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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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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 articlesreviews, 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.

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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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European Journal of Breast Health

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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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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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SYSTEMATIC REVIEW

European Journal of BREAST HEALTH

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Evolving Concepts and Contemporary Management of Early-Stage Breast Cancer: An Evidence-Based Approach to Grey Zones from a Comprehensive Breast Unit Part 1: Locoregional Therapy, Pathology, Radiology

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ABSTRACT

Breast cancer is the most frequently diagnosed malignancy among women worldwide, and significant progress in systemic therapy, surgical techniques, and radiotherapy has contributed to improved clinical outcomes. However, many clinical scenarios encountered in daily practice are not fully addressed by randomized trials, leaving persistent areas of uncertainty in the management of early-stage breast cancer. To meet these challenges, the multidisciplinary panel at Research Institute of Senology, Acıbadem University developed consensus-driven recommendations for clinical scenarios that are encountered in daily practice. Herein, we aim to reflect both current evidence and institutional practice, and to provide practical guidance in areas where uncertainty persists. As breast cancer treatment continues to evolve, updates will be required to integrate emerging data and refine individualized patient care.

Keywords: Breast cancer; early-stage; multidisciplinary; radiation oncology; radiology; pathology; surgery

KEY POINTS

- Early-stage breast cancer management increasingly requires individualized strategies that integrate clinical, radiological, pathological, and molecular data rather than a one-size-fits-all approach.
- Breast-conserving surgery remains oncologically safe for most patients with early-stage breast cancer, provided that adequate surgical margins are achieved and sentinel lymph node biopsy or targeted axillary dissection is performed in accordance with disease stage and treatment response.
- Advances in surgical techniques, such as breast-conserving surgery following neoadjuvant therapy and refined axillary staging, along with hypofractionated radiation schedules, support de-escalation without compromising oncologic safety.

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Introduction

Breast cancer (BC) is consistently reported as the most frequent cancer in women, with an estimated 2.3 million new cases leading to 670,000 deaths in 2022; its uneven global burden highlights the urgent need for standardized and unrestricted access to comprehensive management strategies (1). Through the exceptional efforts of pre-clinical and clinical researchers worldwide, substantial advances in the understanding of biology and treatment have been achieved, leading to a 2.5% decrease in mortality in some high-income countries (2). Because not all clinical scenarios correspond to clinical trial settings, routine management of BC requires a personalized, evidence-guided approach tailored to each patient's needs.

In this article, we provide practical recommendations for common clinical questions that arise during our weekly multidisciplinary tumor board meetings. The problems addressed here reflect our evolving, personalized approach aligned with emerging data on clinical scenarios encountered in daily practice at the Research Institute of Senology, Acıbadem University (RISA). We acknowledge that some of our statements may not have a strong level of evidence or be generalizable to all patients due to disparities in medical care, patient preferences, or lack of treatment availability. However, we believe the recommendations included in this report will provide guidance on various challenging and controversial issues faced by many physicians involved in BC care nationwide. As RISA, we aim to develop institution-specific standards to guide the evaluation and management of patients with early-stage disease. Our panel comprises general and plastic surgeons, medical oncologists, radiation oncologists, radiologists, clinical geneticists, a pathologist, and supportive medical personnel, including nurses, physiotherapists, nutrition specialists, and a psychologist, working in an academic clinical setting specialized in BC. Initially, each clinical group identified questions of clinical relevance, either because of a lack of robust data, pending data from clinical trials, or unique scenarios not addressed by the available evidence and requiring expert opinion. All these questions were discussed in detail in a separate meeting, and if a consensus on an issue was not reached, alternative opinions were put to a vote to determine the best approach reflecting the recommendations of the experts on the panel.

Because treatment for BC rapidly evolving, the statements reported as RISA opinions may be challenged by emerging data from ongoing clinical trials. Therefore, this work will be updated every two years.

Clinical and Research Consequences

1. Radiology

1.1. What is the Optimal Screening for Women?

Mammographic screening and early detection of disease decrease BC mortality (3). In our country, cancer early diagnosis, screening, and education centers offer biannual mammographic screening to women over the age of 40. However, the sojourn time for BC is shorter in younger women. The risk of advanced-stage disease is 21–28% higher with biannual screening than with annual screening, and the reduction in mortality is smaller when the screening interval exceeds 1 year in young women (4). It has been documented that more than 1/3 of BC patients in our country are younger than 50 years of age (5). Therefore, we recommend annual screening for all women aged 40–49. For women over the age of 50, screening intervals should be determined by individual risk factors and breast composition.

Breast density reduces cancer detection rates (CDR) and significantly increases interval cancer risk by masking small cancers; it is an independent risk factor, conferring a 2.9–6-fold higher BC incidence than in fatty breasts (6, 7). Accordingly, women with dense breasts benefit from supplemental screening. The main supplemental screening methods are digital breast tomosynthesis (DBT), ultrasound (US), and contrast-enhanced modalities, such as magnetic resonance imaging (MRI) and contrast-enhanced mammography (CEM) (8). DBT detects lesions similar to those detected by mammography (MMG), may miss more aggressive, benign-appearing tumors, and does not reduce the interval cancer rate. US increases the CDR more than DBT does (by an additional 2.5–4/1,000), particularly for invasive tumors, and reduces interval cancers; however, it is operator-dependent and time-consuming. Because performance is highly user-dependent and benign and malignant features can overlap, US can prompt unnecessary biopsies and short-interval follow-up recommendations for BI-RADS 3 lesions. Automated breast US, designed to mitigate these limitations, yields a similar or slightly lower CDR, but a higher recall rate. Contrast-enhanced modalities (MRI, MMG) provide functional and morphologic information with markedly higher sensitivity, yielding large CDR gains (≈14–16 per 1,000), but require intravenous contrast and are relatively expensive and less accessible (8).

Today, instead of a "one-size-fits-all" approach, risk-based screening is preferred in many centers (9), and we also believe that we can best serve our patients by applying personalized screening. Current guidelines recommend annual MRI screening in addition to MMG/DBT for high-risk patients (those with high-

risk gene mutations, those who have received mediastinal radiotherapy (RT) at a young age, and those with a lifetime risk higher than 20%) (3). It has been demonstrated that patients at intermediate risk for BC (patients who have dense breasts, who have had a diagnosis of an atypical lesion in previous biopsies, who have a history of BC, or who have a lifetime risk of 15–20%) also benefit from supplemental screening (9, 10). We recommend annual US and MMG/DBT screening for these women. Moreover, based on studies showing increased CDR with MRI screening in women with dense breasts (11, 12), we recommend that contrast-enhanced studies (MRI or CEM) replace US every 2–4 years. Screening with MMG or DBT is sufficient for women who do not have any of the above risk factors. We anticipate that artificial intelligence and machine learning programs that can evaluate the complexity of breast tissue will play a role in identifying those patients at increased risk who might benefit from MRI screening (13).

1.2. What is the Optimal Radiologic Modality for Preoperative Staging and Response Evaluation?

Breast MRI is the most sensitive modality for delineating the extent of disease in patients with newly diagnosed BC (14, 15). Preoperative MRI is recommended for patients with dense breasts who are candidates for breast-conserving surgery (BCS), particularly those younger than 50 years. It is also appropriate for patients with invasive lobular carcinoma (ILC) or ductal carcinoma *in situ* (DCIS), for those with suspected multifocal disease, and for those with discordant conventional imaging findings. CEM is an acceptable alternative when MRI is unavailable (16). This strategy may reduce re-excision rates and local recurrence (17, 18). However, any suspicious finding on contrast-enhanced imaging that could alter the treatment plan should be confirmed histologically before surgery.

In patients receiving neoadjuvant chemotherapy, MRI is the most accurate modality for evaluating treatment response (19, 20). Baseline and post-treatment MRIs should be obtained to determine treatment response, and when an interim assessment is required, an MRI can objectively measure early response and support timely modification of the therapeutic plan. For candidates for BCS, the primary tumor should be marked with a clip before systemic therapy. When axillary disease is limited (≤2 biopsy-proven metastatic nodes), the involved nodes should be marked prior to therapy to enable targeted axillary dissection (TAD) (21).

1.3. What is the Optimal Post-Treatment Radiological Modality During Routine Follow-up?

Regardless of age, annual MMG, with or without DBT, is recommended for all women who have undergone BCS (10). The first imaging follow-up should be performed 6 months after completion of therapy. Routine semiannual US surveillance is not indicated. We recommend annual supplemental US for patients after BCS and screening MRI every 2 years for those at increased risk; in years when MRI is performed, supplemental US may be omitted. Patients considered at increased risk include:

- <40 years at diagnosis
- carriers of *BRCA1/BRCA2* pathogenic variants
- patients <50 years at diagnosis with dense breasts
- whose tumor was detected only by MRI at diagnosis
- tumor >5 cm at diagnosis
- multicentric or multifocal tumors treated with BCS
- patients who did not receive RT after BCS
- triple-negative tumors
- ILC
- interval cancers.

Patients not considered at increased risk should return to the population-based screening program 10 years after treatment, and screening should continue as long as they remain in good health.

Although some evidence supports screening after nipple- or skin-sparing mastectomy with reconstruction, current guidelines do not recommend routine radiologic follow-up (20). However, any residual breast tissue—particularly after nipple-sparing procedures—should be evaluated with MMG or MRI 6–12 months after therapy. If substantial residual tissue is present, follow-up should use the same protocol as for patients treated with BCS. If no significant tissue remains, perform a physical examination every 6 months and/or an annual US; MRI may be added every 3–4 years or as clinically indicated. In our experience, US and MRI can detect residual or recurrent breast tumors in these patients earlier than by physical examination.

In patients who have undergone simple mastectomy, physical examination alone is sufficient to evaluate the chest wall and no imaging follow-up is required (22).

2. Pathology

2.1. What is the Optimal Method to Evaluate Ki-67?

Ki-67 is a nuclear proliferation marker expressed in all active cell-cycle phases and has diagnostic and prognostic utility across cancers, including BC, where it is an independent predictor of disease-free survival; for example, five-year disease-free survival was 86.7% with Ki-67 ≤15% versus 75.8% with Ki-67 >45%

(23, 24). By immunohistochemistry (IHC), any brown nuclear staining is considered indicative of Ki-67 positivity in tumor cells; cytoplasmic staining alone is not counted. Only invasive tumor nuclei should be scored, excluding the typically smaller, scattered lymphocytes (often Ki-67–positive) and spindle-shaped stromal cells surrounding tumor nests. Several methodologies have been developed for the estimation of Ki-67–positive cells, including visual estimation, manual counting, and automated digital image analysis. While visual estimation is the fastest and least costly method (typically <1 minute), it suffers from poor reproducibility and limited reliability. Manual counting is a cost-effective alternative, but is time-consuming, requiring approximately 5–6 minutes per case. This method is impractical for routine use due to its low reproducibility (25). Furthermore, inter-observer variability is a known challenge in Ki-67 scoring, and threshold values may vary considerably across institutions (26). Therefore, automated analysis has been developed to minimize such variability and improve reproducibility (27).

Digital image analysis involves identifying hotspots and calculating the mean percentage of brown-stained pixels among all stained pixels. The Ki-67 index is calculated automatically as the number of positively stained tumor nuclei divided by the total number of tumor nuclei × 100.

2.2. What is the Optimal Method for HER2 Evaluation?

HER2 is overexpressed in about 15% of BC cases, due to gene amplification, and is routinely assessed by IHC to determine eligibility for anti-HER2 therapy. IHC scoring per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) evaluate at least 10% of invasive tumor cells and is based on membrane staining completeness and intensity: 0 (null) if <1% of cells stain; 0 (ultralow) if ≥1% stain but without sufficient completeness or intensity; 1+ if ≥10% show weak, incomplete staining (negative/low); 2+ if ≥10% show weak-moderate complete or incomplete staining or if <10% show strong staining (equivocal); and 3+ if ≥10% show strong, complete membranous staining (positive). For IHC 2+ tumors, fluorescence *in situ* hybridization/*in situ* hybridization is required to quantify *HER2* gene amplification using both the HER2/CEP17 ratio and mean HER2 copy number; the results are classified into the five ASCO/CAP-defined interpretive groups. Ambiguous genomic profiles (e.g., Groups 2 and 4) necessitate integration with IHC findings and morphological features to establish a final HER2 status. This combined stepwise evaluation minimizes analytical discrepancies, improves diagnostic precision, and ensures accurate identification of patients most likely to benefit from HER2-targeted therapies (28).

To reduce interobserver variability, digital pathology workflows use automated pipelines comprising slide digitization, tumor-region detection (with optional manual annotation), parameter calibration, cell segmentation, quantitative assessment of membrane completeness and intensity, cell-level classification, and generation of a final HER2 score according to ASCO/CAP criteria (29-31).

In our daily practice;

• Ki-67 and HER2 samples are first digitized using high-resolution slide scanners such as Leica, Hamamatsu, and 3DHİSTECH.

• Once the digital slides are available on the ViraSight platform, superusers can initiate Ki-67 and HER2 analyses directly on the whole slide images.

• Importantly, the algorithms are compatible with all major slide formats, ensuring smooth performance regardless of the scanner vendor (27, 30).

• Upon completion of the analysis, the system automatically sends notifications to the relevant pathologists. The pathologists then review the analyses through the platform.

• The pathologist interprets the ViraSight-generated output and determines their final score or index based on the diagnostic context.

• This workflow not only enhances diagnostic accuracy but also accelerates and standardizes the evaluation process through digital and artificial intelligence-assisted integration.

3. Controversial Issues in Breast Cancer Surgery

3.1. What are the Optimal Surgical Margins for Invasive and In-situ Breast Cancer?

Achieving negative surgical margins in BCS is essential to minimize the risk of local recurrence. After excision, histopathological assessment of the margins is required to confirm adequacy. For patients with invasive breast carcinoma, with or without an associated DCIS component, the “no ink on tumor” criterion (absence of invasive or *in situ* carcinoma at the inked margin) is considered sufficient (32). In contrast, for patients with pure DCIS or DCIS with microinvasion, a wider surgical margin of at least 2 mm is generally recommended to lower the risk of ipsilateral breast tumor recurrence (33). Moreover, when partial breast irradiation (PBI) is planned, margins of ≥2 mm are advised to ensure optimal local control (34, 35).

3.2. What is the Gold Standard Surgical Approach for Invasive Breast Cancer?

With advances in surgical techniques over recent decades, the operative management of BC has become considerably less invasive. BCS followed by RT has been shown to provide overall survival (OS) outcomes comparable to mastectomy, while offering additional benefits such as faster postoperative recovery, fewer

complications, and superior cosmetic results (36, 37). Discussions at the 2025 St Gallen International Breast Cancer Conference delivered one of the clearest messages to date, emphasizing the need to avoid mastectomies that are not clinically indicated and are often driven by misperceived risk or misunderstanding of treatment outcomes (38). Absolute indications for mastectomy include pregnancy during the first trimester, diffuse pleomorphic microcalcifications, or extensive disease that prevents achieving negative margins with an acceptable cosmetic outcome. Relative contraindications to BCS include a prior history of RT to the breast or chest wall, active connective tissue disorders (e.g., scleroderma), persistently positive margins despite re-excision, and known or suspected hereditary BC syndromes (32, 39). We carefully evaluate patients and, when mastectomy is not strictly indicated, discuss the potential benefits of breast-conserving approaches with patients as part of our daily routine.

3.3. When Can Sentinel Lymph Node Biopsy be Omitted in Primary Breast Cancer Undergoing Upfront Surgery?

Axillary staging has long been a standard component of surgical management for BC, with a positive sentinel lymph node biopsy (SLNB) traditionally leading to axillary lymph node dissection (ALND). However, recent studies have increasingly emphasized de-escalation of axillary surgery to reduce morbidity without compromising oncologic outcomes (40, 41). Current consensus guidelines support omission of SLNB in carefully selected patients with early-stage BC undergoing breast-conserving therapy, such as those aged over 70 years with clinical T1N0M0 invasive ductal carcinoma (IDC), grade 1, hormone receptor (+) and HER2(-) disease, and in settings where axillary nodal status is unlikely to alter prognosis or influence adjuvant treatment decisions (42). In our practice, we proceed in accordance with established guidelines. Although evidence supports omitting SLNB in patients older than 50 years, our institutional practice uses a 60-year threshold.

3.4. What is the Optimal Surgical Approach Following Neoadjuvant Therapy in Breast Cancer?

For patients whose BC management begins with neoadjuvant treatment (NAT), BCS is recommended when there are no contraindications or known genetic predispositions are present. Data indicate that BCS is oncologically safe in this setting, with local recurrence rates comparable to or lower than those observed after mastectomy (43, 44). Accurate localization of the primary tumor prior to therapy initiation is critical for surgical planning, particularly in cases where a significant radiologic or pathologic response is anticipated. MRI is strongly recommended both before and after NAT to assess the extent of response and guide surgical decision-making. In patients undergoing BCS after NAT, if a pathologic complete response (pCR) is not achieved, the tumor bed should be marked intraoperatively with at least four surgical clips to facilitate adjuvant therapy and long-term surveillance (45, 46). Although the role of less invasive approaches is expanding in the post-neoadjuvant setting, current evidence does not yet support the complete omission of surgical intervention. Consistent with international guidelines and the current body of evidence, our clinical practice is to prefer BCS as the primary surgical option following neoadjuvant systemic therapyin the absence of contraindications such as multicentric disease, a persistent large tumor burden not amenable to clear margin control, high-risk genetic mutations (e.g., *BRCA1/2*), or other patient-specific factors.

3.5. What is the Optimal Use of Targeted Axillary Dissection and SLNB in Axillary Management Following Neoadjuvant Therapy?

Axillary surgical management following NAT remains the subject of ongoing debate. With the increasing adoption of NAT, strategies for axillary staging and intervention have evolved to reduce the morbidity associated with ALND. Minimally invasive approaches, such as SLNB, may be appropriate depending on both the initial clinical nodal status and the response to therapy (47). Nodal staging can be broadly categorized as follows: clinically node-negative (cN0) before and after NAT; clinically node-positive (cN+) at baseline and pathologically node-negative (ypN0) after NAT; and persistently node-positive (cN+/ypN+) following therapy. In patients who remain cN0 after NAT, SLNB is generally sufficient. In those who convert from cN+ to ypN0, TAD—defined as SLNB combined with removal of previously clipped metastatic nodes—or SLNB with retrieval of at least three sentinel nodes are recommended (48, 49). For optimal post-treatment assessment, we recommend placement of clips in two biopsy-proven positive nodes prior to systemic therapy. If three or more positive nodes are initially identified, clipping may not be required, as adequate sampling at surgery is expected. In contrast, if residual nodal disease persists following NAT, ALND remains the standard of care (47-49).

3.6. How Should the Axillary Management be in Patients with DCIS?

Axillary lymph node involvement remains an important prognostic factor in BC management, and the role of SLNB in DCIS continues to be debated. According to the ASCO, SLNB may be considered in patients with DCIS undergoing mastectomy, in cases with extensive lesions (≥50 mm), or when clinical or radiologic findings suggest a possible invasive component (50). For patients scheduled for BCS, SLNB is recommended in the presence of high-risk features such as grade 3 DCIS, comedo-type necrosis, or a palpable mass, all of which may indicate an increased likelihood of occult invasion (51, 52). These recommendations are supported by the current literature and are consistent with our institutional practice.

3.7. Is Breast-Conserving Surgery a Feasible Option for Patients with Connective Tissue Disorders or Multifocal/ Multicentric Breast Cancer?

Current clinical guidelines identify active connective tissue disorders—such as scleroderma or systemic lupus erythematosus—as relative contraindications to BCS, primarily due to the heightened risk of radiation-induced toxicity (34, 53, 54). However, in patients whose disease is in remission under appropriate medical management, BCS may be considered feasible following careful multidisciplinary evaluation.

The role of BCS in the management of multifocal and multicentric BC also remains a subject of clinical debate, particularly regarding local recurrence and long-term oncologic safety. Results from the American College of Surgeons Oncology Group (ACOSOG) Z11102 (alliance) trial (55) demonstrated that BCS in this setting is associated with acceptable rates of local recurrence. Consistent with these findings, a recent meta-analysis concluded that BCS may represent a viable treatment option for carefully selected patients with multifocal or multicentric disease (54). Accordingly, BCS can be considered in patients who fulfill the criteria outlined by the St Gallen International Expert Consensus Conference (2017), which include the achievement of negative surgical margins, the delivery of adjuvant RT, and the preservation of satisfactory cosmetic outcomes (34). In our clinical practice, when disease remission is achieved with systemic medical management, BCS may be considered a feasible option following a comprehensive multidisciplinary evaluation. BCS also appears to be an appropriate option for carefully selected patients with multifocal or multicentric BC, as modern surgical and adjuvant approaches have helped narrow the gap in local recurrence risk. Meta-analyses demonstrate that local recurrence, DFS, and OS outcomes following BCS are comparable to those observed after mastectomy in this population (54). In our clinical practice, when clear surgical margins and satisfactory aesthetic outcomes can be achieved, we routinely prefer BCS using oncoplastic techniques after thoroughly discussing the expected outcomes with the patient.

3.8. What is the Optimal Localization Method for Non-Palpable Breast Lesions?

Non-palpable breast lesions can be localized using several techniques, including wire-guided localization (WGL), radio-guided occult lesion localization (ROLL), radioactive seed localization, and more recently developed methods such as SAVI SCOUT and magnetic seed localization. WGL was the first widely adopted method and remained the standard approach for many years; however, it carries several limitations, including the risk of wire dislodgement, migration, fracture, patient discomfort, and logistical challenges—particularly the requirement for same-day placement prior to surgery. These drawbacks have been associated with suboptimal cosmetic outcomes and higher rates of non-radical excision (56, 57). ROLL has emerged as a superior alternative, offering improved surgical precision and patient experience. Clinical studies have demonstrated lower rates of positive resection margins, reduced need for re-excision, better cosmetic results, and higher patient satisfaction (56-59). In light of this evidence, we prefer ROLL over WGL owing to its technical advantages and favorable oncologic and aesthetic outcomes.

3.9. What are the Preferred Incision Types in Nipple-Sparing Mastectomy?

Multiple incision types have been described for nipple-sparing mastectomy (NSM); the most commonly used approaches are radial, periareolar, and inframammary fold incisions. None of these techniques has been demonstrated to be definitively superior; therefore, choice of incision should be individualized according to patient-specific anatomical and oncologic considerations. The radial incision remains the most frequently employed, largely due to its compatibility with immediate implant-based reconstruction and its ability to provide adequate access to the axillary fossa without requiring an additional incision.

In recent consensus recommendations, a lateralized parabolic multiplanar incision described by Sağır et al. (59) has been endorsed. This incision begins approximately 4 cm lateral to the nipple-areola complex (NAC) in small breasts and approximately 5 cm lateral to the NAC in larger breasts, extending in a parabolic trajectory toward the mid-axillary line without crossing it, and has a total length ranging from 8 to 13 cm. Compared with the traditional radial approach, this lateral placement reduces the risk of NAC ischemia and necrosis by avoiding disruption of the periareolar vascular supply. It also minimizes lateral displacement of the NAC due to scar contracture, thereby preserving its circular shape and symmetry. In patients with larger breasts, or when NAC excision is anticipated, this technique further supports a more symmetric postoperative breast contour (60).

The inframammary fold incision provides favorable cosmetic results, as the scar is concealed within the natural crease. It is most appropriate for patients with medium-sized breasts and mild ptosis in whom adequate access and reshaping can be achieved safely. However, in patients with larger or more ptotic breasts, this approach may limit surgical exposure and make it more challenging to perform precise tumor resection and optimal glandular remodeling (60). Periareolar incisions provide wide exposure of the breast parenchyma, but are associated with a higher risk of NAC ischemia and necrosis compared with alternative techniques. Where pre-existing surgical scars are present, these can often be incorporated into the planned

incision to minimize additional scarring. In cases requiring skin excision or concurrent reduction mammoplasty, oncoplastic approaches, such as the Wise pattern, may be preferred.

In light of the available evidence and consensus recommendations, our clinical practice has increasingly adopted the lateralized parabolic multiplanar incision as the preferred approach for NSM (59). This technique provides an optimal balance between oncologic safety and aesthetic outcomes, while reducing the risks of nipple-areola complex ischemia and asymmetry. Nonetheless, incision type is ultimately individualized according to each patient's anatomical characteristics and oncologic considerations, with inframammary and oncoplastic approaches reserved for carefully selected cases. This tailored strategy underscores our commitment to optimizing both surgical safety and cosmetic outcomes.

3.10. Who are the Candidates for Nipple-Sparing Mastectomy?

Historically, oncologic eligibility criteria for NSM have included a tumor-to-nipple distance of at least 2 cm, absence of skin involvement, and no clinical or radiologic evidence of Paget's disease or inflammatory BC (61). However, emerging evidence indicates that NSM can be safely performed in carefully selected patients with tumors located close to the nipple without compromising oncologic outcomes (62). Based on evolving data, our consensus group recommends avoiding NSM in patients who have a tumor-to-nipple distance of less than 5 mm, in those with suspicious microcalcifications beneath the nipple-areola complex, or when radiologic findings demonstrate focal contrast enhancement involving the NAC.

4. Controversial Topics in Breast Radiation

The role of RT in BC management continues to evolve, with several aspects remaining the focus of ongoing debate. Key issues include the definition of adequate surgical margins, the extent of axillary treatment, the application of RT following primary systemic therapy (PST), and the selection of optimal fractionation schedules.

In patients with invasive carcinoma undergoing BCS, a negative surgical margin is defined as "no ink on tumor", as previously mentioned, a standard supported by multiple randomized trials demonstrating excellent local control when followed by whole-breast irradiation (WBI) (63). However, for patients treated with PBI, a more conservative margin of at least 2 mm is generally recommended to minimize the risk of recurrence. Surgical margins require special attention after skin-sparing or NSM, as an anterior margin of less than 1 mm has been associated with increased recurrence risk, warranting strong consideration of adjuvant RT. For DCIS, current guidelines recommend margins of at least 2 mm. When narrower margins are reported, evaluation of residual calcifications by specimen radiography and postoperative MMG is essential to guide the need for re-excision. If re-excision is not feasible, whole-breast RT with a tumor-bed boost is advised (64). We recommend moderate hypofractionation (40 Gy in 15 fractions or 42.5 Gy in 16 fractions), which has demonstrated equivalent efficacy, greater convenience and lower toxicity, and is the preferred regimen for the whole breast, chest wall (with or without reconstruction), regional nodes, and after.

Axillary management has undergone a paradigm shift with increasing evidence supporting the omission of ALND in selected patients. The ACOSOG Z0011 and AMAROS trials (65, 66) demonstrated that patients with early-stage, cN0 disease and one or two positive sentinel lymph nodes may safely avoid ALND, provided that appropriate regional nodal irradiation is delivered. These findings have been reinforced by the SENOMAC and SINODAR-ONE trials (67, 68). In contrast, patients with a higher nodal burden or additional high-risk features may still require ALND followed by RT.

The role of RT after PST requires a tailored approach that integrates pretreatment clinical stage, the degree of clinical and pathological response, and the surgical approach. RT is routinely indicated following BCS, regardless of the systemic response. Patients with locally advanced disease, including cT4 tumors or cN2–3 nodal involvement, should receive postmastectomy RT (PMRT) and regional nodal irradiation irrespective of pathological downstaging (69). Conversely, patients with cT1–2N0 disease who achieve a pCR may be spared PMRT. For patients with cT3 tumors or those with triple-negative BC, treatment decisions remain complex and should be individualized within a multidisciplinary tumor board (70).

Special populations also require careful consideration. In women aged 70 years or older with small, estrogen receptor (ER) (+), node-negative tumors who are receiving endocrine therapy, omission of RT after BCS has been shown to be safe in randomized trials, particularly when life expectancy is limited by comorbidity (71, 72). In such cases, PBI or ultra-hypofractionated WBI may be effective alternatives (73, 74). Appropriate candidates for PBI typically include women aged 50 years or older with IDC, stage T1N0 disease, grade 1–2 histology, ER positivity, and margins ≥2 mm (75). Reconstruction strategies must also be considered, as autologous techniques are generally more compatible with PMRT than implant-based approaches, although institutional expertise and patient preference are key determinants.

Fractionation schedules are another area of active refinement. Conventional fractionation with 50 Gy in 25 fractions over five weeks has largely been replaced by moderate hypofractionation (40 Gy in 15 fractions over three weeks), which has demonstrated equivalent efficacy, lower toxicity, and greater convenience (76, 77). More recently, the FAST-Forward trial (74) confirmed the

safety and efficacy of ultra-hypofractionated regimens (26 Gy in 5 fractions over one week) for appropriately selected patients with early-stage disease. The use of a tumor-bed boost remains an important component of local therapy for patients with high-risk features, including young age, grade 3 histology, extensive intraductal components, or triple-negative and HER2(+) subtypes.

Conclusion

In summary, decision-making in breast radiation oncology is increasingly individualized, guided by tumor biology, disease extent, systemic therapy response, patient age, comorbidities, and reconstructive considerations. While consensus exists regarding key principles—such as the margin definition for invasive carcinoma and the adoption of hypofractionated schedules—controversies persist around RT omission in older patients, management of the axilla following systemic therapy, and indications for PMRT in select subgroups. WBI after BCS is standard for early BC. PBI is an option for selected low-risk early-stage patients. Patients with ≥50 years with invazive ductal biology, T1N0, grade 1 or 2, ≥2 mm surgical margins, ER+ tumors are candidates for PBI (75). Patients presenting with cT4 or cN2-N3 generally require PMRT and regional nodal irradiation regardless of pathological response. Ongoing trials and long-term follow-up data are expected to further refine these practices and enhance the personalization of RT in BC care.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ş.T., H.K., E.Ç., O.D., S.B., F.T., S.Y., I.D.S., G.E.İ., N.B., C.U., Y.E.; Concept: A.Y., U.Ö., G.E.İ., N.B., C.U., Y.E.; Design: N.B., C.U., Y.E.; Data Collection or Processing: E.Ş.T., H.K., E.Ç., O.D., S.B., F.T., S.Y., I.D.S.; Analysis or Interpretation: N.B., C.U., Y.E.; Literature Search: E.Ş.T., H.K., E.Ç., O.D., S.B., F.T., S.Y., I.D.S.; Writing: E.Ş.T., H.K., E.Ç., O.D., S.B., F.T., S.Y., I.D.S., A.Y., U.Ö., G.E.İ., N.B., C.U., Y.E.

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REVIEW

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Idiopathic Granulomatous Mastitis: A Comprehensive Review of Etiology, Diagnosis, and Management

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ABSTRACT

Idiopathic granulomatous mastitis (IGM) is a rare, benign, and chronic inflammatory breast disease of uncertain etiology. It often mimics infectious mastitis and inflammatory breast cancer in both clinical and radiologic presentations, leading to diagnostic and therapeutic challenges. This review aims to provide a comprehensive summary of the current literature regarding the etiology, pathogenesis, clinical manifestations, diagnostic strategies, and treatment options for IGM. A narrative review was conducted using an extensive search of the PubMed database, focusing on articles that discuss various aspects of IGM, including its potential autoimmune, hormonal, and infectious origins, as well as current diagnostic and management approaches. IGM most commonly affects women of reproductive age, often within a few years postpartum. Histologically, it is characterized by non-caseating granulomatous inflammation centered on breast lobules. Although corticosteroids are widely used as the first-line therapy, treatment regimens vary significantly across centers, and relapse is not uncommon. Immunosuppressive agents, such as methotrexate, have shown promising results in steroid-resistant cases. Surgical interventions are generally reserved for refractory cases because of the risk of recurrence and unfavourable cosmetic outcomes. The role of infectious agents, particularly *Corynebacterium kroppenstedtii*, remains controversial, and distinguishing between idiopathic and infectious GM is crucial for management. IGM is a multifactorial and clinically heterogeneous condition requiring individualized, multidisciplinary management. There remains a need for further prospective studies and consensus guidelines to optimize diagnosis and treatment, especially in recurrent or refractory cases.

Keywords: Idiopathic granulomatous mastitis; inflammatory breast disease; breast diseases; inflammatory lesions; chronic mastitis

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KEY POINTS

- Idiopathic granulomatous mastitis (IGM) is a rare, benign breast condition that can closely mimic infection or cancer; diagnosis usually requires a tissue biopsy and careful exclusion of other causes.
- Most patients improve with medical therapy—typically corticosteroids—and methotrexate can help when steroids fail or relapse occurs, while surgery is now reserved for complicated or persistent cases due to recurrence risk and cosmetic concerns.
- Because IGM likely has multiple causes and behaves differently across patients, care should be individualized and ideally coordinated by a multidisciplinary team; more prospective studies are needed to guide standardized treatment.

Introduction

Idiopathic granulomatous mastitis (IGM), also called idiopathic granulomatous lobular mastitis, is a benign, chronic inflammatory breast disease of unknown etiology.

