah U, Sharma K, Xiangmei C, Javeria I. Outcomes of chest wall perforator flaps for partial breast reconstruction: a single-center, singlesurgeon experience. Eur J Breast Health. 2026;22(3):294-306. DOI: 10.4274/ejbh.galenos.2026.2025-12-7” a request has been received to update the name of the author Caroline Xiangmei to “Xiangmei Caroline Cui” in the article; the mistake in question was inadvertently made by the author. This correction has been implemented. The sections where corrections were made are detailed below:

Published on page 294;

Waleed Burhamah¹, Unnati Shah², Karisma Sharma³, Caroline Xiangmei³, Iqbal Javeria²

Corrected on page 294;

(The corrected parts are given in bold)

Waleed Burhamah¹, Unnati Shah², Karisma Sharma³, **Xiangmei Caroline Cui**³, Iqbal Javeria²

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Cite this article as: Burhamah W, Shah U, Sharma K, Xiangmei C, Javeria I. Outcomes of chest wall perforator flaps for partial breast reconstruction: a single-center, singlesurgeon experience. Eur J Breast Health. 2026;22(3):294-306

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