GM is a broad clinical entity divided into two categories: specific GM and IGM. Kessler and Wolloch (1) first described IGM in 1972. The etiology of IGM is assumed to involve infectious, autoimmune, and possibly chemical exposure-related mechanisms (2).

The disease typically manifests as an inflammatory mass in the outer part of the breast and may occasionally present as multiple abscesses with ulceration and inflammation of the overlying skin (3). The formation of sinuses, nipple retraction, axillary adenopathy, and peau d'orange-like skin changes represent clinical features that can resemble malignancyare clinical features that may mimic malignancy. Additionally, the imaging features of IGM closely resemble those of mastitis and breast cancer. This similarity in characteristics raises the possibility of misdiagnosis, resulting in delayed and inappropriate medical interventions (4).

There is no single pathognomonic clinical or imaging feature for IGM. However, histopathologic confirmation, most often via core needle biopsy, remains the cornerstone of diagnosis. Treatment options vary widely, ranging from observation and antibiotics to corticosteroids, immunosuppressive agents, and in selected cases, surgery.

This article reviews the current literature on IGM and aims to provide clinicians with an updated and structured overview of its etiology, diagnosis, and management.

Epidemiology

IGM is a rare disease, constituting only 0.44–1.6% of breast biopsies based on cytologic and pathologic diagnosis (5). IGM exhibits a higher incidence in developing countries, possibly owing to underdeveloped public health systems and misdiagnosis as other granulomatous inflammatory diseases, including tuberculosis. IGM is more commonly observed in women of Hispanic descent, particularly among Spanish and Asian women of childbearing age, suggesting a certain degree of genetic predisposition (6). The most prevalent age at which a patient develops this disease is during the childbearing years, occurring mostly five years after breastfeeding. The youngest patient diagnosed with IGM was 11 years old, and the oldest was in her 80s (7).

Etiology and Pathogenesis

The etiology and pathogenesis of IGM remain obscure (8). The pathogenesis of IGM is not yet precisely understood, but different steps may contribute to this disease's pathological process. One of these stages entails a non-specific inflammatory response within lobules, affecting multiple lobules simultaneously, known as lobulitis, which may cause reactive lymphoplasmacytic infiltration. At times, the deformation of a lobule results in granulomas characterized by central suppurative necrosis, leading to abscess formation due to proliferation of these foci (9).

As presented in Figure 1, three main hypotheses have been suggested for the pathogenesis of IGM: infection, autoimmunity, and hormonal disorder (10). Among these three main reasons, certain predisposing factors facilitate the procedure. Risk factors for IGM include pregnancy, breastfeeding, smoking, use of oral contraceptives (OCs),and antitrypsin deficiency (7, 11). The proposed pathogenic mechanisms are not conclusively independent and typically involve multiple contributing factors and mechanisms (12, 13).

α1-Antitrypsin Deficiency

α1-antitrypsin (AAT), a glycoprotein synthesized in the liver by hepatocytes, is a member of the serine protease inhibitor family. It primarily inhibits proteases, including cathepsin G, elastase, and proteinase 3, which are secreted by activated neutrophils. AAT is considered an acute-phase reactant because of its increased levels during inflammation. AAT is considered an acute-phase reactant because it is elevated during inflammation. AAT deficiency primarily contributes to liver and lung pathology.

In 2001, Schelfout and colleagues identified AAT deficiency in a 37-year-old female patient who was diagnosed with IGM. However, the authors did not identify any additional causative factors in this study and proposed that AAT deficiency might be the primary and sole etiological factor. Nonetheless, they recommended further investigation to validate this hypothesis (14).

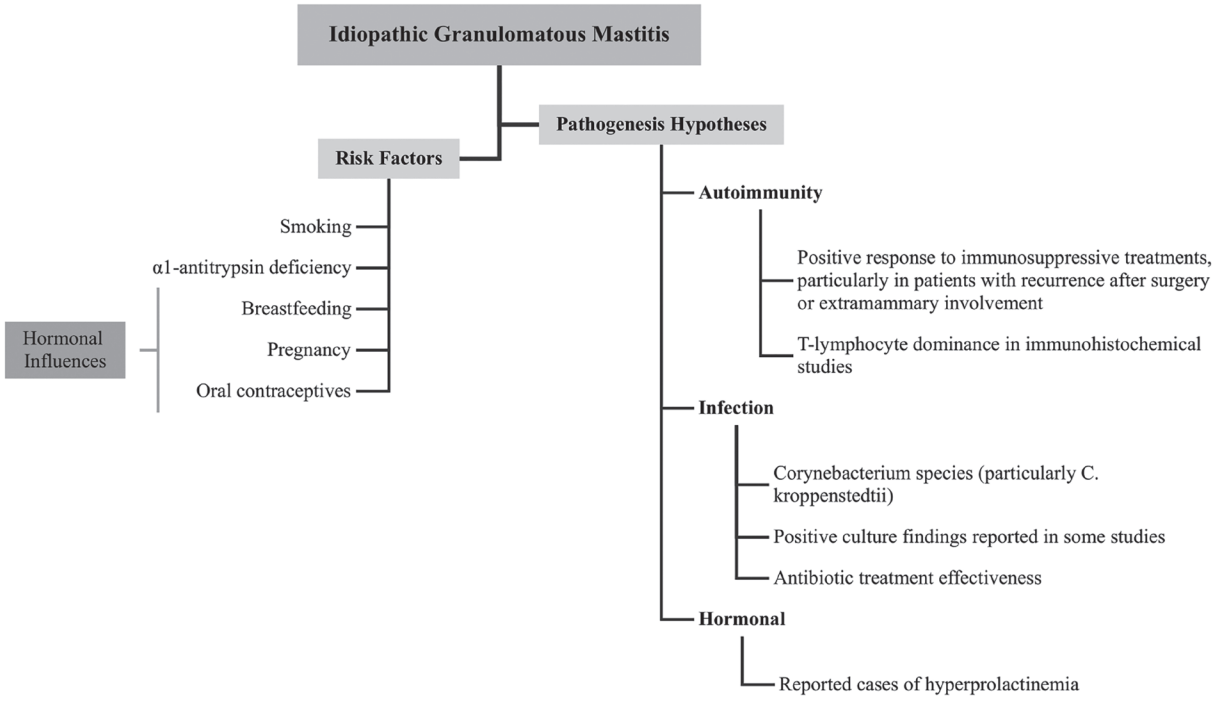

Figure 1. Risk factors and pathogenesis of idiopathic granulomatous mastitis. A tree chart is presented, offering a structured breakdown of IGM's etiology and pathogenesis. The chart branches from the central topic of IGM into primary divisions of "risk factors" and "IGM pathogenesis hypotheses"

C: Corynebacterium; IGM: Idiopathic granulomatous mastitis

Oral Contraceptives

The evidence supporting the relationship between OCs and IGM is controversial. OCs may predispose individuals to IGM by increasing breast secretions (9).

Although no significant association has been found between IGM and OCs, many studies indicate that OCs are potential risk factors. Al-Khaffaf et al. (15), Asoglu et al. (16), Gurleyik et al. (17), Oran et al. (18) and Bani-Hani et al. (7) reported 10 cases (10/46, 21.7%), 8 cases (8/19, 42.1%), 5 cases (5/18, 27.7%), 24 cases (8.3%), and 18 cases (11.1%), respectively. Data indicate the rejection of OCs as a risk factor for IGM, as demonstrated by Baslaim et al. (3), who reported that none of the 20 patients included in their study had a history of OC use. While reported frequencies of OCs use among IGM patients range widely across studies (0–42%), these values primarily derive from small case series and should not be interpreted as reflecting population-level risk. Instead, they suggest that OCP use may act as a potential—but unproven—cofactor in susceptible individuals.

Gestation, Birth, and Breastfeeding

The epidemiology of IGM, characterized by a peak incidence under the age of 50 and a frequent history of recent childbirth and breastfeeding, suggests that these factors are involved in the etiology of this disease. Changes in hormonal levels during this time and their effects on inflammation and secretions may play a significant role in disease pathology (3, 15, 17). In Bani-Hani et al.'s (7) study of 24 cases, only two individuals lacked a history of pregnancy; four were currently pregnant, and another four had given birth and breastfed within the past six months. In a case series of 11 individuals, the authors reported that 10 women had given birth and breastfed within the preceding five years (19). Further, Baslaim et al. (3) all reported cases had a history of pregnancy and breastfeeding; two cases were actively breastfeeding, and one was pregnant. Oran et al. (18) reported that only three of 46 cases were nulliparous. Additionally, Gurleyik et al. (17) reported that among 19 cases, four were actively breastfeeding, while the remaining 15 had previously breastfed.

Individuals diagnosed with IGM, a condition typically occurring during the childbearing years, are likely to have a history of pregnancy and breastfeeding, given that gestation primarily takes place between the ages of 20 and 40. However, the presence in the literature of male cases (20) and individuals spanning a broad age range complicates attributing IGM etiology solely to gestation, childbirth, and breastfeeding.

Hyperprolactinemia

According to the secretion theory, hyperprolactinemia, similar to other hormonal disorders, could also be considered responsible for the pathogenesis of IGM (21, 22). Rowe (21), in his 1984 case presentation, reported that prolactinoma was present as a comorbidity in the IGM case. Nonetheless, further studies did not report detailed prolactin levels. Erhan et al. (23) demonstrated that, in an examination of 18 women, recurrence occurred in three patients (16%), and hyperprolactinemia was identified in two of these patients. Bani-Hani et al. (7) measured prolactin levels in the blood in 7 cases and found increased levels in only one case among 24 patients (4.1%).

Smoking

Although smoking is considered one of the risk factors in the etiology of this disease, a relationship between IGM and smoking has not yet been established. As indicated in the study by Asoglu (16), 14 cases out of 18 (77.8%) had a smoking experience before, meanwhile, Baslaim et al. (3) declaimed that none of their cases was a smoker. Although a causal association between smoking and the development of IGM has not been established, smoking is a well-known inhibitor of wound healing and is associated with delayed resolution of abscesses in inflammatory breast conditions. Several authors therefore caution against surgical intervention in active smokers, as recurrence and poor cosmetic outcomes appear more common in this subgroup. Smoking cessation should be emphasized as part of the therapeutic plan.

Autoimmunity

Among hypotheses about IGM, one theory posits an immunological basis for IGM and has garnered significant attention. Literature reviews show an excellent response to immunosuppressive treatment and steroids, especially in patients with recurrence after surgery, in patients with confirmed T-lymphocyte dominance based on immunohistochemical studies, and in patients who have extramammary involvement (such as arthritis or *erythema nodosum*), which confirms the autoimmunity hypothesis (1, 9, 19, 24-26).

Ozel et al. (27) in a study on 8 cases, reported that 25% of cases were positive for anti-double-stranded DNA (anti-dsDNA), and antinuclear antibody (ANA), and 75% of cases were positive for rheumatoid factor (RF). In the latter study, in which surgery was the chosen treatment option, they demonstrated that two patients with recurrence were anti-dsDNA-positive, ANA-negative, and RF-negative. However, the disease was resolved after steroid treatment. In another study conducted by Erhan et al. (23), they performed an immunohistochemical experiment and determined T-cell dominance in 14 out of 18 cases. This discovery was interpreted as an autoimmune pathophysiological consequence, characterized by the development of centrilobular granulomas in response to ductal damage and reactive T-cell-mediated inflammation. Additionally, literature reports have documented one case of IGM with Sjögren's syndrome, one with *erythema nodosum* and arthritis, two with *erythema nodosum*, and one with Weber-Christian disease (28-31). Although studies have indicated that a coexisting autoimmune disorder represents only a minority of all cases, some research supports the autoimmune hypothesis. Moreover, classical serological tests commonly employed for autoimmune disorders, such as RF and ANA, yielded variable results in IGM cases. Asoglu et al. (16), in their case series of 18 cases, reported that none tested positive for RF or ANA. In the study conducted by Altintoprak et al. (32), they investigated the autoimmunity hypothesis for IGM etiology; in 26 cases, they examined extractable nuclear antibody levels and ANA. However, we did not obtain results sufficient to evaluate the autoimmunity hypothesis (32).

Because of the suspected autoimmune component and frequent coexistence of systemic inflammatory manifestations such as *erythema nodosum* and arthritis, many patients are referred to rheumatology for evaluation and management. This has contributed to the widespread use of systemic immunosuppression and corticosteroids in IGM care. Recent studies have also explored intralesional steroid administration—often performed by breast surgeons or rheumatologists—as a targeted modality to suppress localized inflammation while reducing systemic toxicity.

Microbiological Agents

The indigenous bacterial flora of the normal breast is comparable to that of the skin, with predominant organisms comprising *Corynebacterium* species, coagulase-negative streptococci, and *Propionibacterium* species. These findings have been identified in breast tissue obtained during mammoplasty in nipple discharge cultures (33). These flora may migrate into deeper layers of the breast via ductal pathways (34). Indeed, *Corynebacterium* may cause mastitis in livestock, although these bacteria are not assumed to be pathogenic in humans. Taylor et al. (35), who reported finding *Corynebacterium* in 34 IGM cases, made these bacteria the focus of attention in 2003. *Corynebacteria*, Gram-positive bacteria found in the skin flora, pose a challenge in determining whether they contribute to contamination, infection, or colonization (36). However, because it is hard to distinguish the outcomes, it is essential to confirm >104 colony-forming unit/mL of dominant *Corynebacterium* species or the presence of purulent matter in an abscess (37).

Funke et al. (38) demonstrated that these bacteria might be a potent risk factor if a *Corynebacterium* species is detected in tissue expected to be sterile under normal conditions, or if a Gram-positive bacillus accompanying polymorphonuclear leukocytes is present. In IGM cases, four distinct *Corynebacterium*

species have been identified. *Corynebacterium kroppenstedtii (C. kroppenstedtii)* is the most commonly detected species and, due to its positive esculin test and lipophilic nature, differs from other corynebacteria. In Taylor et al. (35) study, 62 patients were diagnosed with IGM, and 38 of these patients (about 54.8%) had a positive culture for *Corynebacterium*. Comparison of the remaining 28 cases demonstrated that fistulas, fever, and neutrophilia were more frequent in patients with positive bacterial cultures. The most frequently observed species was *C. kroppenstedtii* (14 patients; 41.1%) in the latter study. Paviour and colleagues obtained *Corynebacterium* samples from breast tissue in 24 cases, conducted histopathological examinations in 12 cases, and diagnosed IGM in nine cases. Notably, *C. kroppenstedtii* emerged as the most frequently identified species, with *Corynebacterium tuberculostearicum (C. tuberculostearicum)* and *Corynebacterium amycolatum (C. amycolatum)* being other commonly isolated specieswhile *C. tuberculostearicum* and *C. amycolatum* were also commonly isolated. In a subsequent investigation, a three-week intravenous penicillin treatment was administered to one patient. However, because anticipated benefits were lacking, the treatment was switched to oral doxycycline (100 mg) (36). According to the authors, surgery was not necessary following this treatment. Extensive literature supports the idea that a microbiological etiology is essential (37, 39, 40). Two of these studies did not specify the particular species, but Ang and Brown (37) reported the isolation of *Corynebacterium accolens*. All three studies affirmed the effectiveness of antibiotic therapy.

Diagnosis

Identifying IGM relies on a comprehensive differential diagnosis involving histopathologic and radiologic assessments. To accurately diagnose IGM, it is crucial to exclude potential histopathologic mimics such as fat necrosis, duct ectasia, foreign-body reactions, and granulomatous inflammation (e.g., sarcoidosis, tuberculosis, Wegner's granulomatosis). Concurrently, radiologic evaluations should be conducted to distinguish IGM from other conditions that present with similar imaging findings, including malignancies, abscesses, and necrotic lesions. By employing a precise diagnostic approach, clinicians can significantly impact treatment strategies. A combination of diagnostic modalities is utilized for IGM assessment, including mammography, sonography, magnetic resonance imaging (MRI), and histopathologic examination. Each of these methods is explained below and summarized in Figure 2.

Clinical Presentation

The most typical manifestation of IGM is a mass with indistinct borders in the upper outer quadrants of the breasts of females aged 30–45. This mass could be in any quadrant, but is predominantly located in the upper quadrant (41). The mass exhibits soft borders and may be accompanied by skin abnormalities, such as erythema, peau d'orange, nipple inversion, and skin retraction; it may resemble inflammatory breast cancer. The most common complications of the disease are abscesses, fistulas, ulcerations, infections, and sinus formation. In Aziza et al. (42) study, of 474 cases reviewed, 19.4% had skin changes and 17.7% had nipple inversion. Moreover, patients exhibiting skin changes experienced a higher recurrence rate. In IGM, the presence of both skin changes and a breast mass can make differentiation from inflammatory breast cancer challenging, even with imaging modalities such as ultrasound, mammography, and MRI. Furthermore, it is crucial to consider the rare occurrence of mammary tuberculosis, particularly because it tends to affect the lymph nodes and lungs. Additionally, the presence of caseous necrosis and breast duct involvement should be assessed by histological examination.

Imaging

Mammography

IGM lacks distinctive features on mammography, and the visibility of small lesions is frequently obscured by the dense breast tissue commonly found in women of reproductive age (43, 44). Typically, it appears on mammograms as a mass with asymmetric density and uneven borders, attributed to nipple inversion, local skin thickening, and axillary lymphadenopathy (45). Barreto et al. (46) described the common mammographic manifestation of IGM as structurally distorted, asymmetric masses or nodules. Dursun et al. (45) noted that approximately one-quarter of IGM cases exhibited masses with irregular shapes or obscured borders, with single masses being the most prevalent. However, caution is warranted, as mammograms may appear normal in individuals with dense breast tissue or in those with mild disease (47). Notably, calcifications are seldom observed in IGM and have been reported only in isolated cases (48). Thus, mammographic findings may raise suspicion of IGM, but a definitive diagnosis relies on histopathologic examination rather than imaging alone.

Sonography

Because of numerous sensitivity issues and the lack of diagnostic capability of MRI for IGM, sonography seems valuable for screening breast masses (47). More than 80% of masses detected by sonography are heterogeneous and hypoechoic (43). Because the structure of masses in IGM is highly variable, the specificity is very low due to structural distortion, irregular masses, parenchymal edema, skin thickening, effusion, and axillary lymph node enlargement (49). The most frequent finding on ultrasonography is either a mixed hypoechoic or a hyperechoic mass. However, hypoechoic masses are much more common, exhibiting indeterminate, angular shapes and may have

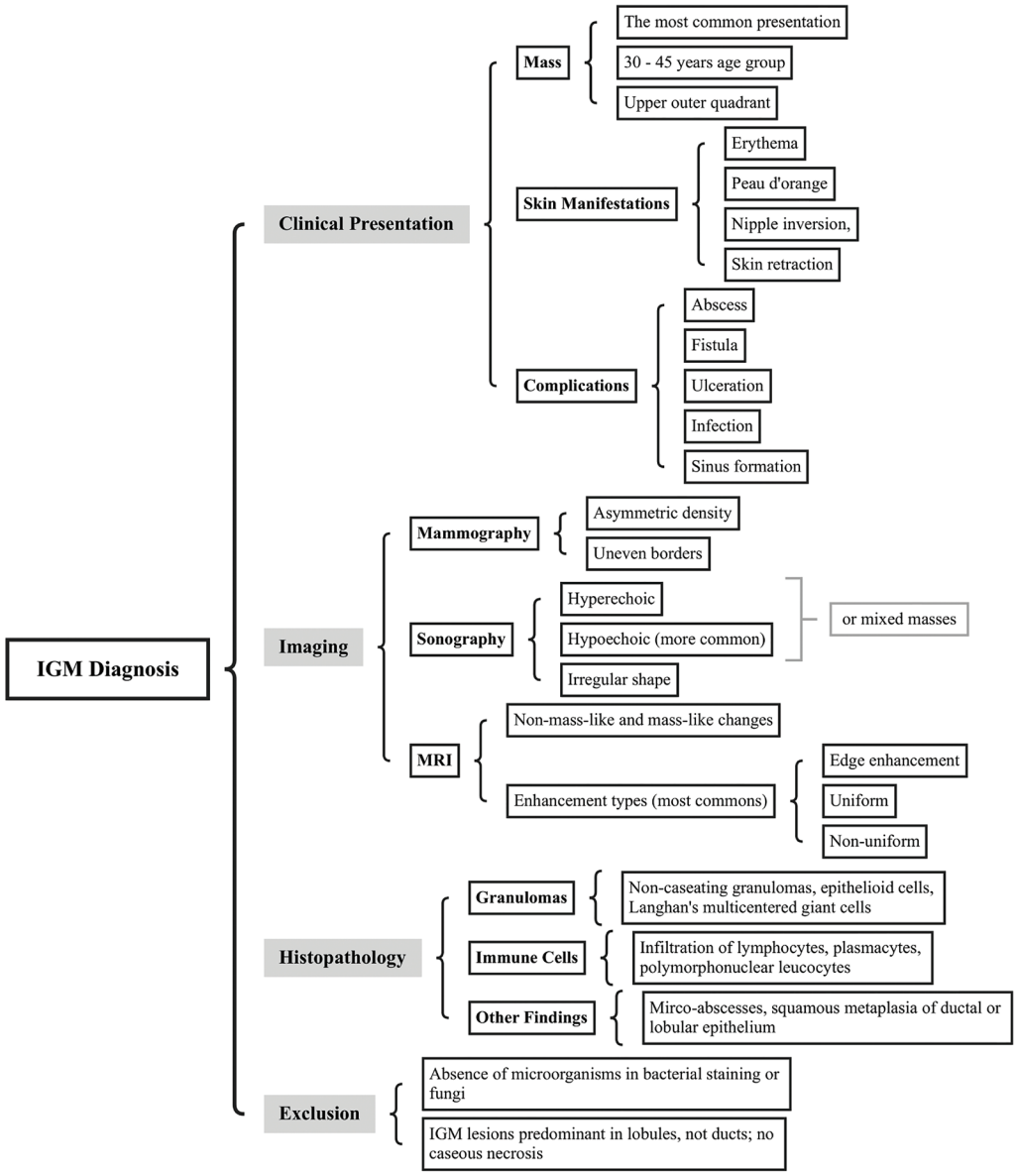

Figure 2. Overview of idiopathic granulomatous mastitis diagnosis. This figure presents a comprehensive, structured representation of the diagnostic approach to idiopathic granulomatous mastitis. It illustrates the four main diagnostic pillars using a brace map format: clinical presentation, imaging, histopathology, and exclusion criteria. Each category further bifurcates into specific components, offering a holistic view of the diagnostic features and methodologies

IGM: Idiopathic granulomatous mastitis; MRI: Magnetic resonance imaging

infiltrated the adjacent parenchyma. The detected masses may be accompanied by posterior shadowing, enhancement, or other posterior acoustic phenomena (50). Doppler imaging may show increased blood flow in masses and adjacent breast tissue, a sign of inflammation (51). Sonography offers the benefits of high sensitivity and non-invasiveness and has potential to effectively screen individuals with mild ailments. Moreover, it can assess the degree of inflammation, the presence of sinus tracts, and lymph node involvement.

Magnetic Resonance Imaging

The MRI features of IGM can differ based on the level of inflammation. Dursun et al. (45) employed the breast imaging reporting and data system, established by the American College of Radiology, to examine MRI images from 35 IGM cases. The results indicated non-mass-like changes in 77% (28 out of 36) of patients and mass-like alterations in 66% (24 out of 36) of patients (45). Morphologically, 23% of patients exhibited oval masses,

while 17% exhibited lobulated masses. Moreover, the affected parenchyma showed substantial enhancement on imaging; common enhancement types included edge enhancement (with or without interior separation), uniform enhancement, and non-uniform enhancement (52). Micro-abscess formation around the lesions may suggest edge enhancement on the T2 signal (19). The parenchymal apparent diffusion coefficient in IGM-affected areas was lower than in non-diseased regions. However, Yilmaz et al. (52) showed that diffusion-weighted-MRI is unreliable for diagnosing IGM and may be misleading because it can resemble breast malignancies. Furthermore, Dursun et al. (45) illustrated that, in 25% of IGM cases, the time-intensity curve exhibited signal changes resembling those observed in breast cancer. As a result, MRI shows limited diagnostic specificity for IGM and can occasionally be unreliable in distinguishing between IGM and breast cancer. Specifically, cases of IGM with non-mass-like changes may be misdiagnosed as invasive or non-invasive breast cancer.

Histopathology

Crucially, the identification of IGM relies on histopathologic results. In certain studies, open biopsy is employed for diagnostic purposes during procedures such as lesion resection or mastectomy. Needle biopsy, a widely endorsed sampling method, is performed by two techniques: percutaneous needle biopsy and fine-needle aspiration cytology (FNAC), the most commonly used method in suspected cases. Advantages of FNAC include its simplicity, rapidity, and minimally invasive nature. However, the primary limitation of FNAC is its low sensitivity (53, 54). Many studies have shown that only about one-fifth of IGM cases can be diagnosed by FNAC. However, for patients who underwent FNAC, further open biopsies may be needed for a definitive diagnosis (55, 56). In complex cases in which needle biopsy is insufficient, open biopsy is essential because the needle biopsy may fail to detect granulomas.

Histologically, IGM is identified by the presence of central non-caseating granulomas consisting of epithelioid cells and Langhans multinucleated giant cells. The chronic inflammation induced by IGM in the mammary stroma is characterized by the infiltration of lymphocytes, plasmacytes, and polymorphonuclear leukocytes. The formation of micro-abscesses is common, and squamous metaplasia of ductal or lobular epithelium may also be be observed.

Exclusion

An essential characteristic of IGM is that no microorganisms are detected on bacterial or fungal staining, which therefore helps to exclude infectious granuloma. Additionally, one difference between tuberculous granuloma and IGM is that tuberculous granuloma has caseous necrosis, whereas IGM does not, and IGM lesions mainly involve the lobules rather than the ducts. However, it is rarely difficult to distinguish culture-negative tuberculous granuloma from IGM.

When performing incision and drainage of a breast abscess in patients with suspected IGM, clinicians should obtain tissue for histopathologic examination. Failure to submit tissue may delay diagnosis and lead to inappropriate management, particularly when distinguishing IGM from infectious and malignant etiologies.

Emerging Classification Systems

Recent studies have attempted to classify IGM into clinically and radiologically meaningful subgroups to guide management. Radiologic classification based on MRI and ultrasound typically differentiates non-mass-like enhancement patterns from mass-like enhancement patterns, which have been associated with differing risks of abscess formation and treatment resistance (45, 46).

Clinically, several authors have proposed stratifying IGM into mild, moderate, and severe disease based on lesion size, presence of abscesses, sinus tracts, skin ulceration, and systemic inflammation. Such classification systems aim to individualize therapy and may help identify candidates for topical therapy, systemic immunosuppression, or combined surgical approaches.

These emerging frameworks highlight the heterogeneity of IGM and underscore the need for standardized, validated classification systems in prospective studies.

Treatment

The establishment of a gold-standard treatment for IGM remains controversial, as no definitive guidelines currently exist. Given the complex interplay of etiologies contributing to IGM's pathophysiology, a multifaceted approach is essential for its management. Primary treatment strategies include watchful waiting, surgical resection, steroid therapy, antibiotics, and immunosuppressive agents. These methods, explained below and summarized in Figure 3, provide a comprehensive framework for addressing IGM.

Expectant Management

Recently, the watch-and-wait approach has been one of the most important treatment modalities. Notably, recent studies report that 50% of IGM patients heal spontaneously. A study by Lai et al. (57) in 2005 showed that 50% of these patients healed after a two-year waiting period without medication. Two other studies by Bouton et al. (58) and Yaghan et al. (20), conducted in 2015 and 2020, reported that healing occurred within 6–12 months of close monitoring. Hur et al. (59) reported that lesion size affects whether expectant treatment is appropriate. The study revealed

that small lesions (1–2 cm in diameter) healed, whereas lesions greater than 5 cm formed breast abscesses. No criteria categorize lesions by size. Hur et al. (59), in their meta-analysis, concluded that, in mild cases, the best treatment is observation. Davis et al. (60) reported that the patient's age at her first childbirth is related to the time required for the wait-and-watch treatment; the older the patient is, the longer the treatment time should be. In another study, Bouton et al. (58) confirmed that the recurrence rate for IGM is about 11%, and recurrence may worsen the disease before spontaneous remission. We should note that expectant management of IGM has disadvantages, such as reliance on patient adherence. Moreover, this method is suitable only for mild cases and sometimes requires a long duration.

Antibiotics

Antibiotics are among the most commonly used treatments for IGM because skin lesions, seen in 20% of patients, and their similarity to bacterial mastitis result in misdiagnosis. If there is no improvement after antibiotic therapy, alternative diagnoses, such as IGM, should be considered. In this situation, a needle biopsy is usually performed, and treatment is determined by pathological findings.

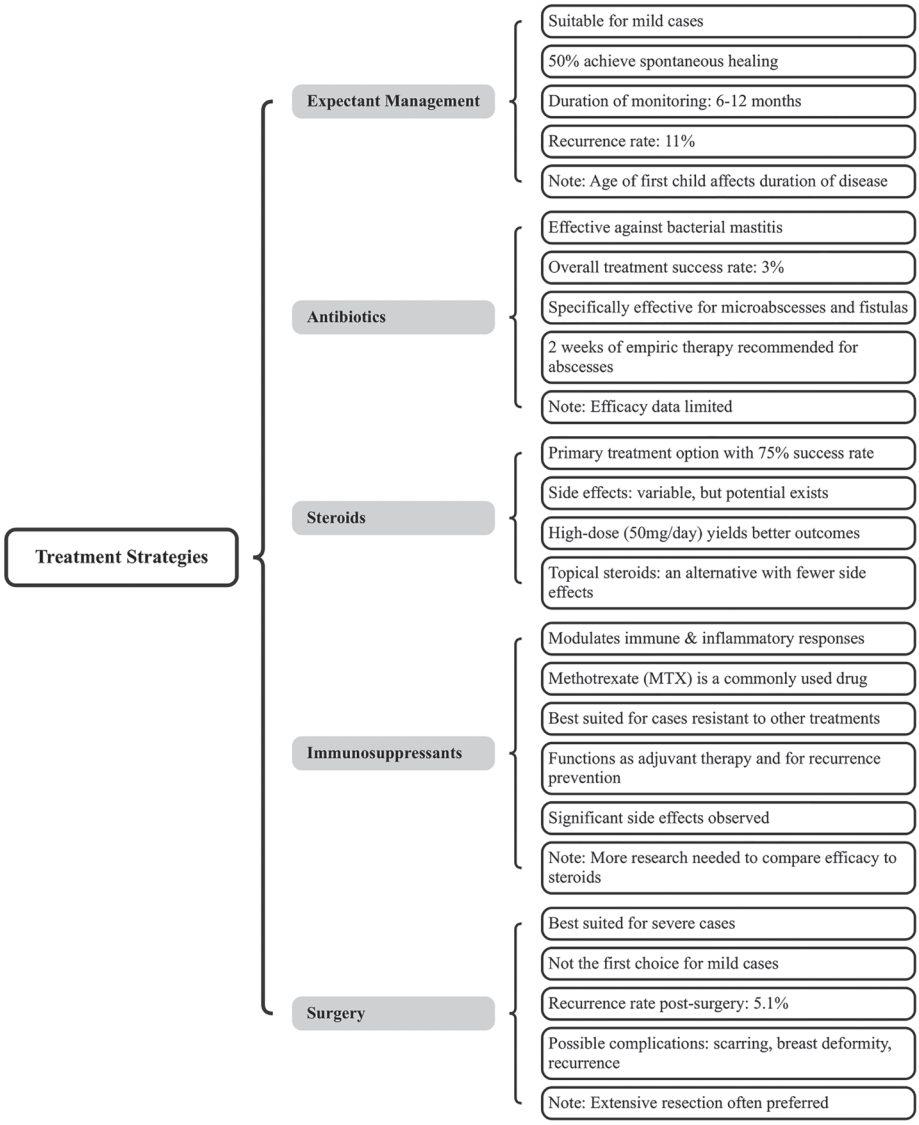

Figure 3. Treatment strategies for idiopathic granulomatous mastitis. This brace map delineates the pivotal treatment strategies for idiopathic granulomatous mastitis. It offers a structured approach, categorizing the primary treatment methods: expectant management, antibiotics, steroids, surgery, and immunosuppressants

MTX: Methotrexate

Aghajanzadeh et al. (61) reported that the treatment rate for IGM with antibiotic therapy was only 3%. The therapeutic effect of antibiotics is minimal. On the other hand, in the study performed by Li (62) in 2019, antibiotic therapy effectively treated microabscesses and fistulas. It can help in the preoperative period as an adjunctive therapy.

According to Benson and Dumitru (63), empiric antibiotic therapy for two weeks is used in IGM with abscess formation and, if not cured, is followed by surgical resection and drainage. Initial antibiotic therapy is indicated if *Corynebacterium* is isolated from the lesion. Although some articles have recommended anti-mycobacterial therapy, there is no solid evidence (64).

Based on the above, antibiotics are not an effective treatment for IGM, and more data are needed to support them as an initial treatment.

Steroids

Steroids are the primary treatment for IGM, with a success rate of 75%, and are preferred to surgery in most cases (43, 65). According to a meta-analysis by Martinez Ramos et al. (2), among 3060 patients, steroid therapy was the most frequent treatment in developing and developed countries (75% and 69%, respectively). Considering the adverse effects of steroids—including impaired glucose tolerance, weight gain, osteoporosis, Cushing's syndrome, peptic ulcer, and mental disorders— the duration and dosage of therapy should be minimized and tailored to the patient's response. Wolfrum et al. (66) and Sakurai et al. (67) suggested 3–6 months of treatment, rather than 3–4 weeks, to prevent disease recurrence. Azlina et al. (68) showed that 50% of patients experienced recurrence after short-course treatment (4 weeks, 60 mg/day). Montazer et al. (69) reported that the high-dose group (50 mg/day) had a significantly better treatment response (93.3% vs. 53.3%) and a lower recurrence rate (0% vs. 37.5%) than the low-dose group (5 mg/day). Steroid therapy is as reliable as initial therapy, and administration of an adequate dose for a sufficient duration is recommended.

In Gunduz et al. (70) study, only 2 of 11 patients experienced recurrence after three months of topical steroid pomade use. Supporting this study, Altintoprak et al. (71) reported that only 3 of 28 patients had a recurrence. Two patients were cured after repeating the same treatment regimen. In both of the latter studies, no adverse effects were reported. In 2019, Çetin et al. (72) conducted a study comparing the efficacy of steroid treatment across routes of administration. The study concluded that there was no significant difference among systemic, combined, and topical steroid administration routes in complete clinical regression, treatment success, or recurrence rate. The author states that topical steroid therapy should be considered the initial treatment route, considering the adverse effects (72). IGM patients should be evaluated for concurrent infection before initiating steroid treatment.

Intralesional steroid injection has recently gained attention as an effective and minimally invasive alternative to systemic steroids. Several prospective and retrospective studies have demonstrated that ultrasound-guided triamcinolone acetonide injection can rapidly reduce inflammation, shorten recovery time, and minimize systemic adverse effects.

Combination regimens involving intralesional and topical steroids have been reported to yield high remission rates with fewer relapses compared with systemic therapy alone (66, 72).

This modality is particularly useful for localized lesions or for patients who have contraindications to systemic corticosteroids.

Studies suggest that IGM may have an autoimmune component in its pathophysiology, e.g., *erythema nodosum*. Patients with both IGM and *erythema nodosum* exhibit an excellent response to systemic immunosuppressive therapy.

Immunosuppressants

The pathway of action of immunosuppressants on IGM is regulation of abnormal immune and inflammatory responses, similar to that of steroids. Methotrexate (MTX) is one of the most widely used immunosuppressants worldwide, acting by inhibiting dihydrofolate reductase and causing serious adverse effects such as pulmonary fibrosis, hepatic and renal damage, and bone marrow suppression. Indications for MTX use in IGM are as follows: first, the most common indication is failure to respond to steroid therapy and surgery (73, 74). The second is to be used as adjuvant therapy with steroids to reduce the duration of steroid use and side effects (75). The third is to eliminate recurrence during steroid dose reduction (76, 77). More data are needed to compare steroids and MTX. However, the first randomized clinical trial conducted by Haddad showed that MTX resulted in significantly higher rates of symptom remission (77). Akbulut revealed that the MTX is a good choice for treatment in her systematic review article, but in some cases still, surgery is neededreported in her systematic review that MTX is a good treatment choice; however, surgery is still required in some cases (73). MTX could be used as one of the initial treatment options for IGM patients.

Surgery

To date, the most effective approach for IGM has been surgical resection till now (59, 63, 78, 79). However, a meta-analysis investigated that surgical treatment had no more apparent profits in comparison with drug therapy and, observation in mild cases (59). In managing patients with IGM and extensive lesions, surgical resection has demonstrated notable advantages

when combined with steroid monotherapy. Wang et al. (80) demonstrated that the recurrence rate in the non-surgical group (22%) was higher than that in the surgical group (5.1%). The study included 200 IGM cases with lesions greater than 5 cm; all received intravenous steroids five days before surgery. Therefore, surgery is a reliable treatment for severe cases (80). According to Shin et al. (81), complications such as scarring, recurrence, and breast deformity are much more common among patients undergoing surgical treatment.

Smoking has been repeatedly associated with impaired wound healing, a higher risk of postoperative complications, and increased recurrence of inflammatory breast diseases. For this reason, several authors recommend avoiding surgical intervention for active smokers unless absolutely necessary and emphasize preoperative smoking cessation strategies.

Surgery should not be the first choice of treatment in IGM cases, but should be considered in the event of complications or recurrence.

Regarding the resection method, most of the literature supports extensive resection because margins or lymph nodes may serve as sources of recurrence or disease flare-up (42, 82, 83).

Because of the heterogeneous nature of IGM, treatment algorithms increasingly emphasize individualized therapy based on clinical severity, radiologic features, and the presence of abscesses or sinus tracts. Recent literature suggests a tiered approach incorporating expectant management for mild disease, topical or intralesional steroids for localized lesions, systemic immunosuppression for moderate-severe disease, and surgery only for refractory or complicated cases. These updates have now been incorporated into the relevant subsections.

Discussion and Conclusion

IGM remains a diagnostic and therapeutic challenge due to its unclear etiology, variable clinical course, and lack of standardized management protocols. While several mechanisms have been proposed—including autoimmune responses, hormonal influences, and infectious triggers—none provides a definitive explanation for all cases, reinforcing the concept that IGM is likely a heterogeneous disease entity.

The role of autoimmunity is supported by the predominance of lymphoplasmacytic infiltration in histopathological specimens and by the clinical response to immunosuppressive agents, particularly corticosteroids and MTX (3, 7, 9). However, a subset of patients fails to respond to these treatments, suggesting that alternative mechanisms may be operative. In this regard, the presence of *C. kroppenstedtii* in some histologic samples has led to the hypothesis that a subset of IGM cases may, in fact, represent chronic bacterial mastitis rather than true idiopathic disease (11, 12). Differentiating these subtypes is clinically relevant, as antibiotic therapy may benefit patients in the latter group, while immunosuppressive treatment may be inappropriate or even harmful.

Diagnosis remains a major hurdle, often requiring a tissue biopsy to rule out malignancy and infectious etiologies, such as tuberculosis and fungal mastitis. Imaging modalities, including mammography and ultrasound, are largely non-specific. Core needle biopsy is currently considered the gold standard for diagnosis (6, 8), but it does not always clarify the pathogenesis or guide management decisions.

Therapeutic strategies for IGM vary considerably. While corticosteroids remain the first-line treatment, the absence of consensus on dosing, tapering schedules, and duration of therapy leads to heterogeneous outcomes (9, 14). Immunosuppressants such as MTX and azathioprine have been employed with some success in refractory or relapsing cases, but long-term safety data are lacking (10, 13). Surgical intervention, once widely used, is now generally reserved for persistent or complicated cases due to the risk of recurrence and disfigurement (15, 16).

The lack of large-scale prospective studies and randomized controlled trials hampers our ability to draw firm conclusions about optimal management. Moreover, most available data derive from single-center studies or small case series with heterogeneous methodologies. There is a pressing need for collaborative multicenter research efforts to stratify patients based on underlying pathophysiology, evaluate the efficacy and safety of treatment regimens—including biologic agents—and develop evidence-based guidelines.

IGM should be considered a complex, multifactorial condition that requires individualized management. Advancing our understanding of its pathogenesis and refining diagnostic criteria are essential steps toward establishing a rational and effective therapeutic framework.

Given the heterogeneity of IGM and the limitations of retrospective, single-center studies, there is an urgent need for well-designed prospective trials and multicenter registries. Standardized diagnostic criteria, validated classification systems, and comparative effectiveness studies of medical versus minimally invasive treatments would greatly improve clinical decision-making and help define evidence-based management pathways.

IGM is a complex disease that continues to pose diagnostic and therapeutic challenges despite decades of investigation. Its resemblance to breast cancer and other granulomatous diseases of the breast and its varied pathophysiology make it challenging to diagnose. However, based on the current literature,

histopathological findings remain the most reliable diagnostic method.

Topical steroid therapy is often used for mild cases of IGM, whereas surgical intervention is typically reserved for severe cases. However, the classification of IGM into mild, moderate, and severe groups remains a topic of debate, and there is still much to learn about prognostic factors for this disease.

A significant limitation in the field of IGM is the need for more guidelines and a global database for the disease. While a wealth of information is available, more research is necessary to understand this illness comprehensively. Overall, there is still much to be learned about IGM, and continued efforts are needed to develop effective diagnostic and treatment strategies for patients.

Footnotes

Authorship Contributions

Concept: P.H.M., S.N.; Design: P.H.M., S.N., A.H., D.S., K.H.; Data Collection or Processing: P.H.M., M.S.C.M., K.H., F.M.A., H.M., R.M.; Analysis or Interpretation: S.N., A.H., M.B., D.S., K.H.; Literature Search: A.H., M.B., M.S.C.M., H.M., R.M.; Writing: P.H.M., S.N., M.B., F.M.A., H.M., R.M.

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ORIGINAL ARTICLE

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Skeletal Muscle Loss During Neoadjuvant Chemotherapy for Breast Cancer: Diabetes as an Independent Predictor

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ABSTRACT

Objective: This study examined body composition changes during neoadjuvant chemotherapy (NACT) for breast cancer and aimed to identify clinical parameters associated with skeletal muscle loss.

Materials and Methods: We retrospectively analyzed women with stage I–III breast cancer who received NACT. Skeletal muscle and subcutaneous fat areas at the third lumbar vertebra were quantified on computed tomography and normalized for height to calculate the skeletal muscle index (SMI, cm²/m²) and subcutaneous fat index (SFI, cm²/m²). Pre- and post-NACT values were compared, and the prevalence of low skeletal muscle mass (LSMM, SMI <38.5 cm²/m²) and sarcopenic obesity (body mass index ≥30 kg/m² with LSMM) was determined. Multivariable linear regression assessed independent predictors of post-NACT SMI.

Results: A total of 177 patients (mean age 51.0±10.7 years; 24% with diabetes) were included. Mean SMI declined significantly after NACT (43.1±7.4 to 41.4±7.1 cm²/m²; mean change -1.7±3.1, $p<0.001$). SFI also decreased (132.9±59.2 to 123.5±55.1 cm²/m²; mean change -9.5±27.0, $p<0.001$). The prevalence of LSMM increased from 27.7% to 37.3% ($p = 0.003$), and sarcopenic obesity from 8.5% to 12.4%. Patients with diabetes experienced greater muscle loss than those without diabetes (-2.7 *vs.* -1.4 cm²/m²). Diabetes mellitus was the only independent predictor of post-NACT SMI decline ($\beta = -1.42$, $p = 0.013$), while age and chemotherapy regimen were not significant.

Conclusion: NACT is associated with significant reductions in skeletal muscle and subcutaneous fat, together with increased rates of LSMM. Diabetes mellitus independently predicted lower post-treatment SMI.

Keywords: Body composition; breast cancer; diabetes; neoadjuvant chemotherapy; sarcopenia

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KEY POINTS

- Patients with breast cancer experienced significant skeletal muscle loss after neoadjuvant chemotherapy, based on computed tomography-derived measurements.
- The proportion with low skeletal muscle mass increased from approximately 28% to 37%, and sarcopenic obesity rose from approximately 9% to 12%.
- Diabetes mellitus was the only clinical factor independently associated with greater muscle loss; patients with diabetes lost more muscle than those without diabetes.
- Neither age nor chemotherapy regimen was independently associated with post-treatment skeletal muscle mass.
- Muscle-preserving care should be prioritized for patients with breast cancer undergoing neoadjuvant chemotherapy, particularly those with diabetes.

Introduction

Breast cancer remains a major global health challenge, representing the most commonly diagnosed malignancy in women worldwide. Approximately 2.3 million new breast cancer cases and 0.66 million deaths occur annually worldwide (1). Neoadjuvant chemotherapy (NACT) plays a central role in the management of breast cancer by downstaging tumors, increasing the likelihood of breast-conserving surgery, and offering prognostic insight. Achievement of a pathologic complete response after NACT is particularly associated with improved outcomes in aggressive subtypes such as human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer (2, 3).

For all its benefits in tumor control, chemotherapy is a double-edged sword in that its systemic action will adversely affect normal tissues. Chemotherapy itself has been recognized as a direct cause of skeletal muscle wasting, independent of cancer cachexia (4). Treatment-induced muscle loss has been linked to higher rates of chemotherapy toxicity and inferior survival outcomes across solid tumors (5). The patient groups most vulnerable to chemotherapy-related muscle loss are not well defined. Although older patients are more likely to have baseline sarcopenia due to age-related muscle decline, current evidence does not indicate that age independently increases the risk of chemotherapy-related muscle loss (6-8). The chemotherapy regimen itself may influence the degree of muscle loss; for example, a dual HER2-targeted NACT regimen [docetaxel, carboplatin, trastuzumab, and pertuzumab; (TCHP)] was recently shown to induce significantly greater skeletal muscle depletion than an anthracycline-taxane regimen (6).

Type 2 diabetes mellitus is an established risk factor for sarcopenia, with meta-analyses showing a 1.5–2.0-fold higher prevalence compared with individuals without diabetes (9, 10). Several mechanisms underlie this association: insulin resistance disrupts the PI3K-AKT-mTOR pathway, leading to reduced protein synthesis, while activation of catabolic transcription factors such as FOXO enhances proteolysis; chronic low-grade inflammation amplifies catabolic signaling; and hyperglycemia-induced oxidative stress with mitochondrial dysfunction further compromises muscle integrity (11). In addition, diabetes promotes myosteatosis, the infiltration of fat into skeletal muscle, which worsens insulin resistance and reduces contractile function (4, 11). Taken together, these data support a strong biological and clinical basis for examining diabetes as a potential contributor to chemotherapy-related muscle loss in patients with breast cancer. Given these gaps in the evidence base, we designed a retrospective cohort study to assess the body composition changes during NACT in patients with breast cancer and to identify clinical predictors of skeletal muscle loss. In particular, we examined the influence of diabetes mellitus and other clinical parameters on post-therapy muscle mass.

Materials and Methods

Study Design and Setting

This retrospective cohort study was conducted at a single tertiary oncology center. Ethical approval was obtained from the Royal Medical Services Ethics Committee, Bahrain (approval number: 2023-717; date: 28.09.2023). The study was conducted in accordance with the Declaration of Helsinki.

Patient Selection

Eligible patients were women aged 18 years or older with histopathologically-confirmed invasive breast carcinoma (clinical stage I–III) who received NACT between November 2018 and July 2024, with a minimum treatment duration of four months, and had baseline and post-treatment radiologic assessments [abdominal computed tomography (CT) or positron emission tomography (PET)-CT] with post-treatment imaging performed ≥4 months after treatment initiation. Patients were excluded if they had metastatic disease at presentation or if imaging data were missing.

Data Collection

Patients were identified from the hospital oncology database. Clinical data were retrieved from electronic medical records and included age, date of diagnosis, clinical stage at presentation, baseline comorbidities, histopathology, NACT regimen, dates of

NACT initiation and completion, number of NACT cycles, NACT duration (days), dates of baseline and post-NACT imaging, body weight, height, and body mass index (BMI) before and after NACT. BMI was categorized according to World Health Organization cut-offs. Comorbidity burden was quantified using the Charlson comorbidity index, based on comorbidities documented before NACT initiation (12).

NACT regimens were classified as: (1) AC-T: anthracycline (doxorubicin or epirubicin) plus cyclophosphamide followed by a taxane-containing regimen, with or without carboplatin, trastuzumab, pertuzumab, or pembrolizumab, as clinically indicated; or (2) TCHP.

Imaging and Body Composition Analysis

Body composition was evaluated on baseline and post-NACT scans using a single axial slice at the third lumbar vertebra (Figure 1). CT (or the CT component of PET-CT) images were analyzed using ImageJ software (National Institutes of Health, Bethesda, MD, USA) to quantify skeletal muscle and subcutaneous fat cross-sectional areas (cm^2) applying the following Hounsfield Unit (HU) thresholds: skeletal muscle -29 to +150 HU, subcutaneous fat -190 to -30 HU (13, 14). Skeletal muscle index (SMI) and subcutaneous fat index (SFI) were calculated by dividing the respective areas by height squared (m^2). All body composition measurements were performed independently by two senior radiology consultants, who were blinded to patient clinical information and each other's results.

Low skeletal muscle mass (LSMM) was defined as an SMI <38.5 cm^2/m^2 (15). Sarcopenic obesity was defined as the coexistence of obesity (BMI ≥30 kg/m^2) and LSMM.

Statistical Analysis

Continuous variables are summarized as mean ± standard deviation (SD) and were compared between groups using two-sided Student's t-tests. Categorical variables are presented as counts (percentages) and were compared using chi-square (χ^2) tests. Within-patient changes from pre- to post-NACT were evaluated using paired t-tests for continuous variables and McNemar's test for paired categorical outcomes. The effect sizes were calculated using Cohen's d for paired samples, defined as the mean pre- to post-NACT change in SMI divided by the SD of the change. Values of 0.2, 0.5, and 0.8 were interpreted as small, moderate, and large effects, respectively.

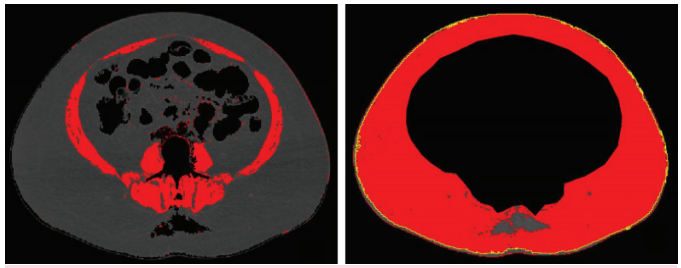

Figure 1. Representative computed tomography images at the third lumbar vertebral level of a 59-year-old woman illustrating segmentation of body composition using ImageJ software, (left) Skeletal muscle area highlighted in red, (right) Subcutaneous fat tissue highlighted in red

Inter-rater reliability between the two radiologists for SMI measurements was assessed using a two-way random-effects intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs). Agreement was interpreted as follows: <0.50, poor; 0.50–0.75, moderate; 0.75–0.90, good; >0.90, excellent.

Predictors of post-NACT SMI were examined using linear regression. The first model was adjusted for baseline SMI. The second model (multivariable-adjusted model) included age, NACT regimen, and presence of diabetes in addition to baseline SMI. Results were reported as regression coefficients with 95% CIs. All tests were two-sided, and statistical significance was set at $p<0.05$. Analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA). Statistical plots were generated in R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) using the "forestplot" and "ggplot2" packages.

Results

Patient Characteristics

A total of 177 breast cancer patients who underwent NACT were included in the analysis. The mean age was 51.0±10.7 years, with diabetic patients being significantly older than non-diabetic patients (58.3±7.7 *vs.* 48.6±10.5 years, $p<0.001$) (Table 1). The most common tumor subtype was HR+/HER2- (32.8%), followed by HR+/HER2+ (26.0%), HR-/HER2+ (19.2%), and triple-negative breast cancer (22.0%). Most patients presented with cT1–2 disease (60.4%) and cN1 nodal status (55.4%). The majority (71.8%) received AC-T-based NACT regimens, while 28.2% were treated with TCHP. Obesity (BMI ≥30 kg/m^2) was present in 54.8% of the cohort, including 69.8% of diabetic patients and 50.0% of non-diabetic patients. The mean NACT duration was 149±37.8 days, with no significant difference between diabetic and non-diabetic patients.

Changes in Skeletal Muscle Index and Fat Index

Inter-rater reliability for SMI measurements was excellent at both pre-NACT [ICC (2.1) = 0.92, 95% CI: 0.90–0.94] and post-NACT [ICC (2.1) = 0.93, 95% CI: 0.91–0.95] assessments. Given the high ICC values, the mean of the two raters' measurements was used for subsequent analyses.

Table 1. Clinical and demographic characteristics of the study cohort by diabetes status

		All (n = 177)	Non-diabetic (n = 134)	Diabetic (n = 43)	p-value
Age (years)		51±10.7	48.6±10.5	58.3±7.7	<0.001
Tumor subtype	HR+/HER2-	58 (32.8)	39 (29.1)	19 (44.2)	0.300
	HR+/HER2+	46 (26.0)	37 (27.6)	9 (20.9)	
	HR-/HER2+	34 (19.2)	28 (20.9)	6 (14.0)	
	TNBC	39 (22.0)	30 (22.4)	9 (20.9)	
cT stage	T1-2	107 (60.4)	79 (59.0)	28 (65.1)	0.761
	T3-4	66 (37.3)	52 (38.8)	14 (32.6)	
	Tx	4 (2.3)	3 (2.2)	1 (2.3)	
cN stage	N0	36 (20.3)	28 (20.9)	8 (18.6)	0.720
	N1	98 (55.4)	76 (56.7)	22 (51.2)	
	N2-3	31 (17.5)	21 (15.7)	10 (23.3)	
	Nx	12 (6.8)	9 (6.7)	3 (7.0)	
NACT type	TCHP	50 (28.2)	42 (31.3)	8 (18.6)	0.106
	AC-T*	127 (71.8)	92 (68.7)	35 (81.4)	
BMI categories	Underweight	3 (1.7)	3 (2.2)	0 (0.0)	0.134
	Normal weight	35 (19.8)	29 (21.6)	6 (13.9)	
	Overweight	42 (23.7)	35 (26.1)	7 (16.3)	
	Obese	97 (54.8)	67 (50.0)	30 (69.8)	
CCI	2	126 (71.2)	126 (94.0)	0 (0.0)	<0.001
	3	43 (24.3)	6 (4.5)	37 (86.0)	
	≥4	8 (4.5)	2 (1.5)	6 (14.0)	
NACT duration (days)		149±37.8	147±37.7	155.1±37.7	0.224

*: AC-T regimens include an anthracycline plus cyclophosphamide followed by a taxane, with or without anti-HER2 agents, pembrolizumab, or carboplatin, AC-T: Anthracycline plus cyclophosphamide followed by a taxane; BMI: Body mass index; CCI: Charlson comorbidity index; NACT: Neoadjuvant chemotherapy; TCHP: Docetaxel, carboplatin, trastuzumab, and pertuzumab; TNBC: Triple-negative breast cancer; HER2: Human epidermal growth factor receptor 2

Mean SMI decreased significantly after NACT, from 43.1±7.4 cm²/m² to 41.4±7.1 cm²/m² (mean change -1.7±3.1 cm²/m², p<0.001) (Table 2). Both diabetic and non-diabetic patients experienced significant SMI loss, although the decline was greater in patients with diabetes (-2.7 *vs.* -1.4 cm²/m²). Similar reductions in SMI were observed in patients aged <50 and ≥50 years. Significant SMI reductions were observed with both chemotherapy regimens, with declines of -1.4 cm²/m² in the TCHP group and -1.8 cm²/m² in the AC-T group. The overall decline in SMI from pre- to post-NACT corresponded to a moderate effect size (Cohen's d = 0.55). When stratified by diabetes status, the magnitude of muscle loss was large among diabetic patients (d = 0.93) and moderate among non-diabetic patients (d = 0.45), indicating a greater degree of treatment-related muscle depletion in patients with diabetes.

SFI also decreased significantly overall (132.9±59.2 to 123.5±55.1 cm²/m², mean change -9.5±27.0, p<0.001). The decline was more pronounced in patients with diabetes (-19.8 cm²/m²) than in those without diabetes (-6.2 cm²/m²). SFI loss was greater in patients aged ≥50 years (-14.2 cm²/m², p<0.001) compared with younger patients (-4.2 cm²/m², p = 0.09). The TCHP group showed greater fat loss than the AC-T group (-13.7 *vs.* -7.8 cm²/m²).

Prevalence of LSMM and Sarcopenic Obesity

The prevalence of LSMM increased from 27.7% before NACT to 37.3% after treatment (p = 0.003) (Figure 2). This increase was significant in both non-diabetic (29.1% to 37.3%, p = 0.028) and diabetic patients (23.3% to 37.2%, p = 0.034). The prevalence of sarcopenic obesity rose from 8.5% pre-NACT to 12.4% post-NACT (p = 0.052). While the increase was not significant overall, it reached significance among diabetic patients (9.3% to 18.6%, p = 0.045), but not in non-diabetic patients.

Predictors of Post-NACT SMI

Linear regression analysis was performed to assess the predictors of post-NACT SMI. In the first model, after adjusting for baseline SMI, diabetes was significantly associated with lower post-NACT

SMI (coefficient -1.21; 95% CI: -2.22 to -0.20; $p = 0.019$). Age and NACT regimen (TCHP vs AC-T) were not significantly associated with post-NACT SMI in this model (Figure 3).

A multivariable-adjusted model was fitted that included age, NACT regimen, and presence of diabetes in addition to baseline SMI. Diabetes remained an independent predictor of lower post-NACT SMI (coefficient -1.42; 95% CI: -2.53 to -0.30; $p = 0.013$). In contrast, age and NACT regimen were not significantly associated with post-NACT SMI (Figure 3). The final multivariable model explained approximately 83% of the variance in post-NACT SMI (adjusted $R^2 = 0.832$). We subsequently performed a sensitivity analysis by including total NACT duration in the multivariable model to account for variability in imaging intervals. The association between diabetes and lower post-NACT SMI remained significant ($\beta = -1.50$, 95% CI: -2.60 to -0.41, $p = 0.007$).

Table 2. Changes in skeletal muscle index and subcutaneous fat index during neoadjuvant chemotherapy by clinical subgroups

	Group	Before NACT	After NACT	Mean change	*p*-value
SMI (cm^2/m^2)	All patients	43.1±7.4	41.4±7.1	-1.7±3.1	<0.001
	Non-diabetic	42.8±7.0	41.4±6.9	-1.4±3.1	<0.001
	Diabetic	44.2±8.5	41.4±7.9	-2.7±2.9	<0.001
	Age <50	44.0±6.8	42.4±6.2	-1.7±3.2	<0.001
	Age ≥50	42.3±7.9	40.6±7.7	-1.7±2.9	<0.001
	NACT type: TCHP	42.3±6.8	40.9±6.1	-1.4±3.2	0.004
	NACT type: AC-T	43.5±7.7	41.6±7.5	-1.8±3.0	<0.001
SFI (cm^2/m^2)	All patients	132.9±59.2	123.5±55.1	-9.5±27.0	<0.001
	Non-diabetic	127.3±58.2	121.2±57.1	-6.2±21.0	<0.001
	Diabetic	150.4±59.7	130.6±48.3	-19.8±38.8	0.0017
	Age <50	128.3±59.7	124.0±59.6	-4.2±22.9	0.09
	Age ≥50	137.2±58.7	122.9±51.1	-14.2±29.5	<0.001
	NACT type: TCHP	113.4±48.6	99.6±44.7	-13.7±19.4	<0.001
	NACT type: AC-T	140.7±61.4	132±56.2	-7.8±29.3	0.003

Reported values are mean ± standard deviation. *p*-values were calculated using paired Student's t-test. AC-T: Anthracycline plus cyclophosphamide followed by a taxane; NACT: Neoadjuvant chemotherapy; SFI: Subcutaneous fat index; SMI: Skeletal muscle index; TCHP: Docetaxel, carboplatin, trastuzumab, pertuzumab

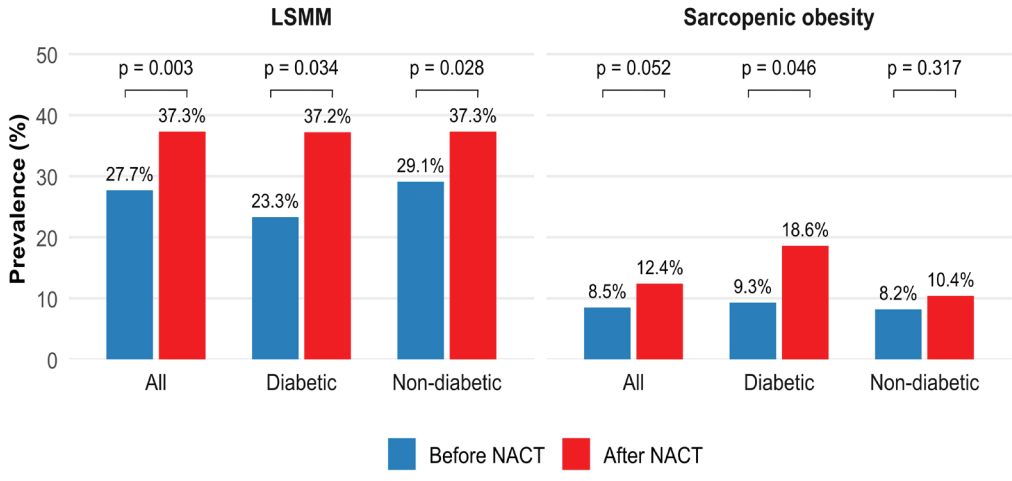

Figure 2. Prevalence of LSMM and sarcopenic obesity before and after NACT. McNemar's test was used to compare paired proportions

LSMM: Low skeletal muscle mass; NACT: Neoadjuvant chemotherapy

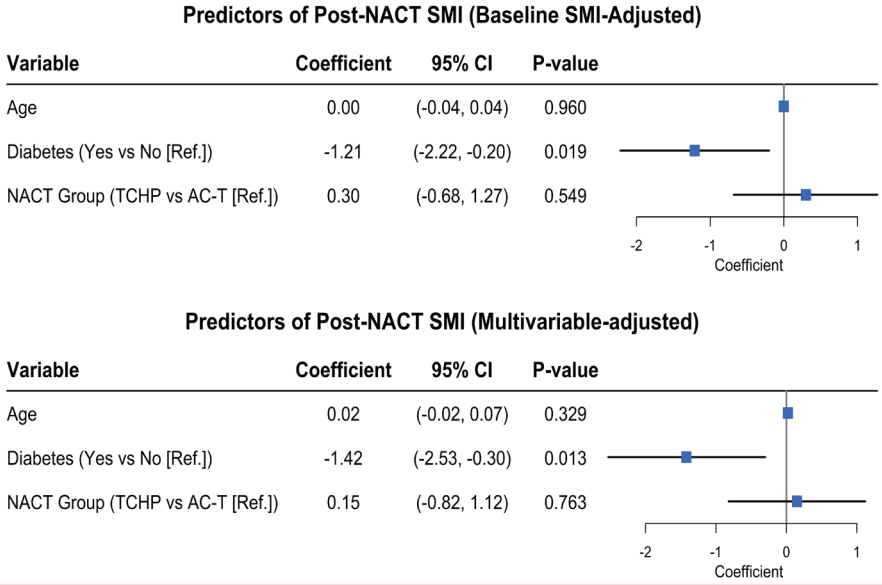

Figure 3. Forest plots of linear regression models for predictors of post-NACT SMI. The upper panel shows the baseline SMI-adjusted model, in which each predictor was evaluated while controlling for baseline SMI. The lower panel shows the multivariable-adjusted model, which included baseline SMI, age, diabetes mellitus, and chemotherapy regimen (TCHP *vs.* AC-T). Regression coefficients are displayed with 95% CIs. Negative coefficients indicate lower post-NACT SMI

NACT: Neoadjuvant chemotherapy; SMI: Skeletal muscle index; TCHP: Docetaxel, carboplatin, trastuzumab and pertuzumab; CI: Confidence interval; AC-T: Anthracycline plus cyclophosphamide followed by a taxane

Discussion and Conclusion

In this retrospective study of breast cancer patients undergoing NACT, we observed a significant decline in SMI from pre- to post-NACT. The loss of muscle mass was evident across the entire cohort, confirming that cytotoxic therapy induces measurable skeletal muscle wasting. Importantly, our analysis identified diabetes as a novel and independent predictor of greater SMI loss. Patients with pre-existing diabetes experienced significantly greater muscle depletion than non-diabetic patients, and this association remained robust after adjusting for age, baseline SMI, and chemotherapy regimen. In contrast, neither patient age nor chemotherapy regimen (TCHP *vs.* AC-T) emerged as significant independent predictors of muscle loss in our multivariable model. Furthermore, the prevalence of LSMM increased from 27.7% to 37.3%, and the prevalence of sarcopenic obesity increased from 8.5% to 12.4% after NACT; these increases were more pronounced in patients with diabetes. Taken together, these findings highlight that muscle loss is a common consequence of NACT and that diabetes may substantially exacerbate this process.

Chemotherapy induces muscle wasting through several interrelated mechanisms. Adverse events of chemotherapy, such as nausea, anorexia, and mucositis can lead to decreased caloric intake, whereas fatigue may reduce physical activity. In addition, chemotherapy may induce systemic inflammation, oxidative stress, and direct activation of catabolic pathways within skeletal muscle (16, 17). Diabetes can exacerbate this process, as chronic hyperglycemia and insulin resistance impair anabolic signaling through the PI3K-Akt-mTOR pathway, while simultaneously amplifying oxidative stress and inflammation. Both conditions converge on similar molecular cascades, including mitochondrial dysfunction and increased pro-inflammatory cytokine activity, leading to enhanced muscle catabolism and reduced protein synthesis (11). This overlap in pathogenic mechanisms provides a biologically plausible explanation for our observation that patients with diabetes experienced greater chemotherapy-related muscle loss. In addition, corticosteroids routinely administered before chemotherapy can worsen insulin resistance and hyperglycemia, thereby worsening glycemic control in patients with diabetes and potentially further contributing to treatment-related muscle loss.

Among the additional clinical parameters assessed, age was not identified as a significant predictor of post-NACT SMI in our study, consistent with findings from prior retrospective cohorts of breast cancer patients undergoing neoadjuvant therapy (6, 7, 18). However, throughout these studies, including ours, the mean patient age was below 55 years, with older individuals being underrepresented. As a result, the potential impact of advanced age on chemotherapy-related muscle loss cannot be ruled out and warrants further investigation in cohorts with a broader

age distribution. We did not find a significant difference in post-NACT SMI between patients treated with TCHP and those treated with AC-T, although the decline in SFI was more pronounced in the TCHP group. These results contrast with the findings of Jang et al. (6), who reported significantly greater muscle loss with TCHP compared to AC-T. This discrepancy may reflect differences in study populations, sample size, or unmeasured confounders.

Our findings reinforce the suggestion that skeletal muscle health deserves attention during breast cancer treatment. LSMM is associated with increased chemotherapy toxicity, which may lead to decreased treatment compliance (19, 20). Furthermore, low baseline SMI is linked to poorer survival across solid tumors (21). A recent study showed that patients who lost significant muscle mass during NACT had inferior disease-free survival compared with those who maintained or gained muscle (22). In particular, patients with diabetes should be considered a high-risk group for chemotherapy-induced skeletal muscle loss, and oncologists should have a low threshold to implement preventive strategies in these individuals. Such strategies may include detailed nutritional assessment and counseling, physical exercise or physiotherapy programs aimed at preserving muscle mass, and close collaboration with endocrinologists to ensure optimal control of blood glucose and other metabolic parameters. A growing body of evidence suggests that exercise programs in patients undergoing chemotherapy and in cancer survivors can improve muscle mass and function, enhance physical capacity, and reduce fatigue (17); and in some populations they can also improve disease-free survival (23, 24). Notably, a randomized clinical trial involving breast cancer patients undergoing adjuvant chemotherapy showed that supervised exercise programs, especially resistance training, improved skeletal muscle mass, and 27% of the patients with sarcopenia experienced a reversal of sarcopenia (25). Accordingly, the American Society of Clinical Oncology guidelines endorse exercise during active, curative-intent treatment to mitigate systemic therapy-related adverse effects (26).

Study Limitations

Several limitations of this study must be acknowledged. First, this was a single-center study, so the generalizability of the findings may be limited. The patient population (in terms of ethnicity, comorbidity prevalence, and lifestyle factors) and practice patterns at our institution may not fully represent other settings. Second, we did not capture certain variables such as dietary patterns, physical activity, or the severity and management of diabetes, which could confound or mediate muscle loss. Third, our assessment of body composition focused on muscle quantity but did not include measures of muscle quality such as muscle density or the presence of myosteatosis due to limitations in imaging analysis. Finally, we did not directly measure functional outcomes related to muscle loss (such as changes in muscle strength, fatigue, or physical performance). Of note, we deliberately used the term "low skeletal muscle mass" rather than "sarcopenia", because the contemporary consensus definition of sarcopenia requires low muscle strength in addition to low muscle quantity (27).

Our study opens several avenues for future investigation. A priority is to conduct prospective studies monitoring body composition in patients with breast cancer receiving NACT to validate our findings under controlled conditions. It remains to be determined whether patients who lose more muscle during treatment have worse tolerance of chemotherapy, higher complication rates, or impaired postoperative recovery. The clinical consequences of the observed muscle loss and its long-term reversibility remain uncertain. In parallel, interventional trials are needed to test strategies to preserve muscle during NACT. These could include randomized evaluations of structured resistance or multimodal exercise programs and targeted nutritional support. It may also be worthwhile to test whether optimizing diabetes management mitigates muscle wasting during cancer treatment.

In conclusion, this study contributes to the growing recognition that NACT for breast cancer may reduce skeletal muscle mass. We identified diabetes mellitus as an independent risk factor for greater treatment-related muscle loss. This is a novel observation that warrants heightened clinical attention. In light of our findings and prior evidence, clinicians should recognize chemotherapy-associated muscle depletion as a clinically meaningful adverse effect and consider integrating muscle-preserving strategies, especially in high-risk patients such as those with diabetes, into routine care.

Ethics

Ethics Committee Approval: This retrospective cohort study was conducted at a single tertiary oncology center. Ethical approval was obtained from the Royal Medical Services Ethics Committee, Bahrain (approval number: 2023-717; date: 28.09.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.G.S., A.A., M.G., S.A., M.S., S.L., N.A., H.A., T.A., M.K.; Concept: Z.G.S., A.A.; Design: Z.G.S., A.A.; Data Collection or Processing: Z.G.S., A.A., M.G., S.A., M.S., S.L., N.A., H.A., T.A., M.K.; Analysis or Interpretation: Z.G.S., A.A., M.K.; Literature Search: Z.G.S.; Writing: Z.G.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Effectiveness of Video Health Education on Breast Cancer Awareness and Self-Examination in the New Age of Digitalisation: Community-Based Evidence from a Developing Nation

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ABSTRACT

Objective: Developing nations with resource limited settings see a higher proportion of presentation at advanced stages of breast cancer compared to developed nations because of poor public awareness and lack of screening guidelines. This study aimed to assess the impact of a video-based teaching module on breast cancer awareness and self-examination among literate women in a developing country.

Materials and Methods: This quasi-experimental, community-based, intervention study was conducted among literate women of a metropolitan city in a developing country, to evaluate the impact of a video-based teaching module on breast cancer awareness and self-examination. Female school teachers over 25 years old with virtual platform access were included. Simple random sampling was used to select participant schools. The target sample size was 103 based on a reference study. An educational video and questionnaires were validated through expert and volunteer feedback, followed by baseline and follow-up surveys at 6 weeks and 10 weeks after intervention. The Friedman test for overall change in scores and Wilcoxon signed-rank test were used for pairwise comparison between time points.

Results: The survey was completed by 181 participants. Mean (standard deviation) age was 41.79 (9.20) years. Median (interquartile range) cumulative score for the knowledge domain was 18 (14–21), 24 (19–32) and 25 (20–33) at baseline, 6 weeks and 10 weeks respectively with significant differences between each of these time points ($p<0.001$). There was a significant increase in the number of participants with a median score of 3 at 6 and 10 weeks compared to baseline in the attitude domain after intervention. The proportion of study participants with a score of ≥3 points in the practices domain increased from 22% (40/181) at baseline to 41.2% (74/181) at 6 weeks and 49.1% (89/181) at 10 weeks of educational intervention.

Conclusion: A video-based educational intervention may enhance breast cancer knowledge, attitudes, and self-examination practices in educated women with access to electronic media. This may contribute to early breast cancer detection in resource-constrained settings with limited screening options.

Keywords: Breast cancer awareness; screening; early detection; breast self-examination

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KEY POINTS

- Breast cancer awareness and practice of breast self-examination uptake is low amongst literate urban dwellers.
- Digital tools can help provide awareness about breast cancer and teach appropriate technique of breast self-examination.

Introduction

High-income countries have achieved a decrease in mortality from breast cancer, partly attributable to early detection. The scenario in low-income countries differs significantly where advanced stage disease at presentation is common because of lack of awareness and absent or ineffective screening programs (1). The Breast Global Health Initiative has recommended awareness-based early detection as an intervention for improving breast cancer survival in low- and middle-income countries (LMIC) (2). Widespread dissemination of knowledge about symptoms and the importance of breast self-examination (BSE) will promote earlier presentation, thus helping improve disease outcomes. Digitalization and the ubiquitous use of social media have revolutionized access to information. Taking advantage of digital platforms for health education is a promising approach to change attitudes and educate about breast cancer and will also enhance teaching of appropriate techniques of BSE. Hence, we conducted this study to assess the impact of a structured video-based teaching module provided across a virtual platform on the existing knowledge on breast cancer awareness and practices of BSE in a cohort of literate women from a metropolitan city in a LMIC.

Materials and Methods

This quasi-experimental, community-based study was conducted over two years in a tertiary medical teaching and research institution in India. Our objective was to assess the impact of a structured, video-based teaching module provided through a virtual platform on the existing knowledge and attitudes towards breast cancer awareness and practices of BSE in school-teachers.

The study was cleared from the Institute Ethics Committee at the All India Institute of Medical Sciences, New Delhi, India vide letter number IECPG/746/23.12.2020, date: 24.12.2020. The list of participant schools was selected using simple random sampling.

A computer-generated random number technique was used to select schools from the list of all schools within the city, downloaded from the Directorate of Education website. The school principals/activity coordinators were contacted, and a participant information sheet was shared with them before recruitment. The principals then invited voluntary participation from schoolteachers. Potential participants were informed that confidentiality would be maintained and personal data anonymized before analysis. Online informed written consent was obtained from the participants prior to their filling in the questionnaire. Inclusion criteria included female school-teachers aged 25 years or more with access to a virtual platform (email and/or WhatsApp™).

Questionnaire Creation and Validation

Baseline and follow-up questionnaires for the assessment of knowledge, attitude, practices of breast cancer awareness and BSE were designed after extensive review of literature. The questionnaires consisted of four domains: (1) sociodemographic details of the participants; (2) knowledge; (3) attitude; and (4) practices. All questions were objective in nature with the maximum score for domains of knowledge, attitude and practices being 36, 3 and 4 points, respectively. The questionnaire was then validated by administering it to three experts in the institute and twenty volunteers meeting inclusion criteria in a phased manner. Their feedback was obtained, and requisite changes were made to the questionnaire.

Educational Tool Creation

An animated audio-video educational tool covering areas of knowledge, attitude and practices of breast cancer awareness and BSE was made in collaboration with the virtual skills lab at our institution. The content and quality of the video was approved by two faculty members of the department of surgical disciplines.

Sample Size Calculation

The study by Singh et al. (3) among community health workers in a similar geographic location observed a minimum 20% increase in knowledge following an educational intervention. Assuming a similar increase in knowledge, with 80% statistical power (1-β), 95% confidence interval and 20% non-response or loss to follow-up rate, the required sample size of 103 women was calculated.

Data Collection and Statistical Analysis

The baseline survey was conducted by virtually sharing the self-administered structured questionnaire developed for this study. Once the questionnaire was filled, the educational video was shared with respondents. The participants were instructed to watch it twice over a period of two weeks, with regular reminders sent to them. Then follow-up surveys were performed using the post intervention questionnaire provided at two intervals of 6–8 weeks and 10–16 weeks from the date of finishing the teaching module, which was confirmed by an email or message.

The responses of participants were entered in an spreadsheet (Microsoft Excel, Microsoft Inc., Redmond, WA, USA) and scores calculated. Each correct response was given one point and cumulative scores for each domain were calculated by summing up the score for all correctly answered questions. For ease of data representation and analysis, responses to questions with multiple options were categorised into "correct" and "incorrect". In addition, the score obtained with respect to questions assessing knowledge about risk factors, symptoms and screening modalities were subclassified into categories of "poor", "average" and "good" based on the number of correct responses marked for that question. For knowledge of risk factors, poor awareness was defined as correct identification of fewer than five risk factors, average awareness as correct identification of five to nine risk factors, and good awareness as correct identification of ten to fourteen risk factors. For knowledge of symptoms, poor awareness was defined as recognition of fewer than four symptoms, average awareness as recognition of four to six symptoms, and good awareness as recognition of seven to nine symptoms. Regarding knowledge of screening methods, poor awareness was defined as awareness of zero to one screening method, average awareness as awareness of two screening methods, and good awareness as awareness of all three screening methods.

Quantitative data was reported as mean ± standard deviation (SD), if normality assumptions were met and otherwise as median [interquartile range (IQR)]. Qualitative data was reported in numbers or as percentages, as appropriate. To establish the association between parameters, chi-square test or Fisher's exact tests were applied. The Friedman test was used to analyse the overall change in scores of knowledge, attitude and practices of breast cancer awareness and BSE after the video based educational intervention. Pairwise comparisons using the Wilcoxon signed-rank test adjusted with Bonferroni correction were used to assess changes between the three different time points. Cochran's Q test was applied to the categorical data of each of the participant's responses before and after the video based educational intervention to assess overall change in binary outcome variables. Furthermore, a pairwise comparison was done using McNemar test with Bonferroni correction to analyse the statistical significance of change between the three time points. A *p*-value of less than 0.05 was considered to represent statistical significance. The Kruskal-Wallis test was used to investigate the statistical significance of differences between subgroups at each time point with respect to the scores for knowledge, attitude and practices. Then pairwise comparison was performed using the Dunn test with Bonferroni correction to analyse the statistical significance of change in between the three time points. All statistical data analyses were performed using IBM SPSS version 24 (IBM Inc., Armonk, NY, USA) and STATA 16.1 (STATA MP, College Station, TX, USA). The questionnaire used in the baseline survey is presented in Appendix 1.

Results

The survey was completed by 181 participants, with a mean ± SD age of 41.79±9.20 years. Around a third (35%; 64/181) of participants were under 40 years of age. In addition, 85% (154/181) were postgraduates and 15% (27/181) graduates. Family history of breast cancer was present in 8.8% (16/181) and 18.2% (33/181) had a history of visiting a medical professional for breast related symptoms.

Knowledge Domain

All study participants were aware of breast cancer and 98.8% (179/181) believed that early detection of breast cancer would have a significant positive impact on disease outcome. At the baseline survey, most participants considered a breast lump as the only mode of presentation. The knowledge about various symptoms improved significantly post intervention. Electronic media was the most common source of information for participants with respect to both breast cancer and BSE, seen in around 73% participants at baseline. Only 30% reported that medical professionals were a source of information. There was a significant increase in participants knowing that breast cancer could afflict either gender. A significant increase in knowledge score was seen for age at risk of developing breast cancer, prevalence of disease, pattern of inheritance, and gender predisposition. These results are shown in Table 1.

Awareness about BSE was present in 89.5% (162/181) participants at baseline, increasing to 100% at 6 and 10 weeks of study. Amongst those with awareness of BSE, 73.5% (119/162) participants had some knowledge of the technique at baseline and most (64.5%) had self-learned it. Knowledge related to technique for BSE along with awareness regarding the age for starting BSE, frequency and the timing for BSE improved significantly after the intervention (Table 1).

There was a significant improvement in knowledge regarding risk factors, symptoms and screening modalities for breast cancer, as shown in Table 2. Before the intervention, only 3.3% (6/181) of the participants were in the category of "good" knowledge about the risk factors, which increased significantly to 47.5% (86/181) after 12 weeks of the intervention ($p<0.001$). In terms of symptoms of breast cancer, a significant improvement in the proportion of participants achieving "good" category from baseline (20.9%) to 6 weeks (42.5%) and 10 weeks (44.2%) after the intervention was observed ($p<0.001$). Knowledge regarding modalities for breast cancer screening also increased significantly, with 54.1% in the "good" category at the baseline which increased to 69.6% and 70.1% at 6 and 10 weeks, respectively.

The maximum possible score for the knowledge domain was 36. The median cumulative score increased from 18 points at baseline to 24 points at 6 weeks and 25 points at 10 weeks,

Table 1. Responses to knowledge domain at baseline, 6 weeks and 10 weeks following educational intervention

S. No	Question	Response	Baseline *n* (%)	6–8 weeks *n* (%)	10–16 weeks *n* (%)	*p*-value
1	Sources of information on breast cancer	Electronic media	132 (72.92)	132 (72.92)	135 (74.58)	0.05
		Lectures/conferences	95 (52.48)	95 (52.48)	96 (53.03)	0.36
		Books/printed material	89 (49.17)	89 (49.17)	93 (51.38)	**0.01**
		Friends or family	79 (43.64)	79 (43.64)	83 (45.85)	**0.01**
		Medical professionals or hospitals	53 (29.28)	53 (29.28)	53 (29.28)	0.99
2	Prevalence of breast cancer	Correct response	132 (72.92)	140 (77.34)	145 (80.11)	**0.03**
		Incorrect responses	49 (27.08)	41 (22.66)	36 (19.89)	
3	Gender at risk of breast cancer	Women only	75 (41.43)	143 (79.0)	148 (81.76)	**<0.01**
		Men & women both	106 (58.6)	38 (21.0)	33 (18.2)	
4	Impact of early detection on outcome	Yes	179 (98.89)	181 (100)	181 (100)	**<0.01**
		No	2 (1.1)	0 (0.0)	0 (0.0)	
5	Mode of presentation	Lump	171 (94.47)	176 (97.23)	176 (97.23)	<0.01
		Nipple discharge	108 (59.66)	141 (77.90)	144 (79.55)	<0.01
		Change in size	103 (56.90)	134 (74.03)	135 (74.58)	<0.01
		Change in shape	100 (55.24)	132 (72.92)	134 (74.03)	<0.01
		Change in nipple position	64 (35.35)	108 (59.66)	109 (60.22)	<0.01
		Nipple destruction	0 (0)	77 (42.54)	102 (56.35)	<0.01
		Redness or rash of skin over breast	87 (48.06)	113 (62.43)	111 (61.32)	<0.01
		Dimpling or thickening of skin overlying breast	90 (49.72)	110 (60.77)	113 (62.43)	<0.01
6	Age at risk for breast cancer	Correct response	144 (79.55)	160 (88.39)	163 (90.05)	**<0.01**
		Incorrect response	37 (20.45)	21 (11.69)	18 (9.95)	
7	Inheritability of breast cancer	Correct response	137 (75.69)	150 (82.87)	152 (83.97)	**<0.01**
		Incorrect response	44 (24.3)	31 (17.1)	29 (16.0)	
8	Pattern of inheritance for breast cancer (*n* = 137/150/152)	Mother	56 (40.87)	50 (33.33)	50 (32.89)	**<0.01**
		Both mother and father	81 (59.12)	100 (66.66)	102 (67.10)	
9	Awareness of technique for BSE (*n* = 162)	Yes	119 (73.5)	181 (100)	181 (100)	**<0.01**
		No	62 (26.5)	0 (0.0)	0 (0.0)	
10	Age for starting BSE	Correct response	41 (22.65)	91 (50.27)	95 (52.48)	**<0.01**
		Incorrect responses	140 (77.35)	90 (49.73)	86 (47.52)	
11	Frequency of BSE	Correct response	89 (49.17)	117 (64.64)	121 (66.85)	**<0.01**
		Incorrect responses	92 (50.83)	64 (35.36)	60 (39.15)	
12	Timing of BSE	Correct response	60 (33.14)	109 (60.22)	117 (64.64)	**<0.01**
		Incorrect responses	121 (66.86)	72 (39.78)	64 (35.36)	

BSE: Breast self-examination

Table 2. Awareness levels for risk factors, symptoms and screening methods at baseline, and after at least 6 weeks and 10 weeks following educational intervention

Knowledge domain factor	Category of knowledge	Baseline *n* (%)	6–8 weeks *n* (%)	10–16 weeks *n* (%)	*p*-value
Risk factors for breast cancer	Poor	132 (72.9)	72 (39.7)	65 (35.9)	<0.001
	Average	43 (23.7)	23 (12.7)	30 (16.5)	
	Good	6 (3.3)	86 (47.5)	86 (47.5)	
Symptoms of breast cancer	Poor	80 (44.2)	44 (24.3)	41 (22.6)	**<0.001**
	Average	63 (34.8)	60 (33.1)	60 (33.1)	
	Good	38 (20.9)	77 (42.5)	80 (44.2)	
Screening modalities for breast cancer	Poor	40 (22.1)	16 (8.8)	16 (8.8)	**<0.001**
	Average	43 (23.7)	39 (21.5)	38 (20.9)	
	Good	98 (54.14)	126 (69.6)	127 (70.1)	

Footnote for Table 2: Risk factors - Poor awareness: <5 risk factors, Average awareness: 5–9 risk factors, Good awareness: 10–14 risk factors, Symptoms -Poor awareness: <4 symptoms, Average awareness: 4–6 symptoms, Good awareness: 7–9 symptoms, Screening methods - Poor awareness: 0–1 screening methods, Average awareness: 2 screening methods, Good awareness: 3 screening methods

respectively. The pairwise comparison between time points showed significant improvement at 6 and 10 weeks, respectively, compared to baseline (p<0.001). The improvement in scores was also significant between 6 weeks and 10 weeks (p<0.001). This is depicted in Figure 1.

Attitude Domain

There was a significant increase in the study participants who considered that periodic BSE can help in early detection of breast cancer (Table 3). The number of participants who would definitely or were likely to visit a medical professional upon developing symptoms or detecting something unusual on BSE showed an improvement from 75.6% to 86.6% at 6 weeks and 91% at 10 weeks. Prior history of screening mammography was present in 22.1% (40/181) participants at baseline. This showed a significant improvement to 27.6% (50/181) at 6 and 10 weeks of the study. The likely medical professional of choice for subsequent evaluation continued to be gynecologist in 81.7% (148/181), 76.7% (139/181), 77.6% (142/181) participants at baseline, 6 weeks and 10 weeks of study, respectively, with no significant change.

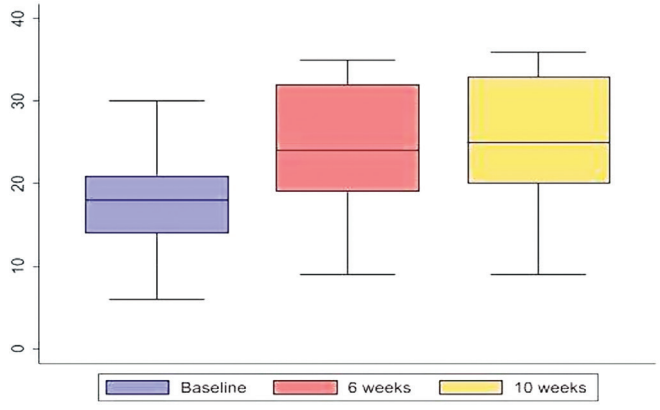

Figure 1. Box and Whisker plot depicting scores for knowledge domain

The maximum score for the attitude domain was 3. The number of study participants with a score of 3 points increased from 58% (105/181) at baseline to 72.8% and 75.1% (136/181) after 6 and 10 weeks of educational intervention. The number of study participants with a score of 2 points decreased significantly from 33.7% (61/181) at baseline to 23.7% at 6 weeks and 23.2.1% at 10 weeks. These results are depicted in Figure 2. The pairwise comparison between time points showed a significant change in the cumulative scores of the attitude domain between baseline and 6 weeks (p = 0.044) and baseline and 10 weeks (p = 0.008), with no significant change between 6 weeks and 10 weeks (p = 0.99).

Practices Domain

BSE was practised by 58.6% (106/181) participants which increased significantly to 70.2% (127/181) at 6 weeks and 74% 10 weeks (134/181) after the intervention. At baseline, only 16% of these participants were practising the correct technique, based on the self-assessment questions asked in the questionnaire. This number increased significantly to 50.3% (64/127) and 57.4% (77/134) at 6 and 10 weeks respectively after being taught the correct technique in the video.

Amongst the 75 participants not performing BSE at baseline, uncertainty regarding the technique for BSE was found to be the leading cause, noted in 77.3% (58/75) of these participants. This uncertainty declined significantly to 57% (31/54) and 48.93% (23/47) at 6 and 10 weeks respectively (Table 4).

Table 3. Responses to attitude domain at baseline, 6 weeks and 10 weeks following educational intervention

S. Nn	Question	Response	Baseline *n* (%)	6–8 weeks *n* (%)	10–16 weeks *n* (%)	*p*-value
1	Role of periodic BSE in earlier detection of breast cancer	Yes	164 (90.6)	173 (95.58)	174 (96.13)	**<0.01**
		No	17 (9.4)	8 (4.4)	7 (3.9)	
2	Role of periodic CBE in breast cancer screening	Yes	150 (82.87)	157 (86.74)	155 (85.63)	0.15
		No	31 (17.1)	24 (13.2)	26 (14.3)	
3	Likelihood of visiting a doctor on noticing signs/symptoms of breast cancer	Definitely visit/likely visit depending on schedule	137 (75.68)	157 (86.73)	165 (91.15)	**<0.01**
		Discuss/read friends family/ Internet etc.,) or undergo imaging and then decide	44 (24.29)	24 (13.24)	16 (14.34)	
4	Medical professional of choice for subsequent evaluation	Gynecologist	148 (81.76)	139 (76.79)	142 (78.45)	0.53
		Surgeon	17 (9.39)	31 (17.12)	32 (17.67)	**<0.01**
		Others	16 (8.83)	11 (11.07)	9 (4.96)	**<0.01**
5	History of undergoing screening mammography	Yes	40 (22.09)	50 (27.62)	50 (27.6)	**<0.01**
		No	141 (77.9)	131 (72.4)	131 (72.4)	

CBE: Clinical breast examination; BSE: Breast self-examination

The maximum score for the practice domain was 4. The baseline median cumulative score was 1 (IQR: 0–2). The number of study participants with a score of 3 or more points increased from 22% (40/181) at baseline to 41.2% (74/181) at 6 weeks and 49.1% (89/181) at 10 weeks of educational intervention. The number of participants with a score of 2 or less points decreased from 77.8% (141/181) at baseline to 58.8% (107/181) at 6 weeks and 50.9% (92/181) at 10 weeks. These findings are depicted in Figure 3.

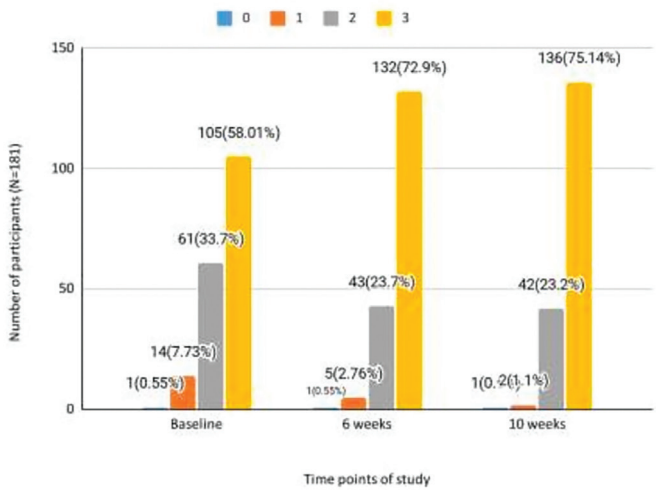

Figure 2. Distribution of cumulative scores for attitude domain

The pairwise comparison between time points showed significant improvement in the attitude of study participants at 6 ($p<0.001$) and 10 weeks ($p<0.001$) respectively compared to baseline, with no significant change between 06 weeks and 10 weeks ($p = 0.54$).

Discussion and Conclusion

Breast cancer in India and several Asian countries typically presents at a younger age and with more advanced disease,

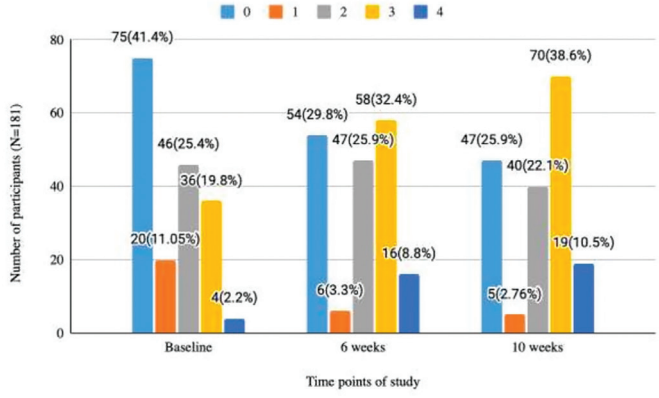

Figure 3. Distribution of cumulative scores for practices domain

Table 4. Responses to practices domain at baseline, 6 weeks and 10 weeks following educational intervention

S. No	Question	Response	At baseline *n* (%)	6–8 weeks *n* (%)	10–16 weeks *n* (%)	*p*-value
1	Practice of BSE among study participants	Yes	106 (58.56)	127 (70.16)	134 (74.03)	**<0.01**
		No	75 (41.4)	54 (29.8)	47 (26.0)	
2	**Reason for not performing BSE (*n* = 75/54/47)**	Lack of time to perform it	13 (17.33)	15 (27.77)	6 (12.76)	**<0.01**
		Unclear about the way to perform it	58 (77.33)	31 (57.40)	23 (48.93)	**<0.01**
		Other reasons	4 (1.33)	8 (14.76)	18 (38.29)	**<0.01**
3	**Frequency of performing BSE (*n* = 106/127/134)**	Once in a month	60 (56.60)	85 (66.92)	91 (67.91)	**<0.01**
		Others	46 (43.39)	42 (33.0)	43 (31.3)	
4	**Technique followed for BSE (*n* = 106/127/134)**	Incorrect technique	89 (83.9)	63 (49.6)	57 (42.5)	**<0.01**
		Correct technique	17 (16.03)	64 (50.39)	77 (57.46)	
5	**Examination of axilla during BSE (*n* = 106/127/134)**	Includes axilla examination always as a part of BSE	54 (50.94)	62 (48.89)	69 (51.49)	**<0.01**
		Does not include axilla as part of BSE	52 (49.0)	65 (51.18)	65 (48.5)	
6	**Detection of abnormality during BSE (*n* = 106/127/134)**	Yes	8 (7.54)	15 (11.8)	15 (11.19)	**<0.01**
		No	98 (92.4)	112 (88.1)	119 (88.8)	

BSE: Breast self-examination

largely due to limited awareness, sociocultural barriers, and healthcare constraints. The median symptom duration at presentation is approximately 5–6 months (4, 5). While early detection of breast cancer is associated with a better disease prognosis and thus highlights the importance of screening and clinical downstaging, population-based mammographic screening poses logistical challenges in resource-limited settings and this is compounded by the absence of national guidelines. Promoting awareness of risk factors, symptoms, and BSE is therefore of high importance, given the prevalence of breast cancer. Virtual media offers a cost-effective platform with wide community reach, even more so now that the "Digital India" campaign has reached the interiors of the country. According to the Internet and Mobile Association of India's 2013 report, 52% of working women and 55% of non-working women use social media in India (6). This societal change in the worlds' most populous country provided the rationale for the present study, investigating the impact of a video-based educational intervention, delivered through virtual platforms, on urban literate women in Delhi.

Our study identified a notable lack of knowledge regarding various modes of breast cancer presentation beyond recognition of a breast lump. At baseline, only just over half of participants were knowledgeable about additional symptoms, such as bleeding or nipple discharge (59.6%), changes in breast size (56.9%), alterations in breast/nipple shape (55.2%), or changes in nipple position (35.3%) as indicators of breast cancer. Post-intervention, awareness had significantly improved across all parameters. These findings are consistent with other studies (7-9). Shankar et al. (8), who reported that while 83.3% of women recognized a breast lump as a symptom, only 48–60% were aware of other presentations, with significant improvement following intervention. Similar results were seen in the meta-analysis by Wang et al. (9), where 71% (95% confidence interval: 62–80%) of participants were aware of breast lumps, while fewer than half of the participants exhibited awareness of the other nine assessed symptoms. Recognizing and comprehending risk factors and modes of presentation are of even greater importance in resource-limited settings. Interventions aimed at enhancing knowledge of these factors is likely to make a positive impact on health promotion and early detection efforts.

Within our cohort, most participants consistently believed that regular BSE facilitated early detection [baseline (90.6%), 6-week (95%), and 10-week (96.1%)]. This collective attitude toward BSE indicates a generally positive disposition within the study population. Despite this favourable perspective, BSE was practised by only 58.6% of participants at baseline. Of those who practised BSE, only 16% were found to employ the correct technique. However, notable enhancement in BSE practice and technique was evident following the intervention. Global prevalence rates of BSE practice vary significantly both within and across countries. In a previous survey of 20 European countries,

only around 54% of women had never practised BSE (10). Dahiya et al. (11) reported that 76.6% women believed BSE aids in early breast cancer detection, yet only 49.1% practised it regularly. Similarly, Singh et al. (7) found that only 10% of participants engaged in BSE. More importantly, their study showed that none were acquainted with the recommended method or frequency.

The scenario is similar in other developing nations. In a study done on future healthcare professionals in Ghana, only 42.6% participants performed BSE (12). An interventional study by Alameer et al. (13) in Saudi Arabia's Jazan region reported an initial BSE practice rate of only 57.3%, which improved significantly to 92% at 6 weeks post-intervention. Sarker et al. (14) showed a significant improvement in BSE practices after an educational intervention using leaflets and brainstorming sessions (21.3% *vs.* 33.8%; $p<0.001$). Another study in Nigeria by Alabi et al. (15) revealed that only 42.2% of the women aware of BSE performed it. Most of the studies however did not assess the technique of performing BSE, unlike our study wherein the questionnaire enquired about the steps of BSE. Moreover, the participants were able to self-assess their technique after watching the video, and this reflected in the post intervention questionnaires as well. Our study as well as the earlier literature review have highlighted the gap between positive attitudes towards BSE and its actual implementation using the correct technique, showing a pressing need for effective educational interventions to bridge this disparity.

In the initial survey, a notable 22% of participants had a history of undergoing screening mammography, which increased to only 27% post intervention. Curiously, even though 63.5% of the study's participants were over 40 years of age, this finding indicated how a lack of awareness coupled with the absence of national guidelines for screening mammography impacted educated participants' health-related choices. The promotion of BSE as a screening approach for breast cancer holds promise for resource-constrained environments where annual mammography is often impossible (16). Throughout the study period, gynecologists emerged as the preferred choice of medical professionals that participants would consult upon detecting breast cancer symptoms. This preference may indicate the influence of certain attitudes and personal inclinations even amongst literate women, such as the preference for female clinicians, that could be resistant to change despite the educational interventions delivered through virtual platforms. This can also be taken as a leading lesson wherein gynecologists can be preferentially trained to teach BSE to patients visiting them as well as convince their patients to seek consultation with a surgeon for breast ailments.

Our and similar studies have shown that electronic media was the most common source of acquiring information about breast cancers (8, 17). Among our participants, 18% had a history of prior doctor visits due to breast-related symptoms, which is comparable to 11% as reported by Alabi et al. (15). Despite limited existing research on the relationship between past doctor visits and breast cancer awareness and knowledge of BSE, the prevalence of individuals seeking medical attention for benign breast-related concerns suggests an opportune moment for implementing interventions to encourage beneficial practices and contribute to the clinical downstaging of breast cancer.

This study demonstrated a significant improvement in the scores of the three domains studied, knowledge, attitude and practices, at six weeks. Similar improvement in scores has been reported in other studies (14, 18, 19). However, a direct comparison is not possible because of different questionnaires and scoring methods used. In our study, only the knowledge domain showed a further improvement at 10 weeks, suggesting that while reinforcement of knowledge may lead to better awareness, the attitude and practices may not change significantly after an initial satisfactory intervention. Previous other studies have also shown that there is not much change between the practice of doing BSE or undergoing mammography between two time points after intervention (8, 19).

The findings of our study suggest clinically useful practical applicability within settings constrained by resources. This study focussed on schoolteachers who may influence a wider population including peers, family, friends and especially their students. Other noteworthy highlights of this study are its quasi-experimental design, evaluating the effect of intervention at two distinct time points, study of various factors encompassing domains of knowledge, attitude and practices about breast cancer and BSE, and comprehensive assessment of technical performance of BSE. The use of a novel audio-visual intervention allowed us to provide information in a comprehensible manner and conduct the study in multiple schools even during the coronavirus disease pandemic. The study was adequately powered.

Nevertheless, the study lacks personalised engagement with women who did not exhibit a positive shift in attitude or behaviour regarding BSE. Self-reporting of outcomes may also invite desirability bias. Furthermore, the absence of a long-term follow-up and the specific focus on an educated group of women may prevent the broad generalisation of these findings.

In the future, we wish to share the audiovisual aid publicly and encourage its use and widespread distribution by community health workers for teaching BSE, who can also help disperse our message into rural areas of our community. We also plan to develop this audio-visual aid in the format of a video game to assess for retainability and greater participant interaction.

Video-based educational interventions improved the knowledge about breast cancer and promoted BSE among a cohort of educated, urban Indian women with electronic media access. In our digitally connected world, such interventions may serve as a valuable tool to encourage self-examination, potentially leading to earlier breast cancer detection and improved outcomes, especially in resource-constrained settings without established routine screening guidelines and programs. These efforts can be further adapted and strengthened through in-person awareness sessions conducted by primary health care workers at the community level, where the correct BSE technique can be demonstrated and reinforced using audio-visual aids, especially in areas with lower literacy levels.

Ethics

Ethics Committee Approval: The study was cleared from the Institute Ethics Committee at the All India Institute of Medical Sciences, New Delhi, India vide letter number IECPG/746/23.12.2020, date: 24.12.2020.

Informed Consent: Informed consent was obtained from all participants prior to study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.R.M., S.S., R.K., M.A.K., M.K.J., H.K.B., R.P.; Concept: R.R.M., S.S., R.K., H.K.B., R.P.; Design: R.R.M., S.S., R.K., M.K.J., H.K.B.; Data Collection or Processing: R.R.M., R.K., M.A.K., H.K.B.; Analysis or Interpretation: R.R.M., S.S., R.K., M.A.K., M.K.J., R.P.; Literature Search: R.R.M., S.S., M.K.J., H.K.B., R.P.; Writing: R.R.M., S.S., R.K., M.A.K., M.K.J., H.K.B., R.P.

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Click the link to access Appendix 1: https://https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/182fb0b1-80c6-43e5-83a2-2e011d1cc598.pdf

ORIGINAL ARTICLE

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Clinicopathological Characteristics of Lesions Diagnosed by MRI-Guided Biopsy in *BRCA1/2* Mutation Carriers

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ABSTRACT

Objective: *BRCA1/2* pathogenic variant carriers face a high risk of breast cancer, making early detection vital for minimizing systemic treatments. Contrast-enhanced magnetic resonance imaging (MRI) outperforms mammography and ultrasound in detecting lesions that are often missed, particularly in individuals with *BRCA1* or *BRCA2* variants. However, the effectiveness of MRI-guided biopsy remains unclear. Thus, the aim was to evaluate the effectiveness of MRI-guided biopsy in detecting malignancy among *BRCA1/2* pathogenic variant carriers with MRI-only-detected breast lesions and compare these findings with those in non-carriers and assess lesion characteristics and diagnostic yield.

Materials and Methods: We retrospectively analyzed. We compared the effectiveness of MRI-guided biopsy for *BRCA1/2* pathogenic variant carriers with MRI-only-detected lesions with that of non-carriers between April 2018 and December 2022. We examined the clinicopathological characteristics and MRI findings of the *BRCA1/2* carriers.

Results: A total of 130 lesions from 126 patients were reviewed. The *BRCA1/2* mutation group had a significantly higher incidence of category 3 lesions on MRI. Invasive carcinoma was more prevalent among *BRCA1/2* carriers, and non-carriers predominantly presented with ductal carcinoma *in situ*. MRI-guided biopsy identified malignant tumors in 30.1% of lesions. The positive predictive values were 42.9% for *BRCA1/2* carriers and 28.6% for non-carriers.

Conclusion: MRI-guided biopsy was effective in detecting early-stage invasive carcinoma in *BRCA1/2* carriers, highlighting its role in tailored surveillance strategies. For new lesions categorized as breast imaging reporting and data system 3 on MRI, biopsy should be considered, particularly for *BRCA1/2* carriers. Prospective studies are needed to validate these findings and assess long-term clinical outcomes to inform personalized management approaches for high-risk populations.

Keywords: Breast cancer; magnetic resonance imaging; image-guided biopsy; *BRCA1* gene; *BRCA2* gene; mutation

KEY POINTS

- Features of magnetic resonance imaging (MRI)-guided biopsies in *BRCA1/2* variant carriers and non-carriers differ.
- Pathogenic variant carriers had invasive cancer; non-carriers had non-invasive cancer.
- MRI-guided biopsy helps detect breast cancer early in *BRCA1/2* mutation carriers.

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Introduction

BRCA1/2 pathogenic variants are associated with a high incidence of breast cancer (1, 2). The detection of breast cancer at an early stage in this population is important to avoid the need for systemic treatment. Contrast-enhanced breast magnetic resonance imaging (MRI) has demonstrated significant advantages in identifying suspected breast cancer lesions that mammography or ultrasound (US) cannot detect (MRI-only detected lesions) in *BRCA1/2* pathogenic variant carriers (3). Both the Japanese and National Comprehensive Cancer Network guidelines for the diagnosis and treatment of hereditary breast and ovarian cancers (HBOC) recommend annual surveillance using contrast-enhanced breast MRI for *BRCA1/2* pathogenic variant carriers who have already developed breast or non-breast cancers (4, 5).

Since April 2020, the Japanese National Insurance scheme has covered breast cancer surveillance using contrast-enhanced breast MRI for *BRCA1/2* pathogenic variant carriers who have developed breast or ovarian cancer. Furthermore, MRI-guided biopsy of lesions detected has been covered by the Japanese National Insurance System since April 2018. However, the availability of this procedure remains limited in facilities. Owing to the scarcity of reports on MRI-guided biopsy findings, the indications and appropriate management of this procedure to avoid unnecessary biopsies have not been well established (6-9).

In this study, we evaluated the utility of MRI-guided biopsy in *BRCA1/2* pathogenic variant carriers with MRI-only detected lesions, compared to non-carriers.

Materials and Methods

Patients and Methods

Patients with and without *BRCA1/2* pathogenic variants who underwent MRI-guided biopsy between April 2018 and December 2022 were included in this study. All patients underwent both mammography and US; cases in which lesions were detected on MRI-targeted US following MRI were excluded.

For *BRCA1/2* pathogenic variant-positive cases, all MRI examinations performed for surveillance were scheduled according to the menstrual cycle. In contrast, MRI examinations performed for preoperative staging did not follow the menstrual cycle, and in some cases, the procedure was halted during biopsy due to a lack of reproducibility.

All the breast MRI images were evaluated by two radiologists who had 25 (M.T.) and 15 years of experience with breast MRI. Lesions were categorized as focus, mass, or non-mass enhancement (NME) according to the breast imaging reporting and data system (BI-RADS) 5th edition of the American College of Radiology (10). For mass lesions, the lesion shape (oval, round, or irregular), margin [circumscribed or non-circumscribed (irregular or spiculated)], and internal enhancement characteristics (homogeneous, heterogeneous, rim enhancement, or dark internal septations) were evaluated, based on BI-RADS for MRI. For NME lesions, distribution (focal, linear, segmental, regional, multiple regions, or diffuse), and the internal enhancement pattern (heterogeneous, homogeneous, clumped, or clustered ring) were evaluated, again based on BI-RADS for MRI. An additional evaluation was performed for the internal enhancement pattern (linear ductal or branching). Linear ductal was defined as enhancement arrayed in a single line, and branching was defined as a line that branches, previously described by Tozaki and Fukuda (11) and Machida et al. (12).

For mass lesions, the intralesional regions of interests (ROIs) were drawn using SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan). A circular ROI was placed in the target lesion, and a kinetic curve assessment was performed, based on BI-RADS for MRI. A circular ROI larger than 3 pixels was placed on the most suspicious region of the enhancement within a mass lesion. Suspicious regions were defined as areas that exhibit a washout in the delayed phase or a rapid rise in the early phase and were usually located at the margin of the tumor. Fatty tissue and non-enhancing areas in the mass lesion were avoided. The kinetic curve assessment was not performed for focus and NME lesions because it is difficult to set the ROI and reproducibility is not guaranteed. The classification for focus, mass, and NME lesions was based on the categories reported by Tozaki and Fukuma (13), with some modifications (Table 1).

We compared the clinicopathological characteristics, MRI findings, and pathological features of *BRCA1/2* pathogenic variant carriers (*BRCA1/2* group) to those of non-carriers (non-carrier group). Sensitivity and positive predictive values were used to assess the accuracy of MRI-guided biopsy for MRI-only detected lesions in *BRCA1/2* pathogenic variant carriers compared with non-carriers. The association between MRI and pathological findings was also examined. This retrospective study was approved by the Ethics Review Board of Showa University (approval no: 2023-033-B, date: February 25, 2025). Informed consent was obtained in the form of an opt-out on our website.

MRI Technique

A breast MRI was performed using a 1.5-T system (Signa HDx Ver. 16; GE Healthcare, Milwaukee, WI, USA). All the patients were examined in the prone position using a dedicated 8-channel breast coil. Before contrast material administration, transverse T1-weighted (TR/TE, 6.1/3; flip angle, 12°; field of view, 20 cm; matrix, 320×192; slice thickness, 2.4 mm; time of acquisition, 158 s) and transverse fat-suppressed T2-weighted fast spin-echo (TR/TE, 3060/102: field of view, 35 cm; matrix size, 320×256; slice

Table 1. Categorization of breast lesions on contrast-enhanced MRI

Breast lesion type and BI-RADS MRI category	Findings on contrast-enhanced MRI
Mass lesion	
Category 5	Spiculated margin
	Irregular lesion: fast washout pattern and rim enhancement
Category 4B/C	Irregular lesion
	Circumscribed margin: washout pattern
Category 4A	Circumscribed margin: non-washout and initial fast rise
Category 3	Circumscribed margin: neither washout nor initial fast rise
Focus lesion	
Category 4A	Not circumscribed margin
Category 3	Circumscribed margin
Non-mass lesion	
Category 5	Segmental distribution and clustered ring enhancement
Category 4B/C	Segmental distribution
	Clustered ring enhancement
	Clumped architecture
	Brancing ductal pattern
Category 4A	Linear ductal pattern
Category 3	Not showing the characteristics of category 4 or 5

BI-RADS: Breast imaging reporting and data system, MRI: Magnetic resonance imaging

thickness, 2.0 mm: time of acquisition, 86 seconds) sequences were performed. Axial diffusion-weighted echo-planar imaging along the x-y-z axes (TR/TE, 5850/85 ms; field of view, 38 cm; matrix, 128×128; slice thickness, 5.0 mm; b-values of 0 and 1500 s/mm^2) was also performed.

Dynamic MRI using a three-dimensional (3D) fat-suppressed volume imaging breast assessment (VIBRANT) sequence with parallel acquisition was obtained before and three times after a bolus injection of Gd-DOTA (0.1 mmol/kg at a rate of 0.8 mL/s), followed by a 60-mL saline flush using an automatic injector. Both breasts were examined in the transverse plane using the first-, second-, and third-phase dynamic images acquired at 30 seconds, 1.5 minutes, and 4.5 minutes, respectively. The dynamic MRI parameters were: TR/TE, 6.1/3.0; flip angle, 12°; field of view, 20 cm; matrix, 320×192; interpolated slice thickness, 2.4 mm; and time of acquisition, 71 seconds. The right and left breasts were examined in the sagittal plane using the VIBRANT sequence without parallel acquisition at 2.5 and 3.5 minutes (between the second- and third-phase images), respectively (TR/TE, 4.2/1.6; flip angle, 12°; field of view, 23 cm; matrix, 320×192; interpolated slice thickness, 2 mm; time of acquisition, 60 seconds).

MRI-Biopsy Procedure

All biopsies were performed by radiologists specializing in breast imaging. A vacuum-assisted breast biopsy unit using a 10-gauge breast biopsy system (EnCor Enspire™ breast biopsy system, Becton, Dickinson and Company, NJ, USA) or a 9-gauge breast biopsy system (ATEC® Breast Biopsy System, Hologic, Inc., Marlborough, MA, USA) was used. The procedure consisted of the following steps.

1. Compression Plate and Marker Placement

A grid-type compression plate was used. Two markers (vitamin E capsule) were placed in the block near the predicted puncture site. A grid and markers were drawn on a transparent sheet, and the sheet was fixed on the monitor of the workstation, with reference to a sagittal image. The scale of enlargement was adjusted to make the size of the blocks on the monitor screen the same as that of the blocks on the sheet.

2. Contrast-Enhanced MRI

MRI was performed before and after intravenous injection of 10 mL of Gd-DOTA. Transverse and sagittal 3D-VIBRANT sequences with fat suppression (TR/TE 5.6/2.7 or 4.0/1.5; flip angle 12°; field of view 20 or 23 cm; matrix 320×192; slice thickness 1 mm; time of acquisition 60–71s) were obtained.

3. Estimation of the Puncture Site

The target lesion was confirmed by contrast-enhanced MRI. The puncture site was detected according to the positional relationships between the grid line, markers, and the lesion on the sagittal image. The depth was measured on the transverse image, as the distance from the skin to the lesion.

4. Sterilization and Anesthesia

The skin within the block to be punctured was sterilized. After an anesthetic was injected into the subcutaneous tissue and around the lesion, an incision of about 4 mm was made in the skin, and an introducer was inserted.

5. Insertion of the Introducer

The introducer was inserted so as to set the lesion at the center of the opening of the vacuum-assisted biopsy (VAB) needle. After the introducer was inserted into the target site, the block was fixed moderately, and the introducer was removed. Then, an obturator was inserted into the introducer cannula, and images were obtained for confirmation.

6. Insertion of the VAB Needle: Tissue Sampling

After confirming that the lesion was set at the appropriate position, the obturator was removed, and the VAB needle was inserted. After obtaining several samples, the obturator was inserted again, and images were obtained again for confirmation. Additional tissue sampling was performed as needed. After the tissue sampling was completed, in many of the cases, markers [UltraClip Dual Trigger Breast Tissue Marker; BD (C.R. Bard, Inc.), Tempe, AZ, or TriMark® Biopsy Site Marker; Hologic, Inc., Marlborough, MA, USA] were retained in the breast.

Statistical Analysis

We analyzed complete-case data comprising *BRCA1/2* pathogenic variant carriers lesions and non-carrier lesions. For the primary binary outcomes, we computed risk ratios (RR), risk differences (RD), and odds ratios (OR) with 95% confidence intervals (CIs) from 2×2 tables. The RR CIs were derived on the log scale and exponentiated back to the RR scale. Holm-Bonferroni correction was applied for primary comparisons, and two-tailed tests with $\alpha = 0.05$ were set. Analyses were conducted in R 4.5.2; the full analysis script is available in the supplementary materials.

Results

A total of 130 lesions from 126 patients were retrospectively analyzed. The clinicopathological characteristics of the 130 lesions are presented in Table 2. All patients were female, with a median (range) age of 50 (25–82) years. Four patients had multiple lesions. The *BRCA1/2* group accounted for 12.3% (16/130) of the lesions, with six patients carrying *BRCA1* and ten carrying *BRCA2*, including one with a variant of uncertain significance and "uncertain/risk may be increased" (Case 7, see Table 3).

MRI Findings

Based on the lesion shapes detected on MRI, the rate of NME was significantly lower in the *BRCA1/2* mutation group (38%) than in the non-carrier group (64%) ($p = 0.04$). The 130 lesions were categorized as follows: category 3, 10 lesions (7.7%); category 4, 117 lesions (90%); and category 5, three lesions (2.3%). The *BRCA1/2* group had a significantly higher rate of category 3 cases (25%, 4/16) undergoing MRI-guided biopsy than the non-carrier group (5.3%, 6/114) ($p = 0.006$). Among the *BRCA genes*, 5 out of 6 *BRCA1* and 7 out of 10 *BRCA2* cases detected by MRI were diagnosed as category 4 (Table 3).

Integrated Statistics (MRI Findings)

The comparisons between *BRCA1/2* carriers and non-carriers showed a statistically significant difference in both the rate of NME and the distribution of categories. Specifically, *BRCA1/2* carriers had a lower rate of NME (38%) compared with non-carriers (64%), with a *p*-value adjusted for multiple comparisons

Table 2. Clinicopathological characteristics of the MRI-detected lesions

			Total n (%)	*BRCA1/2* n (%)	Others n (%)	p
Lesion			130	16 (12)	114 (88)	
Age	**Mean (range)**		50 (25–82)	50 (32–71)	50 (25–82)	0.19
Cancellation of MRI biopsy			4 (3.1)	2 (13)	2 (1.8)	
MRI findings	**Lesion type**	Focus	10 (7.7)	4 (25)	6 (5.3)	0.04*
		Mass	41 (32)	6 (38)	35 (31)	
		NME	79 (61)	6 (38)	73 (64)	
	BI-RADS category	Category 3	10 (7.7)	4 (25)	6 (5.3)	0.01
		Category 4	117 (90)	12 (75)	105 (92)	
		Category 5	3 (2.3)	0	3 (2.6)	
Pathological findings	Malignant		38 (30)	6 (43)	32 (29)	0.33**
	Indeterminate		5 (4.0)	0	5 (4.5)	
	Benign		83 (66)	8 (57)	75 (67)	
	Histological type		38	6	32	
	Invasive (IDC, ILC)		12 (32)	5 (83)	7 (22)	0.00***
	DCIS		25 (66)	1 (17)	24 (75)	
	LCIS		1 (2.6)	0	1 (3.1)	

*: Comparison between focus+mass and NME, **: Comparison between malignant and benign, except for indeterminate, ***: Comparison between invasive cancer and DCIS+LCIS. NME: Non-mass enhancement; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; DCIS: Ductal carcinoma *in situ*; LCIS: Lobular carcinoma *in situ*; MRI: Magnetic resonance imaging; BRCA: Breast cancer; BI-RADS: Breast imaging reporting and data system

(*p*_adj) below 0.05. In addition, *BRCA1/2* carriers exhibited a higher proportion of category 3 lesions (25%) relative to non-carriers (5.3%), also reaching *p*_adj<0.05. The category 3 outcome indicated that *BRCA1/2* carriers had 0.67 times the risk of category 3 lesions compared with non-carriers (RR = 0.67; 95% CI, 0.18–0.76; RD = -0.23; OR = 0.37; *p*_adj<0.05). For lesions with NME, *BRCA1/2* carriers had 0.66 times the risk of NME compared with non-carriers (RR = 0.66; 95% CI, 0.37–1.16; RD = -0.29; OR = 0.54; *p*_adj<0.05).

MRI-Guided Biopsy

The annual number of MRI-guided biopsy cases from 2019-2022 was 30, 18, 24, and 43, respectively (median 27) giving a *BRCA1/2* pathogenic variant-positive rate of about 5% per year. MRI-guided biopsy was discontinued during the examination of four lesions: two in the *BRCA1/2* group and two in the non-carrier group. Consequently, MRI-guided biopsy was performed for 126 lesions: 14 in the *BRCA1/2* group and 112 in the non-carrier group from

Table 3. Characteristics of lesions diagnosed using MRI-guided biopsy

No	Age	BRCA	Menopausal	Purpose	Lesion type	Size (mm)	Kinetic curve assessment	BI-RADS category	Pathological findings on biopsy	Pathological findings on surgical specimen/ size
1	52	*BRCA1*	RRSO	Surveillance	Focus	4		3*	IDC, TNBC, Ki-67 30–40%	Scar/0 mm
2	37	*BRCA1* unexposed	Pre	Surveillance	Mass	5	Fast-washout	4	IDC, TNBC, Ki-67 60–70%	DCIS, luminal A-like, Ki-67 60–70%/1mm
3	48	*BRCA1*	Post	Surveillance	Mass	5	Fast-washout	4	Benign	
4	33	*BRCA1* unexposed	Pre	Surveillance	Mass	7	Fast-persistent	4	Benign	
5	32	*BRCA1*	Pre	Surveillance	NME	15		4	Cancellation	
6	32	*BRCA1*	Pre	Staging	NME	8		4	Cancellation	
7	55	*BRCA2*	RRSO	Surveillance	Mass	5	Fast-persistent	4	IDC, luminal A-like, Ki-67 10-20%	IDC/0.5 mm
8	49	*BRCA2*	Pre	Surveillance	Mass	12	Fast-plateau	4	IDC, luminal B-ike, Ki-67 40–50%	IDC/3 mm
9	67	*BRCA2*	Post	Staging	NME	8		4	IDC, TNBC, Ki-67 10–20%	pCR
10	67	*BRCA2*	RRSO	Surveillance	NME	14		4	DCIS, luminal A-like, Ki-67 10–20%	DCIS, luminal A-like, Ki-67 <5%/1 mm
11	55	*BRCA2* VUS	Post	Surveillance	Focus	4		3*	Indeterminate, atypical lobular hyperplasia	Follow-up
12	50	*BRCA2*	RRSO	Surveillance	Focus	3		3*	Benign	
13	55	*BRCA2*	Unknown	Surveillance	Focus	4		3*	Benign	
14	33	*BRCA2*	Pre	Surveillance	Mass	7	Fast-washout	4	Benign	
15	71	*BRCA2*	Post	Staging	NME	14		4	Benign	
16	56	*BRCA2*	Post	Staging	NME	11		4	Benign	

*: New lesions detected during follow-up period. RRSO: Risk-reducing salpingo-oophorectomy; NME, Non-mass enhancement; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; DCIS: Ductal carcinoma *in situ*; TNBC: Triple negative breast cancer; pCR: Pathologic complete response, BRCA: Breast cancer; BI-RADS: Breast imaging reporting and data system; VUS: Variant of uncertain significance

2018-2022. Malignant tumors were pathologically diagnosed in 38 of the 126 biopsied lesions (30.1%). The sensitivity for detecting malignant tumors did not differ significantly between *BRCA1/2* carriers (37.5%, 6/16) and non-carriers (28.1%, 32/114) (p = 0.56). Positive predictive values were 42.9% (6/14) in the *BRCA1/2* group and 28.6% (32/112) in the non-carrier group. The positive predictive values according to BI-RADS categorization were 10% (1/10) for category 3, 35% (39/113) for category 4, and 100% (3/3) for category 5. Among the four cases in which the examination was discontinued, three were in their 30s, and two were in their early 30s among the *BRCA1* cases. In one *BRCA1* case, a lesion was noted on the surveillance MRI, and the subsequent MRI performed within two years showed no significant changes. Biopsy was performed in the latter half of the menstrual cycle when background parenchymal enhancement (BPE) was strong. In the other case, a lesion was identified using MRI for staging purposes before surgery, but it had disappeared by the time of biopsy. MRI for staging was performed in the latter half of the menstrual cycle; however, the biopsy was performed seven days after the onset of menstruation, when the effects of BPE were at their weakest. The disappeared lesion did not reappear on subsequent MRI scans during the 2-year follow-up period.

Pathological Findings

Of the 38 pathologically malignant tumors detected by MRI-guided biopsy, invasive carcinoma (including invasive ductal carcinoma and invasive lobular carcinoma) was diagnosed in 12 of 126 biopsied lesions (9.5%). This included 5 of the 14 lesions in the *BRCA1/2* group (35.7%) and 7 of the 112 lesions in the non-carrier group (6.2%). Two of the five were *BRCA1* variants, and three were *BRCA2* variants, with the two *BRCA1* variants diagnosed as invasive triple-negative breast cancer. The detection rate of invasive carcinoma using MRI-guided biopsy was significantly higher in the *BRCA1/2* group than in the non-carrier group (p = 0.003). Ductal carcinoma *in situ* (DCIS) was diagnosed in 25 lesions (19.8%): one in the *BRCA1/2* group (7.1%) and 24 in the non-carrier group (21.4%) (Figures 1 and 2).

Integrated Statistics (Pathological Findings)

Invasive cancer among biopsied lesions is more prevalent in *BRCA1/2* carriers, with 5 of 16 lesions showing invasive cancer compared with 7 of 114 in the non-carrier group, yielding a relative risk of 2.29, a RD of 0.17, and an OR of 3.52 (95% CI, 1.11–11.20; p_adj <0.05).

Discussion and Conclusion

The objective of our study was to assess the efficacy of MRI-guided biopsy in identifying breast cancer in *BRCA1/2* pathogenic variant carriers compared to non-carriers. MRI-guided biopsy detected malignant tumors in 30.1% of the studied lesions, with a higher detection rate in *BRCA1/2* pathogenic variant carriers (42.9%) than in non-carriers (28.6%). Furthermore, the higher detection rate of invasive carcinoma by MRI-guided biopsy in *BRCA1/2* carriers compared to non-carriers is a novel finding.

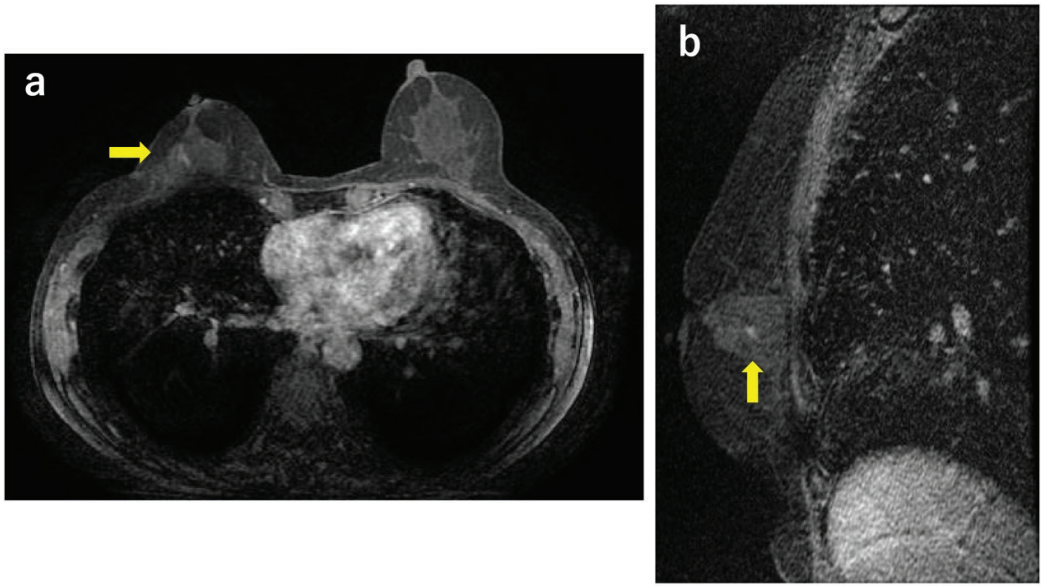

Figure 1. (a, b) case 10: a 67-year-old woman, a *BRCA2* pathogenic variant carrier, developed peritoneal cancer eight years after surgery and risk-reducing salpingo-oophorectomy for right ductal carcinoma *in situ*. She received chemotherapy, and subsequent magnetic resonance imaging (MRI) surveillance showed a category 4 non-mass enhancement with branching in the right outer quadrant. MRI-guided biopsy diagnosed ductal carcinoma *in situ*. The patient underwent right and contralateral prophylactic mastectomies

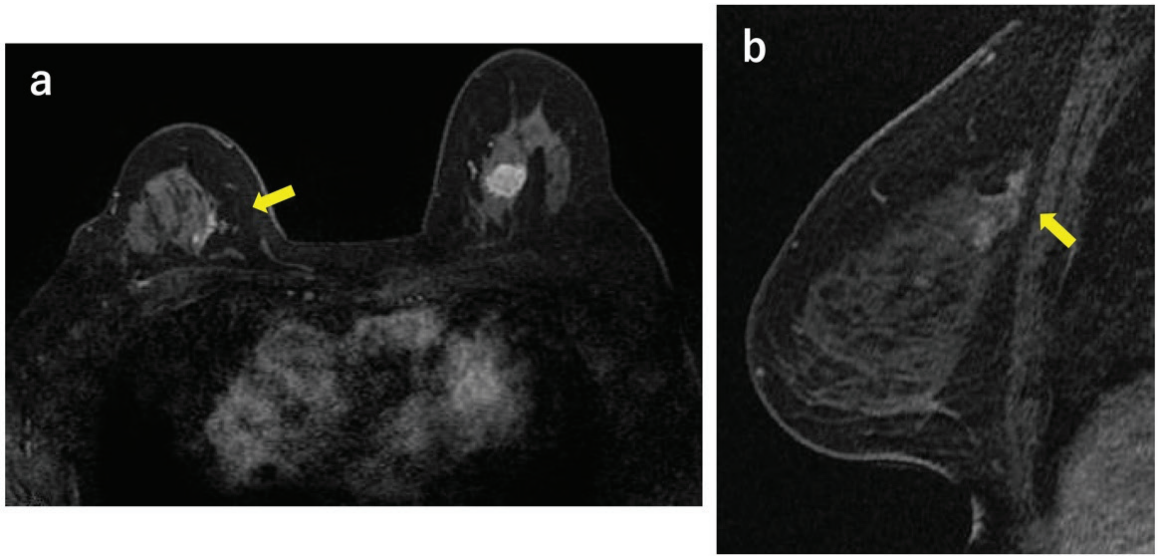

Figure 2. (a, b) case 9: a 67-year-old woman, a *BRCA2* pathogenic variant carrier, was diagnosed with left breast cancer (T2N0, triple-negative breast cancer) 17 years after right breast-conserving surgery and sentinel node biopsy with preoperative chemotherapy for right breast cancer. Preoperative staging magnetic resonance imaging (MRI) revealed category 4 non-mass enhancement with branching in the right inner upper quadrant. MRI-guided biopsy identified triple-negative invasive ductal carcinoma. She was diagnosed with in-breast recurrence in the conserved right breast. Bilateral surgery was performed after preoperative chemotherapy

Early detection of breast cancer is particularly beneficial in *BRCA1/2* pathogenic variant carriers because of the higher risk of developing the disease.

Takahama et al. (7) reported that 38% (115 of 301) of lesions subjected to MRI-guided biopsy in Japan were diagnosed with breast cancer. Our findings support this earlier finding and highlight the efficacy of MRI-guided biopsy in detecting breast lesions, particularly in high-risk populations, such as *BRCA1/2* carriers.

The most significant difference in the MRI findings between the *BRCA1/2* and non-carrier groups was the shape of the detected lesion. NME was detected at a significantly lower rate in the *BRCA1/2* mutation group than in the non-carrier group (p = 0.04). This finding may be attributed to the higher prevalence of invasive cancer in the *BRCA1/2* group, in contrast to the 75% of cases in the non-carrier group that presented with DCIS (p = 0.003).

Interestingly, early-stage breast cancer in *BRCA1* pathogenic variant carriers may appear as benign findings, such as cysts and fibroadenomas, based on US findings (14, 15). Case 1, which was diagnosed with malignant C3, was depicted as a focus. Due to the small size of the lesion, evaluating the margins was challenging, and the contrast pattern did not exhibit washout findings, raising suspicion of a fibroepithelial tumor. As this was a new finding, a biopsy was performed, which confirmed the malignant diagnosis.

In addition, it has been reported that *BRCA2* pathogenic variant carriers often show features of intraductal lesions (16, 17). Murakami et al. (16) reported that NME was absent in *BRCA1* pathogenic variant carriers (0/30) and present in 24% (6/25) of *BRCA2* pathogenic variant carriers. In cases diagnosed as malignant, these characteristics were not observed.

Typically, biopsy is indicated for cases of category 4 or higher; however, in this study, four cases in the *BRCA1/2* group were classified as category 3, and one of them was diagnosed as malignant. All four cases had new lesions during MRI surveillance. Considering that all six cases in category 3 of the control group yielded benign results, we believe that MRI-guided biopsy should be considered for new lesions during MRI surveillance for *BRCA1/2* pathogenic variants, even if the imaging findings indicate category 3.

According to the subtype of invasive carcinoma, *BRCA1* variants have a poor prognosis because of rapidly progressing triple-negative breast cancer (18), whereas the luminal type accounts for the majority of *BRCA2* pathogenic variant carriers. However, more than 60% of these cases are regarded as high-risk by multigene assays and may require chemotherapy if the tumor enlarges (19, 20). Thus, the higher detection rate of invasive cancer with worse prognosis in *BRCA1/2* pathogenic variant carriers undergoing MRI-guided biopsy underscores the importance of early detection, intervention, and tailored surveillance strategies for high-risk populations. In our study, chemotherapy was deemed unnecessary for all patients

because of early tumor removal, which is an advantage of MRI surveillance and MRI-guided biopsy (21). Our findings support the periodic use of MRI for the surveillance of *BRCA1/2* carriers, emphasizing the need for expanded access to this procedure to facilitate timely diagnosis and treatment.

Study Limitations

This study has several limitations that should be considered when interpreting the results. First, the retrospective nature of the study may have resulted in selection bias. Secondly, a relatively small sample size, particularly for *BRCA1/2* carriers, was analyzed. In addition, the lack of long-term follow-up data for benign lesions diagnosed using MRI-guided biopsy limits the assessment of clinical outcomes. Finally, the MRI-guided biopsy was discontinued in some patients in the *BRCA1/2* (13%) and non-carrier (1.8%) groups. *BRCA1* variant carriers were in their early 30s. In general, MRI can exhibit significant variations owing to the menstrual cycle and associated BPE (22-24). Therefore, the optimal imaging time for breast MRI with contrast is 7–14 days after the onset of menstruation (10, 24). *BRCA1/2* pathogenic variant carriers tend to be younger when they develop breast cancer. Performing MRI scans periodically, taking into account the menstrual cycle of *BRCA1/2* pathogenic variant carriers, is warranted to avoid unnecessary biopsies (25).

In conclusion, our study revealed that MRI-guided biopsy can more frequently detect early-stage invasive carcinoma in *BRCA1/2* carriers than in non-carriers. Moreover, periodic MRI follow-up should be recommended for BRCA carriers in high-risk groups, and even newly developing BI-RADS 3 lesions may warrant biopsy to facilitate early diagnosis. Future research prospectively validating our findings in larger cohorts of *BRCA1/2* carriers and non-carriers is needed to assess the clinical outcomes and long-term survival associated with MRI-guided biopsy-detected lesions in this population and to inform personalized management approaches for high-risk populations.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ethics Review Board of Showa University (approval no: 2023-033-B, date: February 25, 2025).

Informed Consent: Informed consent was obtained in the form of an opt-out on our website.

Footnotes

Authorship Contributions

Concept: A.N., M.T., K.T., S.N., N.H.; Design: A.N., M.T., K.T.; Data Collection or Processing: A.N.; Analysis or Interpretation: A.N., M.T., K.T., S.N., N.H.; Literature Search: A.N.; Writing: A.N., M.T., K.T., S.N., N.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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*Author Seigo Nakamura has passed away.

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ORIGINAL ARTICLE

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Minimally Invasive Nipple-Sparing Mastectomy: Early Experience With Endoscopic and Robotic Techniques

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ABSTRACT

Objective: Minimally invasive nipple-sparing mastectomy (NSM), performed via endoscopic or robotic-assisted approaches, has been developed to improve cosmetic and psychosocial outcomes without compromising oncologic safety. While international experience is growing, data from low- and middle-income countries remain limited.

Materials and Methods: We conducted a retrospective case series of five consecutive patients (six breasts) who underwent minimally invasive NSM between January 2024 and June 2025 in an Indian center. Three patients underwent conventional endoscopic NSM and two underwent robotic-assisted NSM (one unilateral and one bilateral). Data collected included demographic and genetic status, tumor biology, operative details, reconstruction method, perioperative complications, pathology, and short-term follow-up. Primary endpoints were feasibility and safety; secondary endpoints were margin status, early oncologic outcomes, and cosmetic satisfaction.

Results: All procedures were completed successfully without conversion to open surgery. Median (range) operative time was 210 (180–300) minutes, with robotic procedures requiring longer duration. No intraoperative complications, nipple-areolar necrosis, or implant losses were observed. Two patients developed minor seromas that resolved with aspiration. Pathological margins were negative in all cases. At a median follow-up of six (4–18) months, all patients were alive, disease-free, and reported good-to-excellent cosmetic satisfaction.

Conclusion: Our early experience demonstrates that both endoscopic and robotic-assisted NSM are feasible and safe in carefully selected patients, providing satisfactory oncologic and esthetic outcomes. However, these results should be interpreted with caution due to the very small sample size, short follow-up, and absence of a comparator group. Larger prospective multicenter studies with long-term outcomes are required to confirm oncologic safety and define the role of minimally invasive NSM India.

Keywords: Endoscopic mastectomy; robotic mastectomy; nipple-sparing mastectomy; breast cancer; minimally invasive surgery; reconstruction; India

KEY POINTS

- First report of MI NSM from India.
- Feasible with minimal complications.

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Introduction

Breast cancer remains the most common malignancy in women worldwide, and surgical treatment has evolved substantially over the last decades (1, 2). While mastectomy continues to be an essential option for many patients, advances in technique have sought to balance oncologic safety with cosmetic and psychosocial outcomes. Nipple-sparing mastectomy (NSM) represents one such innovation, offering preservation of the nipple–areolar complex without compromising local control when carefully selected criteria are applied (3-6). However, conventional NSM performed through visible breast incisions can be associated with compromised esthetics, sensory loss, and in some cases, ischemic complications of the nipple-areolar complex (7). These limitations have driven the development of minimally invasive approaches, such as endoscopic and robotic-assisted NSM, which relocate incisions to the axilla or lateral chest wall, thereby concealing scars and potentially reducing flap ischemia (8-10).

Recent systematic reviews and meta-analyses have confirmed that endoscopic NSM achieves oncological outcomes comparable to conventional NSM, with the added advantages of higher patient satisfaction and lower necrosis rates when single-incision techniques are used (11, 12). Robotic-assisted NSM has further expanded minimally invasive options by providing enhanced visualization and instrument dexterity, although at the expense of longer operative times and increased costs (13, 14). Despite these advances, published experience with minimally invasive NSM remains limited, particularly in low- and middle-income country settings where adoption has been slower. In this report, we present our initial institutional experience with both endoscopic and robotic-assisted NSM in an Indian center, focusing on perioperative safety, pathological adequacy, and short-term patient outcomes.

Materials and Methods

This is a retrospective case series of six consecutive patients who underwent minimally invasive NSM between June 2024 and June 2025. Four patients underwent conventional endoscopic NSM and two underwent robotic-assisted NSM (one unilateral and one bilateral). Ethics committee approval was obtained from Institute Ethics Committee Netaji Subhash Chandra Bose Medical College Jabalpur (approval number: IEC/2025/8988, date: 03.09.2025).

Patient selection: Patients were included if they had early breast cancer or *BRCA1* mutation warranting risk-reducing mastectomy, with tumor-to-nipple distance >2 cm and no radiological or clinical evidence of nipple-areolar complex involvement. Contraindications included inflammatory breast cancer, extensive skin involvement, or contraindications to general anesthesia.

Preoperative assessment: All patients underwent clinical evaluation, digital mammography, and/or breast magnetic resonance imaging or positron emission tomography-computed tomography as indicated. *BRCA1* mutation was confirmed in two patients. Neoadjuvant chemotherapy was administered in one patient with locally advanced triple-negative breast cancer.

Surgical technique: For conventional endoscopic NSM, an axillary incision was used with CO_2 insufflation to create a working space. Endoscopic dissection was carried out to excise the glandular tissue while preserving the skin envelope and nipple-areolar complex. In both approaches, a GelPOINT® or Regisport® device was inserted through a single axillary or anterior axillary incision, creating the operating window (Figure 1). CO_2 insufflation at a pressure of 8–10 mmHg was maintained throughout the dissection to establish the working space. Procedures began with lateral breast dissection, progressing towards the nipple-areolar complex, followed by medial, superior, and inferior flap creation. The gland was then separated from the pectoral fascia and removed *en bloc*. Reconstruction was performed using either implant-based techniques with mesh reinforcement or autologous options, depending on patient preference and oncologic considerations (Figure 2).

Reconstruction: Five patients underwent immediate implant-based reconstruction with TiLOOP mesh placement. Implant size was chosen based on preoperative breast volume and intraoperative assessment. One patient opted for delayed reconstruction (Figure 3). All five reconstructions were performed using a pre-pectoral, single-plane implant pocket following endoscopic or robotic-NSM. Pocket selection was based on: Flap integrity and thickness, assessed intraoperatively by surgeon palpation and optical evaluation; indocyanine green angiography-assisted perfusion assessment (used in two cases);

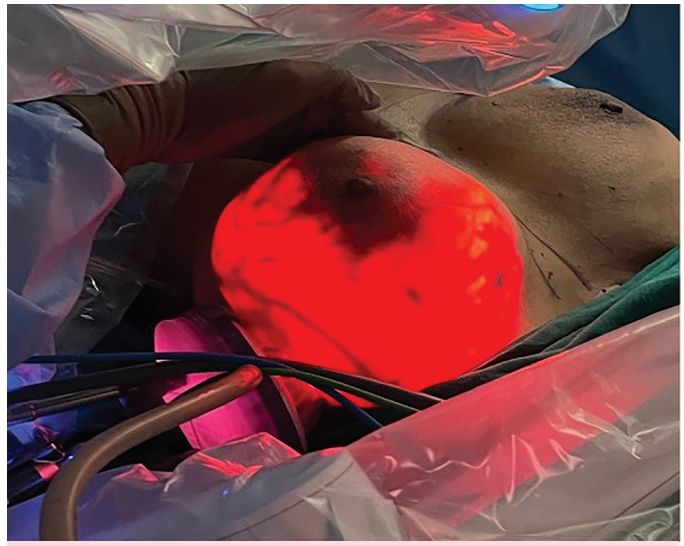

Figure 1. Robotic assisted dissection through GelPOINT® ports

and absence of prior radiation or significant comorbidities affecting vascularity (Figure 4). Pocket stabilization was achieved using TiLoop® mesh fixation along the lateral border, facilitating anatomical contour restoration and preventing implant migration. The implant-mesh construct was completely wrapped (total anterior coverage) after pre-soaking in antibiotic saline. The assembly was inserted through the 3–4 cm working incision using a lateral-to-lateral push technique optimized for minimally invasive access. Fixation was performed using interrupted PDS 3–0 sutures, securing the mesh laterally to prevent postoperative displacement and to recreate natural ptosis. No intraoperative mesh folding or bunching occurred. All implants were round, moderate-profile, smooth-surface silicone gel implants either a Motiva Round SilkSurface® Plus silicone breast implant (Establishment Labs S.A., Alajuela, Costa Rica) or a Silimed silicone gel breast implant (Silimed Indústria de Implantes Ltda., Rio de Janeiro, Brazil; distributed in India by Technomed India Pvt. Ltd., New Delhi, India).

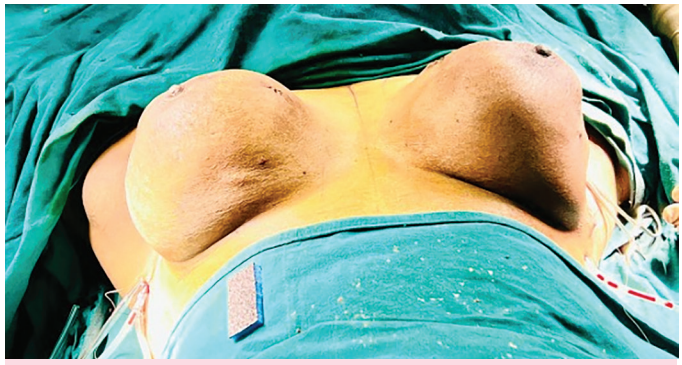

Figure 2. Immediate postoperative image after implant placement

Postoperative care and follow-up: Patients received standardized analgesia and drain management. A single 14F vacuum closed-suction drain was placed in the pre-pectoral/periprosthetic plane in all cases. Drain removal criteria was when output was <30 mL/24 hours. Patients were discharged on postoperative day 2 if stable. Follow-up was scheduled for 2 weeks, 1 month, 3 months, and 6 months, including clinical examination and, where indicated, imaging.

Outcomes: Primary endpoints were operative feasibility, perioperative complications (bleeding, seroma, infection, skin/nipple necrosis, implant loss), and length of stay. Secondary endpoints were margin status, early oncologic outcomes, and patient-reported cosmetic satisfaction (graded on a five-point Likert scale). Given the very small sample size and the purely descriptive intent of this early feasibility case series, no inferential statistical analyses were performed. Continuous variables were summarized using median and range, and categorical variables using counts and proportions. These descriptive calculations were performed using standard spreadsheet software.

Results

Six patients (eight breasts) underwent minimally invasive NSM with a median (range) age of 39.5 (33–45) years. Five

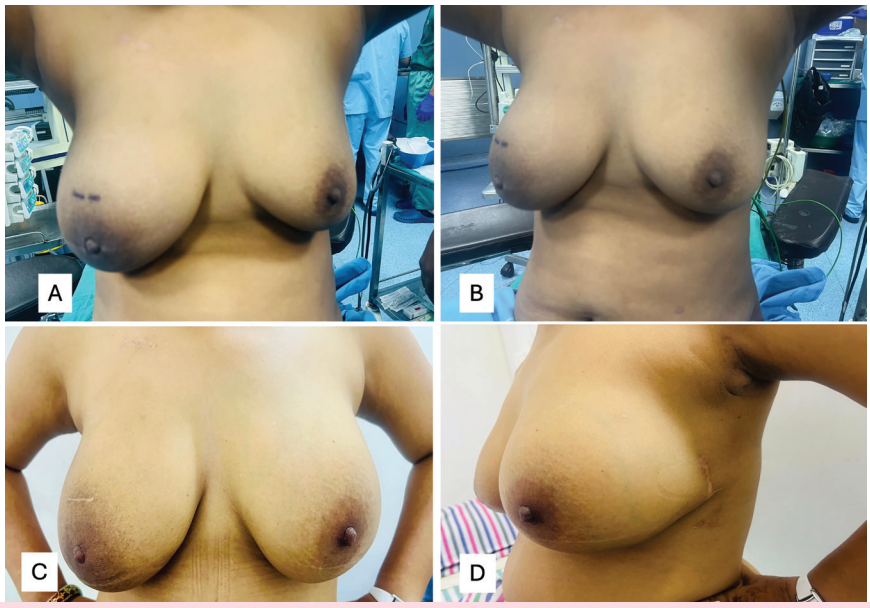

Figure 3. Outcomes of left robotic NSM, (A) Pre-operative front view, black mark on right side is previous scar of BCS, (B) Pre-operative lateral view, (C) Post-operative 6 months front view, (D) Post-operative 6 months lateral view

NSM: Nipple-sparing mastectomy; BCS: Breast-conserving surgery

patients were *BRCA* mutation carriers, and one had sporadic breast carcinoma. Four procedures were performed using a conventional endoscopic technique and four using a robotic-assisted approach (one unilateral, one bilateral) (Table 1).

Operative details: All procedures were completed successfully without conversion to open surgery. The median operative time was 210 (180–300) minutes, with robotic procedures taking longer than conventional endoscopic cases. Estimated blood loss was minimal (<100 mL in all patients). Five patients underwent immediate implant-based reconstruction with TiLOOP mesh placement (n = 3) or prolene mesh (n = 2). Axillary surgery was performed as described above.

Pathological findings: All resection specimens had negative surgical margins. One patient who received neoadjuvant chemotherapy for locally advanced triple-negative breast cancer achieved a complete pathological response with no residual invasive carcinoma in the breast or axillary lymph nodes. The remaining cases included invasive ductal carcinoma with or without associated ductal carcinoma *in situ*. No occult nipple involvement was detected in any case.

Postoperative outcomes: Median hospital stay was 2 (2–3) days. There were no intraoperative complications, or nipple-areolar necrosis, implant loss, or re-explorations. Three patients had partial skin flap necrosis and were managed conservatively. Median indwelling time of drainage catheters was 5–7 postoperative days. Two patients developed minor seromas that resolved with aspiration. No surgical site infections occurred. Two patients received adjuvant radiotherapy (VMAT, 50 Gy/25 fractions targeting chest wall and supraclavicular fossa). Patients receiving post-mastectomy radiotherapy demonstrated acceptable early cosmetic and oncologic outcomes, with no mesh exposure or implant complications.

Follow-up: At a median follow-up of four (2–12) months, all patients were alive and disease-free. The five *BRCA1*-positive patients remained recurrence-free. Patient-reported cosmetic satisfaction was high in all cases, with all patients rating their cosmetic outcome as "good" or "excellent." Preservation of nipple-areolar sensation was partial in five breasts and absent in the other three.

Discussion and Conclusion

Our early adoption of both approaches, including the first reported robotic NSM with TiLoop® mesh reconstruction for a *BRCA*-positive patient in India, highlights their feasibility and applicability in our national context. Our experience supports international evidence that these minimally invasive procedures can be safely performed with favorable short-term oncologic and esthetic outcomes when applied to selected patients. Importantly, these outcomes mirror those reported in high-volume centers internationally, despite our series representing the initial learning curve for the technique.

The wider literature increasingly supports the oncologic safety of minimally invasive NSM (13, 15). Our series is consistent with

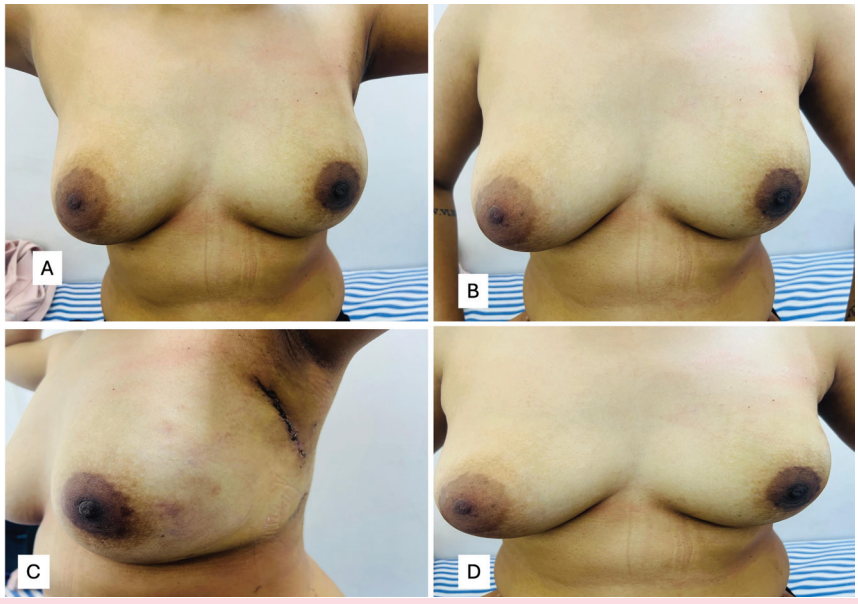

Figure 4. Outcomes of left endoscopic NSM, (A&B) Pre-operative front views, (C) Post-operative immediate view, (D) Post-operative 4 months view

NSM: Nipple-sparing mastectomy

Table 1. Baseline characteristics, operative details, and outcomes of patients undergoing minimally invasive nipple-sparing mastectomy

Case	Age (years)	Genetic status	Histology	Procedure	Axillary procedure	Reconstruction	Op time (min)	Drainage duration (days)	Hospital stay (days)	Complications	Follow-up (months)	Status
1	42	*BRCA1*+	IDC, TNBC, multifocal	Unilateral robotic NSM (left)	Prior axillary clearance	Pre-pectoral, smooth-surface silicone gel Implant + TiLOOP mesh anterior coverage	240	5 days	2	None	6	NED
2	33	*BRCA1*+	IDC, TNBC, LABC	Bilateral robotic NSM	ALND (right)	Pre-pectoral, smooth-surface silicone gel Implant + TiLOOP mesh anterior coverage	300	10 days	2	None	4	NED
3	36	*BRCA1*+	IDC, TNBC	Endoscopic NSM	SLNB	Pre-pectoral, smooth-surface silicone gel Implant + TiLOOP mesh anterior coverage	200	6 days	2	Partial skin flap necrosis	4	NED
4	45	*BRCA1*+	IDC, ER+	Endoscopic NSM	SLNB	Pre-pectoral, smooth-surface silicone gel Implant + TiLOOP mesh anterior coverage	250	5 days	3	Seroma	2	NED
5	37	Negative	IDC, TNBC	Endoscopic NSM	SLNB	Planned for delayed reconstruction	200	4 days	5	Seroma and Partial skin flap necrosis	12 months	NED
6	45	*BRCA1* +	IDC, TNBC	B/L Endoscopic	SLNB	Pre-pectoral, smooth-surface silicone gel Implant + TiLOOP mesh anterior coverage	350	7 days	2	Superficial necrosis	2 months	NED

IDC: Invasive ductal carcinoma; TNBC: Triple-negative breast cancer; LABC: Locally advanced breast cancer; ER+: Estrogen receptor positive; NSM: Nipple-sparing mastectomy; ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy; B/L: Bilateral; BRCA1+: BRCA1 mutation positive; NED: No evidence of disease; min: Minutes

these findings, with robotic cases requiring more operative time but achieving excellent cosmesis and early recovery (16-20). The absence of major ischemic complications in our small cohort may reflect careful patient selection, avoidance of periareolar incisions, and the use of mesh-supported immediate reconstruction.

From a health systems perspective, the integration of robotic NSM into a low- and middle-income country setting has several limitations. Challenges remain huge, including access to robotic platforms, and cost considerations that may limit widespread adoption. However, these techniques respond to increasing patient demand for less visible scarring and breast preservation, aligning oncologic surgery with quality-of-life goals. Hence, careful adoption of endoscopic NSM innovations may be implemented, even in resource-constrained environments as has been demonstrated for other surgeries (20).

Our results highlight the importance of careful patient selection for minimally invasive NSM. Ideal candidates in our early experience were those with early-stage tumors, tumor-to-nipple distance greater than 2 cm, no radiological or intraoperative evidence of nipple–areolar involvement, and patients undergoing risk-reducing surgery for *BRCA1* mutation. These strict criteria likely contributed to the absence of major complications in our series.

Study Limitations

Our study has limitations inherent to a small, retrospective series, including short follow-up and absence of a comparator group. Longer-term oncologic outcomes, impact on nipple sensation, and durability of reconstruction could not be fully assessed. Despite small sample size, by reporting our initial experience, we contribute real-world evidence from a resource-limited context where published data are scarce. These early results support the feasibility of establishing minimally invasive NSM programs beyond high-income centers and provide a foundation for larger prospective studies to refine patient selection, optimize technique, and confirm long-term safety. However, robotic mastectomy is not economically feasible for widespread adoption in many low- and middle income countries. Our experience represents a selective, early institutional effort supported through existing infrastructure, not routine practice. TiLoop® mesh and robotic platforms have cost implications and our results should be interpreted as proof-of-concept, not as an endorsement for broad application.

Our early experience with endoscopic and robotic-assisted NSM demonstrated that these approaches are technically feasible and can be performed safely in carefully selected patients. Short-term outcomes in terms of oncologic adequacy, complication rates, and cosmetic satisfaction were favorable and consistent with international reports. However, given the small sample size, short duration of follow-up, and absence of a comparator group, these findings should be interpreted with caution. Larger prospective studies with long-term follow-up are needed to validate oncologic safety, assess durability of reconstruction, and define the cost-effectiveness of minimally invasive mastectomy in the Indian context.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Institute Ethics Committee Netaji Subhash Chandra Bose Medical College Jabalpur (approval number: IEC/2025/8988, date: 03.09.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.M.B., S.K.Y., R.G., J.T., S.C.; Design: S.M.B., S.K.Y., R.G., J.T., S.C.; Data Collection or Processing: S.M.B., S.K.Y., R.G., J.T., S.C.; Analysis or Interpretation: S.M.B., S.K.Y., R.G., J.T., S.C.; Literature Search: S.M.B., S.K.Y., R.G., J.T., S.C.; Writing: S.M.B., S.K.Y., R.G., J.T., S.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Assessment of Surgical Approach and Overall Survival in Young Women With Breast Cancer

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ABSTRACT

Objective: Mastectomy rates are increasing in young patients despite few data supporting improved outcomes. We investigated the association between surgical approach and survival in young patients with breast cancer.

Materials and Methods: Retrospective review identified women ≤40 years old with operable, non-metastatic invasive breast cancer treated between 2010–2019. Cox proportional hazard analyses, stratified by hormone receptor and human epidermal growth factor receptor 2 (HER2) status, identified factors associated with increased risk of recurrence and death.

Results: Of 588 patients, 65% underwent mastectomy and 35% breast conserving surgery (BCS). Median follow-up was 5.9 years. Overall recurrence and mortality rates were 15% and 12%, respectively. On multivariable analysis, black race [hazard ratio (HR), 2.14 (1.26–3.61), p = 0.005], lymphovascular space invasion (LVSI) [HR, 1.98 (1.17–3.36), p = 0.01], and extranodal extension [HR, 2.12 (1.09–4.12), p = 0.03] were associated with increased risk of death. Stage III disease [HR, 2.06 (1.05–4.03), p = 0.04] and LVSI [HR, 2.18 (1.43–3.32), p<0.001] were associated with increased risk of recurrence. Increasing age decreased the risk of death [HR, 0.94 (0.88–0.99), p = 0.02] and recurrence [HR, 0.95 (0.90–0.99), p = 0.02]. Mastectomy versus BCS did not impact recurrence [HR, 1.18 (0.73–1.92), p = 0.51] or overall survival (OS) [HR, 0.86 (0.46–1.58), p = 0.62] in the entire cohort. BCS was associated with increased risk of recurrence in the hormone receptor-/HER2+ subtype [HR, 9.06 (1.03–80.00), p = 0.047] but did not affect survival.

Conclusion: OS does not differ by surgery type in young patients with breast cancer. Future research should focus on racial disparities in breast cancer care.

Keywords: Breast cancer; lumpectomy; mastectomy; overall survival; young women

KEY POINTS

- Mastectomy rates are increasing in young patients with breast cancer despite no evidence of improved survival.
- We assessed surgical approach and survival in a large cohort of young patients with breast cancer.
- Overall survival did not differ based on mastectomy versus lumpectomy.

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Introduction

Breast cancer in women under 40 years of age is uncommon, with <5% of those at average-risk being affected (1). However, the incidence in this population has been increasing over time (1). Younger patients are burdened by highly proliferative and poorly differentiated tumors, which often translates to less favorable outcomes when compared to their older counterparts (1-5). Contemporary breast cancer management is driven by results of landmark trials that historically excluded young women, and this often results in the universal application of guidelines irrespective of age (4-7). However, recent data suggest that age itself may play a role in tumor heterogeneity, biology, and hormonal factors (4, 6-9).

Although there is a clear difference among age groups with respect to breast cancer recurrence (10), an abundance of literature supports the use of breast conserving surgery (BCS) with lumpectomy and adjuvant radiation in the appropriate setting. However, a reluctance to apply this therapy to young patients persists (11). Young patients frequently report being offered more "aggressive" treatment based upon their age alone. The consensus by the European School of Oncology and the European Society of Medical Oncology recommends that surgical management of young patients mirror that of older women, reporting no survival benefit to mastectomy, unless clinically indicated (12, 13). Despite lack of data supporting improved outcomes with more extensive surgery, there is a national trend towards mastectomy, and even contralateral prophylactic mastectomy in young women (14).

In this study, we evaluated a large cohort of patients with breast cancer aged 40 years or younger and treated with contemporary standard of care therapy at a single institution to determine whether surgical approach was an independent risk factor for outcomes. We also aimed to identify clinical, pathologic, and molecular features that may be utilized to predict recurrence-free survival (RFS) and overall survival (OS) in young women with breast cancer.

Materials and Methods

Patient Selection

Wake Forest University Health Sciences Institutional Review Board approval was obtained (approval number: IRB00083094, date: 09.05.2024). Patients 40 years or younger diagnosed with histologically confirmed, primary, non-metastatic, invasive breast carcinoma who underwent oncologic resection between 2010 and 2019 at the Levine Cancer Institute were identified. Patients with inflammatory or pregnancy-associated breast cancer were not excluded. Data pertaining to patient demographics, tumor characteristics, treatment details, and clinical outcomes were extracted from the prospectively maintained Sandra Levine Young Women's Database. Patients who presented with stage IV disease, were diagnosed with ductal or lobular carcinoma *in-situ*, and those with male sex assigned at birth were excluded from the analyses.

Primary and Secondary Endpoints

The primary objective of this study was to determine whether surgical approach with either BCS or mastectomy was an independent risk factor for OS in young women with breast cancer. Additionally, we aimed to identify clinical and pathologic variables that may help to predict both RFS and OS in young women with breast cancer. The standardized definitions for efficacy endpoints criteria were used to report these outcomes. RFS was defined as time from breast cancer diagnosis to first recurrence of breast cancer (ipsilateral breast, local-regional, or distant) or death from any cause. OS was defined as date of diagnosis to death from any cause. Survival and recurrence data were censored at the date of last follow-up.

Statistical Analysis

Patients were stratified into four molecular subtypes based upon hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status: HR+/HER2-, HR+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC). Baseline demographics and clinical characteristics were summarized for all subjects and for each surgery type, with frequencies or medians and interquartile ranges (IQR), as appropriate. Comparisons of categorical variables between surgery types were conducted using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the independent samples t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data.

Pathologic stage was not included in the analyses as some patients received chemotherapy in the neoadjuvant setting. Pathologic stage data are provided in Supplemental Table 1. Univariable and multivariable proportional hazards regression analyses were used to study the effect of surgery type on RFS and OS. In multivariable proportional hazards regression analysis, the following covariates were adjusted in the model: age at diagnosis, race, body mass index (BMI), clinical stage, the presence of lymphovascular space invasion (LVSI), the presence of extranodal extension (ENE), use of hormonal therapy, use of chemotherapy, and use of radiation therapy. Multivariable proportional hazards regression was performed for the entire cohort, and then for each molecular subtype separately. Both the hazard ratio and overall *p*-values are presented in the tables. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the difference between two categories while the overall *p*-value assesses difference across all

categories together. When a specific category is compared to the reference category, the hazard ratio *p*-value is referenced in the text. All statistical tests were two-sided with a significance level of $\alpha = 0.05$.

Results

Patient Population

Of 885 patients assessed for eligibility, 588 were included in the analysis (Figure 1). Demographic and clinical characteristics are shown in Table 1. Patients were 66% white, 26% black, and 8% other race with a median age at diagnosis of 37 years (IQR, 34–39). The median follow-up time was 5.9 years. The proportion of women within each molecular subtype was 53% (*n* = 314) HR+/HER2-, 21% (*n* = 122) HR+/HER2+, 7% (*n* = 39) HR-/HER2+, and 19% (*n* = 113) TNBC. Patients with *BRCA1* and *BRCA2* mutations represented 7.7% (*n* = 45) and 4.8% (*n* = 28) of the cohort, respectively. A higher percentage of patients underwent mastectomy (64.6%; *n* = 380) compared with lumpectomy (35.4%; *n* = 208), a trend that persisted among the four molecular subtypes. A higher percentage of patients who underwent lumpectomy received radiation therapy (99.5%; n = 207) compared to those who underwent mastectomy (47.9%; *n* = 182) (*p*<0.0001). Chemotherapy was administered in 81.3% (*n* = 478) of patients, with 53.4% (*n* = 314) in a neoadjuvant setting and 27.9% (*n* = 164) in an adjuvant setting. Surgical approach was not statistically different *p* = 0.47 between neoadjuvant and adjuvant chemotherapy settings (neoadjuvant, 65.6% mastectomy; adjuvant, 68.9% mastectomy). The majority of patients had either stage I or II tumors on surgical pathology (34.5% and 52.6%, respectively). With a median follow-up time of 5.9 years (IQR 3.8–8.8), 15.1% (*n* = 89) of patients in the entire cohort experienced a recurrence, with distant metastatic disease (67.4%; *n* = 60) being more common than a local (22.5%; *n* = 20) or regional event (10.1%; *n* = 9).

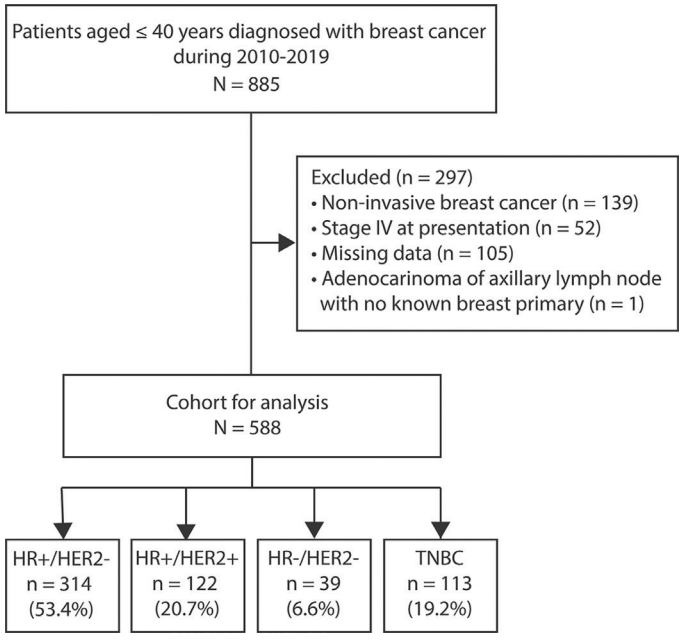

Figure 1. Flow chart of the study cohort

HR: Hormone receptor; TNBC: Triple negative breast cancer

The patients with TNBC and HR-/HER2+ subtypes presented with higher grade tumors compared with the remainder of patients, had a higher rate of recurrence, and worse long-term survival (Supplemental Table 2). The overall mortality rate across all molecular subtypes was 12.1% (*n* = 71). The best survival outcomes were observed among those with HR+ disease, 89.5% for the HR+/HER2- subtype and 89.3% for HR+/HER2+ subtype.

Survival Analysis of Entire Patient Population

Univariate analysis indicated that among the entire cohort, younger age at diagnosis was associated with increased risk of recurrence and death (Table 2). For RFS, each additional year of age was associated with a 6% reduction in the risk of recurrence or death [hazard ratio, 0.94 (0.90–0.98), *p* = 0.005]. For OS, each additional year of age was associated with a 7% reduction in the risk of death [hazard ratio, 0.93 (0.88–0.98), *p* = 0.007]. Increasing stage, the presence of LVSI, and the presence of ENE were associated with an increased risk of both recurrence and death. There was a significant difference in OS between races (overall *p* = 0.002), with black race associated with an increased risk of death compared to white race [hazard ratio, 2.33 (1.43–3.82), hazard ratio *p*<0.001]. There was no significant association between surgical approach and RFS [Figure 2A; hazard ratio, 0.92 (0.62–1.38), *p* = 0.70] or OS [Figure 2B; hazard ratio, 0.72 (0.43–1.22), *p* = 0.22] in this cohort of young women with breast cancer.

To account for imbalances between treatment groups, multivariable analysis was conducted with adjustment for potential confounders included in the model. On multivariable analysis of the entire cohort, race remained significantly associated with an increased risk of death (overall *p* = 0.01), with women of black race at two times higher risk of death compared to women of white race [hazard ratio, 2.114 (1.26–3.61), hazard ratio *p* = 0.005] (Table 3). Increasing age at diagnosis decreased the risk of death [hazard ratio, 0.94 (0.88–0.99), *p* = 0.02]. The presence of LVSI [hazard ratio, 1.98 (1.17–3.36), hazard ratio *p* = 0.01], and the presence of ENE [hazard ratio, 2.12 (1.09–4.12), *p* = 0.03] were associated with increased risk of death. Increasing age decreased the risk of recurrence [hazard ratio, 0.95 (0.90–0.99), *p* = 0.02]. Stage III disease [hazard ratio, 2.06 (1.05–4.03), hazard ratio *p* = 0.04] and the presence of LVSI [hazard ratio, 2.18 (1.43–3.32), hazard ratio *p*<0.001] increased risk of recurrence.

Table 1. Demographic and clinical characteristics by surgical approach				
Characteristic	**Total (*n* = 588)**	**Lumpectomy (*n* = 208)**	**Mastectomy (*n* = 380)**	***p*-value**
Age at diagnosis, years				0.20
Median (IQR)	37 (34–39)	38 (34–40)	37 (34–39)	
Follow-up time (OS), months				0.69
Median (IQR)	73 (45–105)	71 (43–105)	74 (48–105)	
Minimum	6	9	6	
Maximum	148	139	148	
Follow-up time (RFS), months				0.83
Median (IQR)	71 (45–105)	71 (43–103)	71 (46-105)	
Minimum	6	9	6	
Maximum	148	139	148	
BMI, kg/m^2				0.05
Mean ± SD	28.6±7.5	29.5±8.2	28.0±7.0	
Race				**0.001**
Black	153 (26.0%)	72 (34.6%)	81 (21.3%)	
White	388 (66.0%)	125 (60.1%)	263 (69.2%)	
Other	47 (8.0%)	11 (5.3%)	36 (9.5%)	
Hormone status				0.60
HR+/HER2-	314 (53.4%)	104 (50.0%)	210 (55.3%)	
HR+/HER2+	122 (20.7%)	44 (21.2%)	78 (20.5%)	
HR-/HER2+	39 (6.6%)	15 (7.2%)	24 (6.3%)	
TNBC	113 (19.2%)	45 (21.6%)	68 (17.9%)	
Radiation therapy				**<0.0001**
No	199 (33.8%)	1 (0.5%)	198 (52.1%)	
Yes	389 (66.2%)	207 (99.5%)	182 (47.9%)	
Chemotherapy				**0.03**
No	110 (18.7%)	49 (23.6%)	61 (16.1%)	
Yes	478 (81.3%)	159 (76.4%)	319 (83.9%)	
Chemotherapy timing				0.06
Neoadjuvant	314 (53.4%)	108 (51.9%)	206 (54.2%)	
Adjuvant	164 (27.9%)	51 (24.5%)	113 (29.7%)	
No chemotherapy	110 (18.7%)	49 (23.6%)	61 (16.1%)	
Hormone therapy				0.47
No	64 (10.9%)	22 (10.6%)	42 (11.1%)	
Yes	372 (63.3%)	126 (60.6%)	246 (64.7%)	
Not applicable	152 (25.9%)	60 (28.8%)	92 (24.2%)	
Stage group				**0.004**
I	203 (34.5%)	78 (37.5%)	125 (32.9%)	
II	309 (52.6%)	116 (55.8%)	193 (50.8%)	
III	76 (12.9%)	14 (6.7%)	62 (16.3%)	
T classification				0.09
cT0	1 (0.2%)[a]	0 (0.0%)[a]	1 (0.3%)[a]	

Table 1. Continued

Characteristic	Total ($n = 588$)	Lumpectomy ($n = 208$)	Mastectomy ($n = 380$)	*p*-value
cT1	202 (34.4%)	77 (37.0%)	125 (32.9%)	
cT2	279 (47.4%)	105 (50.5%)	174 (45.8%)	
cT3	103 (17.5%)	26 (12.5%)	77 (20.3%)	
cT4	3 (0.5%)	0 (0.0%)	3 (0.8%)	
N classification				**0.02**
cN0	412 (70.1%)	160 (76.9%)	252 (66.3%)	
cN1	155 (26.4%)	46 (22.1%)	109 (28.7%)	
cN2	12 (2.0%)	1 (0.5%)	11 (2.9%)	
cN3	9 (1.5%)	1 (0.5%)	8 (2.1%)	
Grade				0.66
1	52 (8.8%)	19 (9.1%)	33 (8.7%)	
2	243 (41.3%)	79 (38.0%)	164 (43.2%)	
3	281 (47.8%)	105 (50.5%)	176 (46.3%)	
Unknown	12 (2.0%)	5 (2.4%)	7 (1.8%)	
Lymphovascular invasion				**0.002**
No	385 (65.5%)	156 (75.0%)	229 (60.3%)	
Yes	148 (25.2%)	39 (18.8%)	109 (28.7%)	
Indeterminate	55 (9.4%)	13 (6.3%)	42 (11.1%)	
Extranodal extension				**0.02**
No	528 (89.8%)	195 (93.8%)	333 (87.6%)	
Yes	60 (10.2%)	13 (6.3%)	47 (12.4%)	
Status				0.18
Alive	517 (87.9%)	188 (90.4%)	329 (86.6%)	
Deceased	71 (12.1%)	20 (9.6%)	51 (13.4%)	
Recurrence				0.91
No	499 (84.9%)	177 (85.1%)	322 (84.7%)	
Yes	89 (15.1%)	31 (14.9%)	58 (15.3%)	
Recurrence site $n = 89$				0.27
Local	20 (22.5%)	10 (32.3%)	10 (17.2%)	
Regional	9 (10.1%)	3 (9.7%)	6 (10.3%)	
Distant	60 (67.4%)	18 (58.1%)	42 (72.4%)	

BMI: Body mass index; HR: Hormone receptor; SD: Standard deviation; TNBC: Triple negative breast cancer; OS: Overall survival; IQR: Interquartile range; HER2: Human epidermal growth factor receptor 2; RFS: Recurrence-free survival. Bold indicates $p<0.05$. [a]: cT0N1

The hormone therapy not applicable category is equivalent to the combination of HR-/HER2+ and TNBC subgroups. As a result, the model was not able to estimate the effect of TNBC when hormone therapy was included (Table 3). We also ran an alternative model (result not shown), where the categories of hormone therapy and hormone status were combined to resolve the collinearity issue. Neither of the two models found significant effect from hormone treatment or hormone status or the combination of the two. The administration of chemotherapy in any setting was not associated with RFS or OS in multivariable analysis.

Table 2. Univariable recurrence-free survival and overall survival analysis for all subjects

Variable	n	Recurrence-free survival			Overall survival		
		Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Age at diagnosis, 1-yr increase	588	0.94 (0.90–0.98)	**0.005**	**0.005**	0.93 (0.88–0.98)	**0.007**	**0.007**
BMI, kg/m^2							
<25	232	ref		0.38	ref		0.18
≥25	356	1.19 (0.81–1.77)	0.38		1.41 (0.86–2.31)	0.18	
Race							
White	388	ref		0.06	ref		**0.002**
Black	153	1.60 (1.06–2.40)	**0.03**		2.33 (1.43–3.82)	**<0.001**	
Other	47	1.56 (0.80–3.05)	0.19		2.10 (0.93–4.75)	0.08	
Surgical approach							
Mastectomy	380	ref		0.70	ref		0.22
Lumpectomy	208	0.92 (0.62–1.38)	0.70		0.72 (0.43–1.22)	0.22	
Radiation therapy							
Yes	389	ref		0.74	ref		0.96
No	199	0.93 (0.62–1.40)	0.74		1.01 (0.62–1.65)	0.96	
Chemotherapy							
No	110	ref		0.07	ref		0.24
Yes	478	1.72 (0.96–3.07)	0.07		1.52 (0.76–3.07)	0.24	
Hormone therapy							
No	64	ref		0.16	ref		**0.046**
Yes	372	0.79 (0.43–1.47)	0.47		0.63 (0.30–1.31)	0.22	
Not applicable	152	1.19 (0.62–2.30)	0.60		1.18 (0.55–2.53)	0.67	
Stage group							
I	203	ref		**0.001**	ref		**0.008**
II	309	1.85 (1.14–2.98)	**0.01**		1.92 (1.05–3.53)	**0.04**	
III	76	2.94 (1.64–5.28)	**<0.001**		3.11 (1.52–6.37)	**0.002**	
T classification							
cT1	202	ref		**<0.001**	ref		**<0.001**
cT0[a]	1	8.98 (1.21–66.68)	**0.03**		13.20 (1.72–101.2)	**0.01**	
cT2	279	1.63 (0.99–2.68)	0.05		1.89 (0.99–3.61)	0.06	
cT3	103	3.68 (2.17–6.23)	**<0.001**		4.31 (2.20–8.43)	**<0.001**	
cT4	3	2.13 (0.29–15.81)	0.46		3.33 (0.43–25.63)	0.25	
N classification							
cN0	412	ref		0.22	ref		0.40
cN1	155	1.38 (0.91-2.08)	0.13		1.20 (0.71–2.03)	0.50	
cN2	12	1.69 (0.53–5.37)	0.374		2.11 (0.66–6.80)	0.21	
cN3	9	2.40 (0.75–7.61)	0.14		2.31 (0.56–9.51)	0.25	
Grade							
1	52	ref		0.29	ref		0.11
2	243	1.49 (0.63–3.53)	0.36		1.90 (0.57–6.34)	0.30	
3	281	1.98 (0.85–4.57)	0.11		3.04 (0.94–9.82)	0.06	

Table 2. Continued

Variable	n	Recurrence-free survival			Overall survival		
		Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Unknown	12	1.49 (0.30–7.38)	0.66		3.17 (0.53–19.01)	0.21	
Hormone status							
HR+/HER2-	314	ref		0.12	ref		0.17
HR+/HER2+	122	1.04 (0.63–1.72)	0.88		0.96 (0.50–1.82)	0.90	
HR-/HER2+	39	2.12 (1.13–3.97)	**0.02**		1.53 (0.64–3.67)	0.34	
TNBC	113	1.25 (0.76–2.06)	0.38		1.77 (1.01–3.12)	**0.047**	
LVSI							
No	385	ref		**<0.001**	ref		**0.002**
Yes	148	2.42 (1.64–3.59)	**<0.001**		2.28 (1.41–3.69)	**<0.001**	
Indeterminate	55	1.21 (0.58–2.55)	0.61		0.92 (0.33–2.59)	0.87	
Extranodal extension							
No	528	ref		**<0.001**	ref		**<0.001**
Yes	60	2.64 (1.67–4.19)	**<0.001**		2.83 (1.62–4.96)	**<0.001**	

BMI: Body mass index; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; CI: Confidence interval; LVSI: Lymphovascular space invasion; TNBC: Triple negative breast cancer; ref: Reference. Bold indicates $p<0.05$. [a]: cT0N1. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the statistical significance of the comparison between a specific category and the reference category, while the overall *p*-value assesses whether there is a difference across all categories combined. For continuous or binary variables, the hazard ratio *p*-value and overall *p*-value are identical because there is only one comparison

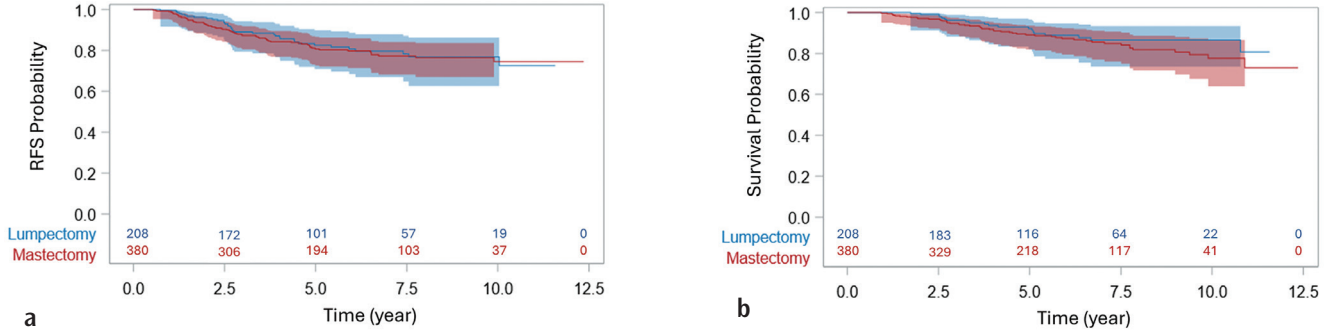

Figure 2. Kaplan-Meier curves for RFS (A) and OS (B) by surgical approach. In both plots, Kaplan-Meier curves, 95% confidence intervals (shaded bands), and the number of patients at risk at each time interval are provided for lumpectomy (blue) and mastectomy (red). Surgical approach was not significantly associated with RFS ($p = 0.95$) or OS ($p = 0.22$)

RFS: Recurrence-free survival; OS: Overall survival

Outcomes by Molecular Subtype

Using multivariable analysis, increasing age [hazard ratio, 1.40 (1.02–1.92), $p = 0.04$], higher BMI [hazard ratio, 8.45 (1.14–62.76), $p = 0.04$], stage III disease [hazard ratio, 129.94 (2.84–5583), hazard ratio $p = 0.01$], and lumpectomy [hazard ratio, 9.06 (1.03–80.0), $p = 0.047$] increased the risk of any recurrence in patients with the HR-/HER2+ subtype (Supplemental Table 3). Black race as compared to white race increased the risk of any recurrence [hazard ratio, 3.36 (1.16–9.71), hazard ratio $p = 0.03$] in patients with TNBC. Patients in the HR+/HER2- subgroup with LVSI had an increased risk of recurrence (overall $p = 0.02$) as compared to patients without LVSI.

In the HR+/HER2- subgroup, increasing age was significantly associated with a decreased risk of death [hazard ratio, 0.90 (0.82–0.98), hazard ratio $p = 0.01$] (Table 4). Black race as compared to white race increased the risk of death in the TNBC [hazard ratio, 4.20 (1.27–13.90), hazard ratio $p = 0.02$] subgroup. In this stratified analysis according to molecular subtype, despite controlling for other demographic and tumor characteristics, there was no difference in OS based upon surgical approach in any of the molecular subtypes.

Table 3. Multivariable recurrence-free survival and overall survival analysis for all subjects

Variable	n	Recurrence-free survival			Overall survival		
		Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Age at diagnosis, 1-yr increase	588	0.95 (0.90–0.99)	**0.02**	**0.02**	0.94 (0.88–0.99)	**0.02**	**0.02**
BMI, kg/m^2							
<25	232	ref		0.87	ref		0.69
≥25	356	1.04 (0.68–1.57)	0.87		1.12 (0.65–1.91)	0.69	
Race							
White	388	ref		0.19	ref		**0.01**
Black	153	1.46 (0.95–2.25)	0.08		2.14 (1.26–3.61)	**0.005**	
Other	47	1.40 (0.69–2.83)	0.35		1.87 (0.80–4.39)	0.15	
Surgical approach							
Mastectomy	380	ref		0.51	ref		0.62
Lumpectomy	208	1.18 (0.72–1.92)	0.51		0.86 (0.46–1.58)	0.62	
Radiation therapy							
Yes	352	ref		0.15	ref		0.23
No	236	1.46 (0.87–2.44)	0.15		1.47 (0.79–2.77)	0.23	
Chemotherapy							
No	110	ref		0.91	ref		0.82
Yes	478	1.04 (0.53–2.02)	0.91		0.91 (0.40–2.08)	0.82	
Hormone therapy							
No	64	ref		0.39	ref		0.17
Yes	372	0.76 (0.40–1.43)	0.39		0.58 (0.27–1.26)	0.17	
Not applicable	152	1.02 (0.48–2.20)	0.95		1.21 (0.49–2.95)	0.68	
Stage group							
I	203	ref		0.10	ref		0.34
II	309	1.58 (0.94–2.65)	0.09		1.49 (0.77–2.89)	0.24	
III	76	2.06 (1.05–4.03)	**0.04**		1.86 (0.80–4.30)	0.15	
Hormone status							
HR+/HER2-	314	ref		0.34	ref		0.85
HR+/HER2+	122	0.90 (0.53–1.52)	0.68		0.82 (0.41–1.64)	0.58	
HR-/HER2+	39	1.69 (0.82–3.51)	0.16		0.94 (0.36–2.44)	0.90	
TNBC	113	NA	NA		NA	NA	
LVSI							
No	385	ref		**0.001**	ref		0.03
Yes	148	2.18 (1.43–3.32)	**<.001**		1.98 (1.17–3.36)	**0.01**	
Indeterminate	55	1.24 (0.58–2.65)	0.59		0.91 (0.32–2.63)	0.86	
Extranodal extension							
No	528	ref		**0.006**	ref		**0.03**
Yes	60	2.14 (1.25–3.66)	**0.006**		2.12 (1.09–4.12)	**0.03**	

BMI: Body mass index; HR: Hormone receptor; CI: Confidence interval; LVSI: Lymphovascular space invasion; HER2: Human epidermal growth factor receptor 2; TNBC: Triple negative breast cancer; ref: Reference; NA: Not applicable. Bold indicates $p<0.05$. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the statistical significance of the comparison between a specific category and the reference category, while the overall *p*-value assesses whether there is a difference across all categories combined. For continuous or binary variables, the hazard ratio *p*-value and overall *p*-value are identical because there is only one comparison

Table 4. Multivariable overall survival analysis stratified by molecular subtype

	HR+/HER2- (*n* = 314)			HR+/HER2+ (*n* = 122)			HR-/HER2+ (*n* = 39)			TNBC (*n* = 113)		
Characteristic	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**
Age at diagnosis, 1-yr increase	0.90 (0.82–0.98)	**0.01**	**0.01**	0.96 (0.83–1.12)	0.62	0.62	1.10 (0.78–1.56)	0.57	0.57	0.93 (0.81–1.06)	0.29	0.29
BMI, kg/m^2												
<25	ref		0.42	ref		0.43	ref		0.78	ref		0.69
≥25	1.40 (0.62–3.20)	0.42		1.75 (0.44–7.03)	0.43		1.39 (0.14–13.49)	0.78		0.79 (0.25–2.52)	0.69	
Race												
White	ref		0.14	ref		0.31	ref		0.10	ref		0.05
Black	0.84 (0.34–2.09)	0.71		3.44 (0.69–17.22)	0.13		16.63 (0.97–286)	0.05		4.20 (1.27–13.90)	**0.02**	
Other	2.64 (0.93–7.48)	0.07		2.42 (0.08–71.92)	0.61		0.90 (0.03–27.33)	0.95		3.10 (0.60–16.18)	0.18	
Surgical approach												
Mastectomy	ref		0.47	ref		0.57	ref		0.81	ref		0.65
Lumpectomy	0.70 (0.27–1.84)	0.47		0.60 (0.10–3.49)	0.57		0.68 (0.03–15.30)	0.81		0.75 (0.21–2.62)	0.65	
Radiation therapy												
Yes	ref		0.33	ref		0.78	ref		0.93	ref		0.95
No	1.56 (0.64–3.77)	0.33		0.76 (0.12–4.97)	0.78		1.16 (0.04–37.10)	0.93		1.05 (0.27–4.10)	0.95	
Chemotherapy												
No	ref		0.68	ref		0.08	ref		0.39	ref		0.37
Yes	0.80 (0.29–2.25)	0.68		0.12 (0.01–1.31)	0.08		0.05 (0.00–53.52)	0.39		0.37 (0.04–3.32)	0.37	
Hormone therapy												
No	ref		0.15	ref		0.16	NA	NA	NA	NA	NA	NA
Yes	0.49 (0.19–1.30)	0.15		0.27 (0.04–1.69)	0.16		NA	NA		NA	NA	

Table 4. Continued

Characteristic	HR+/HER2- (*n* = 314)			HR+/HER2+ (*n* = 122)			HR-/HER2+ (*n* = 39)			TNBC (*n* = 113)		
	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Stage group												
I	ref		0.15	ref		0.89	ref		0.44	ref		0.94
II	1.86 (0.71–4.89)	0.21		1.23 (0.21–7.23)	0.82		8.90 (0.11–758)	0.34		0.83 (0.21–3.37)	0.80	
III	3.58 (1.00–12.83)	0.05		0.84 (0.11–6.45)	0.86		25.52 (0.18–3620)	0.20		0.99 (0.17–5.71)	0.99	
LVSI												
No	ref		0.26	ref		0.70	ref		0.99	ref		0.25
Yes	1.77 (0.84–3.73)	0.14		1.80 (0.36–9.01)	0.47		1.08 (0.05–24.97)	0.96		2.99 (0.83–10.76)	0.09	
Indeterminate	0.72 (0.12–4.17)	0.71		2.52 (0.21–30.92)	0.47		0.98 (0.01–76.78)	0.99		1.36 (0.28–6.60)	0.70	
ENE												
No	ref		0.16	ref		0.20	ref		0.73	ref		0.68
Yes	1.92 (0.77–4.83)	0.16		3.43 (0.52–22.81)	0.20		0.45 (0.01–43.23)	0.73		0.62 (0.06–6.27)	0.68	

BMI: Body mass index; HR: Hormone receptor; ENE: Extranodal extension; CI: Confidence interval; HER2: Human epidermal growth factor receptor 2; TNBC: Triple negative breast cancer; LVSI: Lymphovascular space invasion; ref: Reference; NA: Not applicable. Bold indicates $p<0.05$. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the statistical significance of the comparison between a specific category and the reference category, while the overall *p*-value assesses whether there is a difference across all categories combined. For continuous or binary variables, the hazard ratio *p*-value and overall *p*-value are identical because there is only one comparison

Discussion and Conclusion

After the published results of landmark trials demonstrated oncologic equivalence between BCS and mastectomy, BCS became the treatment of choice for patients with early-stage breast cancer (15). However, women under 40 years of age were underrepresented in these trials, fueling the ongoing debate of whether BCS is safe in young patients. Randomized trials to determine whether surgical approach impacts survival in women ≤40 years are unlikely to surface given currently available information. Several observational studies have investigated whether surgical approach might impact OS in young patients with early-stage breast cancer; however, many of these included patients treated over a decade ago. Systemic therapy for breast cancer has rapidly developed in recent years, especially with respect to treatment of specific molecular subtypes, and updated data are required to make relevant clinical decisions (10, 12). Our retrospective study contributes to the literature by analyzing a large cohort of almost 600 young women with breast cancer who have been treated with modern-day systemic and local therapies. This research utilized data from the Sandra Levine Young Women's Program, a prospectively collected database, which is updated regularly to minimize missing data variables. After 5.9 years of follow-up, our analysis indicates that mastectomy does not offer improved OS compared with BCS in young women with breast cancer. Despite lack of improved survival, our patient population was more likely to undergo mastectomy. Currently, about 60% of women of all ages with early-stage breast cancer undergo BCS (16, 17); however, despite no survival benefit, a national trend towards mastectomy in young patients persists. Our patient population echoed this finding, with 65% of patients undergoing mastectomy and only 35% choosing lumpectomy. This trend towards mastectomy was consistent among all molecular subtypes.

Young patients with breast cancer are plagued with notoriously poor outcomes and are up to 1.5 times more likely to die from their cancer (18) and experience a local recurrence (2, 19-21). Breast cancer in young women is characterized by highly proliferative molecular subtypes (2, 21). While HR+/HER2- (53.4%) disease was most common in our analysis, we did see a preponderance of HR+/HER2+ (20.7%) and TNBC (19.2%), molecular profiles that are consistent with breast cancer in young women (13). In addition, the HER2+ and TNBC tumors were more likely to demonstrate poorly differentiated pathology. Patients with TNBC also had the highest

mortality rate (16.8%) of all molecular subtypes, compared with the 12.1% mortality rate of the entire cohort. Furthermore, in our entire cohort of young women, black race was associated with an increased risk of death, emphasizing the importance of addressing racial disparities in future studies (22). Biological factors, lower socioeconomic status, and limited access to care may contribute to the poorer OS observed among young black women in our study. The difference in survival by race is consistent with a recent National Cancer Database analysis, which found that black women under forty had higher odds of death (odds ratio 1.50; 95% confidence interval: 1.46–1.55, $p<0.0001$) compared to their non-black peers after adjusting for age, tumor characteristics, and treatment (23).

Mastectomy is being replaced by a more conservative approach as the standard for local control of breast cancer (24-29), a paradigm shift that safely de-escalates surgery without compromising oncologic outcomes. More recently, multiple studies have questioned whether mastectomy continues to be a valid surgical option compared to BCS, which can be associated with not only improved esthetic outcomes, but also higher breast cancer-specific survival rates when compared to mastectomy alone (30-32). The Netherlands population-based cohort study demonstrated that BCS in conjunction with radiation resulted in improved 10-year OS when compared to mastectomy (31). Mastectomy is generally associated with an increased risk of complications including bleeding, infections and wound complications (33). Multiple studies support the benefits of BCS over more extensive surgery including improved patient satisfaction with cosmetic outcome (34), psychosocial well-being, body image, and quality of life (35). However, routine BCS in women younger than 40 is controversial, not only because of a lack of prospective data to support it in this high-risk population, but also because young age has been shown to be independently associated with local recurrence after breast conservation (10, 11, 36, 37). Nguyen et al. (11) recently compared the cumulative incidence of local recurrence in patients ≤40 years with breast cancer treated with lumpectomy and radiation versus mastectomy. Among 428 women with early-stage breast cancer, they found the lumpectomy group experienced a 2.5-fold increased risk of local recurrence. Furthermore, patients with isolated local recurrences after lumpectomy showed poor prognosis despite undergoing salvage therapies (11). Miles et al. (38) assessed patients treated from 1988 to 2011, which confirmed these findings (only 5.6% of the patients were <40 years old) and found that risk factors for local recurrence after BCS include node positivity, ER negativity, absence of adjuvant radiation therapy, and age <40 years. In our analysis, BCS increased the risk of local recurrence in patients with the HR-/HER2+ molecular subtype; however, it is important to note that only 7% of our patients were HR-/HER2+. A literature review revealed no studies with similar findings. The existing literature shows that the HR-/HER2+ subtype is seen in approximately 10% of women under the age of 40 (39). As previously noted, only 7% of our cohort was HR-/HER2+. Therefore, we recommend cautious interpretation of these results given the small sample size. Larger studies with longer follow-up are needed to confirm these findings.

Another interesting question is whether the timing of chemotherapy administration impacts young women. Several studies have found that the use of neoadjuvant chemotherapy (NAC) in the treatment of breast cancer has been increasing over time (40), despite trends towards a survival advantage for NAC in only specific cancer subtypes among young women (41). NAC offers the opportunity to de-escalate breast cancer surgery. The majority of patients in our study underwent chemotherapy; most commonly in a neoadjuvant approach. In addition, most of our patients who received NAC also underwent mastectomy, which implies that there were indications for neoadjuvant therapy other than to facilitate breast preservation. Previous studies have shown equivalent survival regardless of timing of chemotherapy (42, 43).

Study Limitations

This study has several limitations, including its retrospective design, patient exclusion due to missing data (archived medical records), and the 6-year duration of follow-up evaluation. In addition, our patient population may not be representative of all young women with breast cancer in the United States. Although the HR-/HER2+ molecular subtype was associated with an increased risk of local recurrence, the number of patients with HR-/HER2+ disease in our cohort was small, resulting in wide confidence intervals and unstable hazard ratio estimates. These findings should be interpreted with caution. Larger studies would be needed to confirm the findings in patients with HR-/HER2+ disease. We did not collect data pertaining to the surgical approach decision-making process. High-risk status, family history (e.g., *BRCA* mutation status), patient preference, genetic counseling, and cultural differences may all play a role in determining the surgical approach. Our cohort included 7.7% ($n = 45$) *BRCA1* carriers and 4.8% ($n = 28$) with *BRCA2* mutations. Although the number of patients with *BRCA* mutations was relatively small, *BRCA* status was not considered in the analyses, which is acknowledged as a limitation. Future studies of young patients with *BRCA* mutations could assess the influence of *BRCA* status on surgical choice and its effect on oncologic outcomes. Lastly, we did not include detailed information regarding specific chemotherapy protocols and radiation therapy fields for patients, which is a limitation of this study. However, chemotherapy administration was according to the standard of care following NCCN and ASCO guidelines. Radiation therapy

also followed standardized treatment per ASTRO guidelines.

In conclusion, our study reinforces the data demonstrating equivalent survival with breast conservation when compared to mastectomy in young women with breast cancer. Recurrence and mortality rates are associated with tumor subtypes and race, and not with surgical intervention. This information should be used to guide shared decision-making. Future research should focus on ethnic and racial disparities and whether this impacts breast cancer care in young patients.

Ethics

Ethics Committee Approval: Wake Forest University Health Sciences Institutional Review Board approval was obtained (approval number: IRB00083094, date: 09.05.2024).

Informed Consent: Waived informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.L.W., L.H-G.; Concept: L.H-G.; Design: R.L.W., L.H-G.; Data Collection or Processing: S.J.T., W.S., C.R.S.; Analysis or Interpretation: C.V.P., S.J.T., W.S., M.L.W., L.H-G.; Literature Search: C.V.P.; Writing: C.V.P., S.J.T., W.S., C.R.S., M.L.W., R.L.W., L.H-G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluating the Role of Artificial Intelligence in Enhancing Multidisciplinary Team Decisions for Breast Cancer Management

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ABSTRACT

Objective: Multidisciplinary teams (MDTs) are essential for optimizing breast cancer treatment, yet the role of general-purpose artificial intelligence (AI), such as ChatGPT, in supporting these teams remains underexplored. This study compared ChatGPT versions 3.5 and 4 with a hospital-based MDT in making treatment and follow-up recommendations, using St. Gallen, European Society for Medical Oncology, National Comprehensive Cancer Network, and American Society of Clinical Oncology guidelines as a reference.

Materials and Methods: A retrospective analysis of 100 consecutive breast cancer patients diagnosed between January 2023 and January 2024 at a training hospital in İstanbul, Türkiye, was conducted. The MDT provided consensus-based recommendations, while anonymized patient data were processed by ChatGPT using English prompts based on guideline summaries. Two experienced breast surgeons independently rated recommendation appropriateness on a five-point scale post-treatment, focusing on clinical outcomes, with agreement assessed using weighted Cohen's kappa across cancer stage, molecular subtype, and proliferation index.

Results: ChatGPT-4 (with a knowledge cut-off of March 2023) demonstrated substantial agreement with the MDT for primary treatments (weighted $\kappa = 0.712$), whereas ChatGPT-3.5 showed moderate agreement ($\kappa = 0.600$). Agreement for additional recommendations, such as genetic counseling, was lower (GPT-4: $\kappa = 0.398$; GPT-3.5: $\kappa = 0.302$), with better performance in early-stage and less aggressive subtypes compared to advanced or aggressive cases. Discrepancies were noted in complex or aggressive cases.

Conclusion: The study suggests ChatGPT, particularly version 4, may serve as a supportive tool for breast cancer teams, especially in early-stage cases, though clinical expertise remains vital for complex scenarios, warranting further research to refine AI integration.

Keywords: Breast cancer; breast neoplasms; treatment

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KEY POINTS

- Breast neoplasms
- Artificial intelligence
- Multidisciplinary team
- Large language models
- Treatment concordance
- Clinical decision support

Introduction

Breast cancer, the most prevalent malignancy among women globally, necessitates a multidisciplinary approach to optimise patient outcomes (1). Multidisciplinary teams (MDTs), integrating expertise from medical oncology, surgical oncology, radiology, histopathology, gynecology, nuclear medicine, and radiation oncology, reduce 5-year mortality by up to 20% through collaborative decision-making (2). However, patient heterogeneity because of variables such as molecular subtypes and comorbidities, and high caseloads have been shown to impair the benefits of MDT management, particularly in complex cases (3).

Artificial intelligence (AI) is transforming medicine, including oncology, with applications in diagnostics, risk stratification, and treatment planning (4). Specialised AI systems, such as IBM Watson for Oncology, have undergone rigorous clinical validation but are costly and less accessible (5). In contrast, general-purpose large language models (LLMs) like ChatGPT from OpenAI have access to vast, uncurated datasets, offering cost-effective flexibility but concerns about clinical reliability and patient-specific applicability remain (6). The ability of ChatGPT to process complex clinical data has the potential to enhance MDT efficiency by providing rapid, evidence-informed recommendations.

Few studies have evaluated general-purpose LLMs in breast cancer management, particularly in complex scenarios requiring open-ended treatment plans (7-9). Lukac et al. (7) reported that ChatGPT-4 outperformed ChatGPT-3.5 in breast cancer treatment recommendations, though concordance with guidelines remained suboptimal. Nguyen et al. (8) noted improved diagnostic accuracy with ChatGPT-4. Kus et al. (9) found moderate concordance for ChatGPT-4 in adjuvant treatment for stage II colon cancer (9). These studies often used categorized recommendations or small cohorts, limiting their reflection of real-world MDT processes.

This study evaluated the role of ChatGPT (GPT-3.5 and GPT-4) in supporting MDT decisions in breast cancer management by comparing open-ended treatment and follow-up plans with those of an in-house MDT. By focusing on a diverse breast cancer cohort, including complex cases, and aligning recommendations with St. Gallen (2023), European Society for Medical Oncology (ESMO) (2023), National Comprehensive Cancer Network (NCCN) (2025), and American Society of Clinical Oncology (ASCO) (2023) guidelines, we aimed to address literature gaps and assess the clinical applicability of these general purpose LLMs.

Materials and Methods

Study Design and Patient Selection

This retrospective study was conducted at University of Health Sciences Türkiye, İstanbul Bağcılar Training and Research Hospital, İstanbul, Türkiye, and approved by the Non-Invasive Ethics Committee (approval number: 2023/12/12/089, date: 22.12.2023). We included 100 consecutive patients newly diagnosed with breast cancer between January 2023 and January 2024. All personally identifiable information was anonymized as per General Data Protection Regulation (GDPR) guidelines. Inclusion criteria required complete clinical data on diagnosis, staging, treatment history, and follow-up. Patients with incomplete data were excluded. Complex cases were defined as those with: (1) no clear treatment algorithms in St. Gallen (2023), ESMO (2023), NCCN (2025), or ASCO (2023) guidelines; (2) multiple treatment options needing multidisciplinary evaluation; (3) high-risk profiles due to comorbidities (such as dementia or heart failure); or (4) need for personalized approaches based on molecular characteristics (e.g.triple-negative subtype) or clinical factors.

Patient Evaluation Form

A standardized patient evaluation form was developed to capture comprehensive clinical data, reflecting routine MDT documentation. The form included age, sex, menopausal status, histopathological subtype, tumor necrosis factor classification, cancer stage, Ki-67 index, imaging findings (e.g., positron emission tomography-computed tomography, magnetic resonance imaging), biopsy and surgical pathology reports, comorbidities, current medications, allergy history, family history, and physical examination findings. Oncotype DX scores, available for 20 patients, were noted but excluded from primary analysis due to limited availability. The form ensured consistency in both MDT and AI evaluations.

MDT and AI Evaluation

An MDT, led by breast surgeons and including a radiologist, histopathologist, gynecologist, nuclear medicine specialist, medical oncologist, and radiation oncologist, reviewed cases through consensus-based discussions. The MDT formulated treatment and follow-up recommendations, including primary treatment (surgery, neoadjuvant chemotherapy, or adjuvant therapy) and additional interventions (e.g., clip placement, genetic counseling), aligned with St. Gallen, ESMO, NCCN, and ASCO guidelines, prioritizing evidence-based and patient-specific approaches. For AI evaluation, anonymized patient evaluation forms were processed using ChatGPT (GPT-3.5, knowledge cut-off January 2022; GPT-4, cut-off March 2023) via web interfaces. Summarized versions of the St. Gallen, ESMO, NCCN, and ASCO guidelines were uploaded to ChatGPT before each evaluation to ensure alignment with evidence-based standards. A standardized English prompt was used: "Based on the provided guideline summaries and the following patient evaluation form, propose a detailed, open-ended treatment and follow-up plan for a breast cancer patient: (patient summary)." Each patient evaluation was started with a new ChatGPT session with cleared cache to prevent data cross-contamination. No additional training was provided to assess the model's baseline performance. English prompts were chosen to better fit with ChatGPT's access to English-language resources and enhance guideline integration. Prompt examples and guideline summaries are provided in the Supplementary Appendix.

Evaluation Process

MDT and ChatGPT recommendations were independently assessed by two breast surgeons with over five years of clinical experience in breast cancer management, using a five-point scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). Assessments were conducted retrospectively at least 12 months after initial treatment decisions to evaluate appropriateness, including early treatment response, such as tumor regression or disease progression post-therapy. This duration allowed observation of clinical outcomes, such as response to neoadjuvant chemotherapy or surgical outcomes, to inform the evaluation. Patient identifiers were anonymized as per GDPR guidelines to ensure confidentiality. Evaluators knew the recommendation sources (MDT or ChatGPT), which may have introduced bias. Assessments were performed separately, with evaluators blinded to each other's scores to ensure independence. The evaluation focused on guideline adherence and clinical appropriateness based on patient outcomes.

Statistical Analysis

Data were analyzed using SPSS, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics, including age, sex, menopausal status, histopathological subtype, molecular subtype, cancer stage, Ki-67 index, and comorbidities. Inter-rater reliability and agreement between MDT and ChatGPT recommendations were assessed using weighted Cohen's kappa, suitable for ordinal five-point scale data. Weighted kappa accounts for the degree of disagreement, with values interpreted as: <0.00 (poor), 0.00–0.20 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (almost perfect). Differences in scores were analyzed using the Wilcoxon signed-rank test for paired ordinal data. Normality was assessed with the Shapiro-Wilk test. Subgroup analyses by Ki-67 index (<20% *vs.* ≥20%), cancer stage [early (stages 1–2) *vs.* advanced (stages 3–4)], and molecular subtype (Luminal A, Luminal B, HER2-positive, triple-negative) used χ^2 tests. Sensitivity analyses excluded patients with major comorbidities to assess their impact on agreement. A *p*-value <0.05 was considered statistically significant, with exact *p*-values reported.

Results

The cohort included 100 patients (99% female, 1% male), with a mean age of 54.8±11.9 years and a median (range) age of 55 (28–85) years. Menopausal status was premenopausal in 47.47% and postmenopausal in 52.52%. Histopathological subtypes were invasive ductal carcinoma (90%), invasive lobular carcinoma (6%), and mixed types (4%). Molecular subtypes included Luminal A (50%), Luminal B (15%), HER2-positive (28%), and triple-negative (7%). Cancer stages were stage 1 (20%), 2a (40%), 2b (15%), 3a (5%), 3b (3%), 3c (2%), and 4 (15%). Stage 4 metastases included bone (n = 6), lung (n = 4), liver (n = 3), and multiple sites (n = 2). Median Ki-67 was 18% (interquartile range: 8–30), with 60% ≥20%. At least two comorbidities (≥2) were present in 30% of patients while 40% had none (Table 1).

MDT decisions included primary surgery (50%), neoadjuvant chemotherapy (30%), and adjuvant therapy (20%). GPT-4 recommended surgery (52%), neoadjuvant chemotherapy (29%), and adjuvant therapy (19%); GPT-3.5 recommended surgery (49%), neoadjuvant chemotherapy (30%), and adjuvant therapy (21%) (Table 2). GPT-4 achieved full agreement in 83 cases, clinically acceptable alternatives (e.g., mastectomy *vs.* breast-conserving surgery) in 12 cases, and discrepancies in 5 cases, and all five patients had comorbidities (dementia, n = 3; heart failure, n = 2). GPT-3.5 achieved full agreement in 75 cases, acceptable alternatives in 15 cases, and discrepancies in 10 cases, often due to outdated knowledge or limited patient-specific integration.

Inter-rater reliability was high [κ = 0.92, 95% confidence interval (CI): 0.88–0.96, p<0.001]. Primary treatment agreement was substantial for GPT-4 (κ = 0.712, 95% CI: 0.62–0.80, p<0.001) and moderate-to-substantial for GPT-3.5 (κ = 0.600, 95% CI: 0.50–0.70, p<0.001). Agreement for additional recommendations

(e.g., clip placement, genetic counselling) was fair (GPT-4: κ = 0.398, 95% CI: 0.28–0.51; GPT-3.5: κ = 0.302, 95% CI: 0.19–0.42; both $p<0.001$). Subgroup analyses by Ki-67 (<20% *vs.* ≥20%), cancer stage [early (stages 1–2) *vs.* advanced (stages 3–4)], and molecular subtype showed no significant differences ($p = 0.38$, $p = 0.29$, and $p = 0.45$, respectively). However, GPT-4 achieved higher concordance in Luminal A cases (κ = 0.750, 95% CI: 0.65–0.85) compared to Luminal B cases (κ = 0.680, 95% CI: 0.58–0.78), HER2-positive cases (κ = 0.650, 95% CI: 0.55–0.75), and triple-negative cases (κ = 0.620, 95% CI: 0.50–0.74), possibly reflecting challenges in managing aggressive subtypes. Sensitivity analysis excluding patients with comorbidities ($n = 10$) improved agreement: GPT-4 primary treatment (κ = 0.765, 95% CI: 0.68–0.85), additional recommendations (κ = 0.432, 95% CI: 0.31–0.55); GPT-3.5 primary treatment (κ = 0.650, 95% CI: 0.55–0.75), additional recommendations (κ = 0.356, 95% CI: 0.24–0.47) (Table 3). Wilcoxon signed-rank tests showed significant differences between MDT and ChatGPT recommendations (Rater 1: Z = +4.20, $p<0.001$; Rater 2: Z = +4.15, $p<0.001$), with MDT decisions receiving higher scores in 35 (Rater 1) and 33 (Rater 2) cases.

Table 1. Patient characteristics

Characteristic	Value
Age (years)	Mean 54.8±11.9; median 55 (range 28–85)
Sex	Female: 99 (99%)
	Male: 1 (1%)
Menopausal status	Premenopausal: 47 (47.47%)
	Postmenopausal: 52 (52.52%)
Histopathological subtype	Invasive ductal: 90 (90%)
	Invasive lobular: 6 (6%)
	Mixed: 4 (4%)
Molecular subtype	Luminal A: 50 (50%)
	Luminal B: 15 (15%)
	Human epidermal growth factor receptor 2 -positive: 28 (28%)
	Triple-negative: 7 (7%)
Cancer stage	Stage 1: 20 (20%)
	Stage 2a: 40 (40%)
	Stage 2b: 15 (15%)
	Stage 3a: 5 (5%)
	Stage 3b: 3 (3%)
	Stage 3c: 2 (2%)
	Stage 4: 15 (15%)
Stage 4 metastases	Bone: 6
	Lung: 4
	Liver: 3
	Multiple: 2
Ki-67 (%)	Median 18 (interquartile range: 8–30); ≥20%: 60 (60%)
Comorbidities	≥2: 30 (30%); None: 40 (40%)

Table 2. Treatment plan concordance by patient subgroups (percentage distribution and differences)

Subgroup	n	PS % MDT/GPT-4/Diff	NAC % MDT/GPT-4/Diff	AT % MDT/GPT-3.5/Diff
Menopausal status				
Premenopausal	47	49/51/+2	32/31/-1	19/20/+1
Postmenopausal	53	51/53/+2	28/27/-1	21/22/+1
Molecular subtype				
Luminal A	50	58/60/+2	22/21/-1	20/21/+1
Luminal B	15	47/49/+2	33/32/-1	20/21/+1
HER2-positive	28	43/45/+2	36/35/-1	21/22/+1
Triple-negative	7	29/31/+2	57/56/-1	14/15/+1
Overall	100	50/52/+2	30/29/-1	20/21/+1

PS: Primary surgery; NAC: Neoadjuvant chemotherapy; AT: Adjuvant therapy; HER2: Human epidermal growth factor receptor 2. Cells show MDT/GPT-4/Diff (e.g., 47/50/+3 = MDT 47%, GPT-4 50%, difference +3%). GPT-3.5 diffs shown only for AT column (space saving; full in supplementary if needed). Percentages maintain cohort totals (e.g., overall PS 50% MDT). Differences highlight concordance (positive: GPT overestimates PS; negative: underestimates NAC). HR status: HR-positive includes Luminal A/B and HR+ HER2-enriched (78%); HR-negative includes TN and HR- HER2 (22%). Distributions proportional to subtypes (e.g., higher PS in HR+/Luminal A per guidelines; higher NAC in HR-/TN for aggressive cases). No significant differences (χ^2, $p>0.05$).

Table 3. Weighted Cohen's kappa for breast cancer cohort

Concordance	κ (weighted)	*p*-value	95% CI
MDT (rater 1-rater 2)	0.92	<0.001	0.88–0.96
GPT-4 (rater 1-rater 2)	0.90	<0.001	0.85–0.95
GPT-3.5 (rater 1-rater 2)	0.88	<0.001	0.83–0.93
Rater 1 (MDT-GPT-4)	0.712	<0.001	0.62–0.80
Rater 2 (MDT-GPT-4)	0.705	<0.001	0.61–0.79
Rater 1 (MDT-GPT-3.5)	0.600	<0.001	0.50–0.70
Rater 2 (MDT-GPT-3.5)	0.595	<0.001	0.49–0.69
GPT-4 (early-stage, stages 1–2)	0.740	<0.001	0.65–0.83
GPT-4 (advanced-stage, stages 3–4)	0.650	<0.001	0.55–0.75
GPT-4 (Luminal A)	0.750	<0.001	0.65–0.85
GPT-4 (Luminal B)	0.680	<0.001	0.58–0.78
GPT-4 (HER2-positive)	0.650	<0.001	0.55–0.75
GPT-4 (triple-negative)	0.620	<0.001	0.50–0.74

HER2: Human epidermal growth factor receptor 2; MDT: Multidisciplinary team; CI: Confidence interval

Discussion and Conclusion

This study evaluated ChatGPT, versions 3.5 and 4, as supportive tools for MDT decisions in breast cancer management in a diverse cohort of 100 patients with varying molecular subtypes, stages, and comorbidities. The substantial agreement between ChatGPT-4 and human experts for primary treatments (weighted Cohen's kappa = 0.712, $p<0.001$) reflects a remarkable alignment with St. Gallen, ESMO, NCCN, and ASCO guidelines in standard cases, and was similar to the findings reported by Lukac et al. (7). The moderate agreement identified for ChatGPT-3.5 (kappa = 0.600, $p<0.001$) also reflects earlier reports which found kappa values of 0.4–0.6 for general-purpose LLMs in clinical settings (10). The superior performance of ChatGPT-4 is attributable to its more advanced architecture and March 2023 knowledge cut-off, further enhanced by the decision to use English prompts, which likely optimized access to guideline-aligned resources (11).

Furthermore, the fair agreement for additional recommendations (GPT-4: kappa = 0.398; GPT-3.5: kappa = 0.302; both $p<0.001$) may be a subtle limitation when AI systems attempt to integrate patient-specific factors, such as comorbidities or genomic data (e.g., Oncotype DX), and post-2022 guideline updates (e.g., ASCO's CDK4/6 inhibitor recommendations) (12). Unlike oncology-specific tools like IBM Watson (kappa >0.8) (5), the reliance on uncurated data in the present study introduces a trade-off that must be recognized; limited reliability offset by cost-effective accessibility (13). This study has highlighted these discrepancies, particularly in complex cases, where MDT expertise proved indispensable (6), reinforcing the role of human-AI synergy.

Our findings extend prior research. Lukac et al. (7) and Nguyen et al. (8) noted the strengths of ChatGPT-4, while Kus et al. (9) and Park et al. (14) highlighted limitations in AI accuracy and reliability for clinical or patient-facing applications. We believe one of the strengths of our study lies in its focus on open-ended treatment and follow-up plans, capturing real-world MDT processes across a challenging cohort (25% advanced-stage, 30% comorbid). The higher concordance of ChatGPT-4 in early-stage (kappa = 0.740) and Luminal A cases (kappa = 0.750) compared to advanced-stage (kappa = 0.650) or triple-negative cases (kappa = 0.620) (15) reflects its prowess in scenarios with clear guideline algorithms, a finding that supports the clinical relevance of using general AI systems when resources are limited and dedicated systems such as IBM Watson for Oncology are not available. Evaluator bias from source awareness may have favored MDT suggestions, as evidenced by significantly higher MDT scores, underscoring this as a key limitation that must be acknowledged; nevertheless, the indispensable role of human expertise in complex cases aligns with emerging evidence on human-AI synergy in precision oncology (16).

A strength of this work lies in its rigorous design, including a 12-month data collection period and independent, but possibly biased, expert reviews, which ensured robust outcome assessment. However, other limitations, including retrospective design, single-center cohort, limited Oncotype DX data (20 patients), and the March 2023 cut-off should also be acknowledged. Future studies should employ double-blind, multicentre prospective designs with real-time data integration (e.g., genomic profiles, up-to-date guidelines) and compare with specialized AI tools. The non-blinded evaluation may have introduced observer bias favoring MDT recommendations (as evidenced by significantly higher MDT scores, Wilcoxon $p<0.001$), while the identified limitations in complex scenarios underscore the irreplaceable role of clinical expertise-yet prospective blinded studies are warranted to substantiate the potential of general-purpose AI as a supportive tool in MDT decision-making for resource-limited settings.

ChatGPT, particularly GPT-4, emerged as a promising supportive tool for breast cancer MDTs, especially in early-stage and less complex cases. The limitations identified for these two general AI systems in complex scenarios highlight the irreplaceable value of clinical expertise, yet there is potential to assist MDTs in streamlining decision-making and enhancing guideline adherence. In our opinion this offers an exciting avenue for future exploration. Ongoing research and collaboration between AI developers and clinicians may further refine this technology, making it a more valuable tool for improving patient outcomes.

Ethics

Ethics Committee Approval: This retrospective study was conducted at University of Health Sciences Türkiye, İstanbul Bağcılar Training and Research Hospital, İstanbul, Türkiye, and approved by the Non-Invasive Ethics Committee (approval number: 2023/12/12/089, date: 22.12.2023).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T., T.P., S.C., B.T., O.T., E.C., N.E., A.Ö., N.S.A., Ş.B., A.Ç.; Concept: M.T., T.P., E.C., A.Ç.; Design: M.T., T.P., E.C., A.Ç.; Data Collection or Processing: M.T., T.P., S.C., B.T., O.T., E.C., N.E., A.Ö., N.S.A., Ş.B., A.Ç.; Analysis or Interpretation: M.T., T.P., E.C., A.Ç.; Literature Search: M.T., T.P., S.C., B.T., O.T., E.C., N.E., A.Ö., N.S.A., Ş.B., A.Ç.; Writing: M.T., T.P., E.C., A.Ç.

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ORIGINAL ARTICLE

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Tomosynthesis-Guided Vacuum-Assisted Excision of B3 Breast Lesions: Reducing Overtreatment Without Compromising Safety

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ABSTRACT

Objective: Breast lesions of uncertain malignant potential (B3) pose a diagnostic and management challenge. Surgical excision (SE) has traditionally been the standard for definitive diagnosis, but it may represent overtreatment. Percutaneous vacuum-assisted excision (VAE) offers a minimally invasive alternative. This study aimed to evaluate the safety and efficacy of VAE compared with SE for the management of B3 breast lesions, with the aim of reducing overtreatment.

Materials and Methods: This retrospective single-center study included 64 patients with histologically confirmed B3 lesions diagnosed by tomosynthesis-guided vacuum-assisted breast biopsy between January 2018 and January 2024. Patients were managed by SE, VAE, or imaging follow-up, based on multidisciplinary team recommendations. Imaging characteristics, histopathology, upgrade rates, and follow-up outcomes were analyzed.

Results: Most lesions presented as microcalcifications (92%). The most common histological subtypes were atypical intraductal epithelial proliferation (37.5%) and lobular neoplasia (25%). SE was performed in 26 patients (40%), VAE in 22 (34%), and 16 (25%) underwent follow-up. Malignant upgrades occurred in 8 of 26 SE-treated lesions (30.8%), predominantly atypical intraductal epithelial proliferation, while no upgrades were observed in the VAE group ($p = 0.007$). Mean follow-up was longer for SE (42 months) than VAE (21 months, $p = 0.036$). One SE patient developed invasive carcinoma at 48 months; no malignant progression occurred after VAE.

Conclusion: VAE is a safe, minimally invasive and effective alternative to SE for carefully selected B3 lesions, particularly those without atypia and with imaging-pathology concordance, potentially reducing overtreatment. Multidisciplinary evaluation remains essential.

Keywords: Lesions of uncertain malignant potential; second-line breast biopsy; surgery; vacuum-assisted biopsy; vacuum-assisted excision

KEY POINTS

- B3 breast lesions represent a heterogeneous group with variable malignant potential and remain a management challenge.
- Vacuum-assisted excision (VAE) demonstrated safety and efficacy in carefully selected B3 breast lesions, avoiding surgical excision (SE) in more than one-third of patients in this single-centre series.

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- All malignant upgrades (30.8%) occurred in the SE group, while no malignant upgrades were observed after VAE, though follow-up duration was shorter compared to SE (21 vs. 42 months).
- Findings support VAE as a safe, effective and minimally invasive alternative to SE in selected B3 lesions, but larger prospective studies with longer follow-up are required.

Introduction

B3 lesions, which account for 3-21% of all breast lesions, represent a heterogeneous group with a low but significant risk of malignancy, ranging from 21% to 35% (1). The increasing use of mammography screening has contributed to these lesions being detected more frequently, especially in asymptomatic patients. Breast biopsies are usually performed to assess these suspicious lesions, which can be further classified according to the presence or absence of atypia. Some authors suggest a histological subdivision into B3a (without atypia) and B3b (with atypia) to achieve better risk stratification (2, 3).

The treatment of B3 breast lesions continues to be the subject of considerable debate, as reflected in various guidelines, including those of the American Society of Breast Surgeons (4), the UK National Health Service (NHS) (5) and the 2016 (6) and 2018 (7) international consensus conferences with a European focus. Possible management options for B3 lesions include surgical biopsy, percutaneous vacuum-assisted excision (VAE), and imaging surveillance (8, 9).

Traditionally, surgical excision (SE) has been considered the standard of care for many B3 lesions in order to exclude associated malignancy. Nevertheless, accumulating evidence suggests that routine SE may constitute overtreatment in a substantial proportion of patients, given the relatively low upgrade rates for selected lesions and the morbidity, cost, and psychological burden associated with surgery. Consequently, minimally invasive alternatives have gained increasing attention (5, 10-12).

Vacuum-assisted breast biopsy (VABB) and VAE are percutaneous techniques performed under imaging guidance, most commonly stereotactic or ultrasound guidance, using large-core needles (typically 7- or 8-gauge). While VABB is primarily a diagnostic procedure aimed at obtaining larger and more representative tissue samples compared with core needle biopsy (CNB), VAE is designed to achieve complete or near-complete removal of the targeted lesion through a single percutaneous approach. The technical principle involves continuous tissue aspiration and cutting, allowing sequential sampling or excision without repeated needle insertions (5, 10).

Initially introduced for the management of benign breast lesions, such as fibroadenomas up to 2 cm, VAE has progressively been adopted for the treatment of selected B3 lesions. Several consensus statements and national guidelines now support VAE as a safe and effective alternative to SE for a substantial proportion of B3 lesions, particularly those without atypia and with imaging-pathology concordance. This approach offers the advantages of reduced invasiveness, shorter recovery time, improved cosmetic outcomes, and lower healthcare costs, while maintaining diagnostic accuracy (4-12). In this setting, diagnostic VAE is used as a replacement for surgical diagnostic biopsy.

Beyond its established role in benign and high-risk lesions, VAE has also been explored as a therapeutic tool in carefully selected malignant breast lesions. In particular, small, low-grade ductal carcinoma *in situ* (DCIS) and selected invasive carcinomas diagnosed on VABB have been evaluated in feasibility studies and observational series (13-16). These studies suggest that, in carefully selected cases, VAE may achieve complete lesion removal and provide valuable pathological information regarding tumor extent, margins, and biological characteristics. Although VAE is not intended to replace surgery in malignant disease, its role as a therapeutic or staging tool in specific clinical scenarios is increasingly recognized and contributes to the evolving spectrum of minimally invasive breast interventions.

Thus, VAE represents a pivotal technique at the intersection of diagnosis and treatment, challenging the traditional dichotomy between biopsy and surgery. Even in cases where malignancy is subsequently identified, VAE may reduce the extent of surgical intervention by obviating diagnostic surgery and streamlining definitive treatment planning.

This retrospective, single-center study evaluated the safety and efficacy of VAE, compared with SE in the management of B3 breast lesions, with the objective of reducing overtreatment.

Materials and Methods

This retrospective, single-centre study was approved by the Ethical Committee of Clinical Hospital Centre Rijeka, Croatia (date: 24 June 2020; approval number: 003-05/20-1/92), which waived the requirement for individual informed consent.

Study Population

At the Clinical Hospital Centre Rijeka, all B3 lesions were routinely managed with SE until 2018. However, the final pathological results frequently revealed benign outcomes, which raised concerns about overtreatment. Since 2018, all B3 lesions diagnosed at the institution have been reviewed

by a multidisciplinary team (MDT). In the absence of national guidelines in Croatia, management decisions have been guided by the UK NHS recommendations for lesions of uncertain malignant potential (5). Within this framework, the present study was designed to evaluate the safety and efficacy of VAE as a complementary procedure to SE.

The study cohort was identified from the institutional database and consisted of consecutive patients with histologically proven B3 lesions diagnosed between January 2018 and January 2024. All lesions were confirmed histologically using tomosynthesis-guided VABB.

Before undergoing biopsy, all patients were informed about both VABB and VAE procedures and provided written informed consent.

The inclusion criteria were: female patients with complete clinical data; mammographically detected lesions not visible on ultrasound; referral for VABB after mammography or digital breast tomosynthesis; histopathological confirmation of a B3 lesion and subtype after VABB; referral for either VAE or SE after VABB; and availability of follow-up data at the Clinical Hospital Centre Rijeka.

The exclusion criteria were: technically inadequate VABB or VAE procedures; lesions that were unsuitable for VAE due to their location in the breast (for example, too close to the skin or nipple-areolar complex); patients with biopsy-proven cancer elsewhere in the breast; and lesions classified as malignant on histopathology after VABB.

Clinical and demographic characteristics, including age, prior breast surgery or biopsy, date and type of procedure, histopathological findings, and follow-up data, were obtained from institutional records. For patients in the VAE group, mammograms were re-evaluated to measure lesion size at three time points, before VABB, after VAE, and during follow-up imaging, in order to assess for residual disease. The follow-up period was defined as the interval between the initial VABB and the final imaging assessment.

Interventional Procedures and Data Collection

Tomosynthesis-guided vacuum-assisted biopsies were performed using 10-gauge needles ("Mammotome Revolve", Devicor Medical Products, Cincinnati, OH, USA), while 8-gauge needles were used for tomosynthesis-guided VAE on a Selenia Dimensions mammography unit (Hologic, Bedford, MA, USA), with patients lying in the prone position. According to the needle specifications, 12 core samples per lesion and 4 g of tissue were collected. A marking clip ("Mammotome HydroMARK 8G", Devicor Medical Products, Cincinnati, OH, USA) was placed at the end of each procedure for both VABB and VAE, to mark the site of biopsy and subsequent excision. After the procedure, a mammogram was performed to determine whether the lesion and/or a previously placed marking clip had been removed and whether the clip placed after the VAE was in a satisfactory position. Radiological data, including morphology, distribution and extent of calcifications, and presence or absence of microcalcifications after VABB on mammography were analysed. Radiological suspicion was assessed according to the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) (17).

In the absence of national guidelines, institutional management recommendations were developed through a structured multidisciplinary approach and were aligned with the International Consensus Guidelines for B3 lesions and the UK NHS recommendations. All B3 lesions were systematically reviewed in MDT meetings, attended by a breast radiologist, histopathologist, cytologist, oncologist, and surgeon, with explicit assessment of radiologic-pathologic concordance. MDT allocation was guided by predefined, objective criteria, including lesion type, imaging characteristics, adequacy of sampling, presence or absence of atypia, and the degree of concordance between imaging findings and histopathological results (Table 1). Lesions demonstrating adequate sampling and radiological-pathological concordance without high-risk features were preferentially managed with VAE, whereas discordant findings or features suggestive of potential underestimation prompted SE. Specifically, lesions such as radial scars, as well as lesions with complete radiological-pathological concordance were considered suitable for VAE, with additional factors including lesion size, patient age, and presence of residual calcifications taken into account. In contrast, lesions with atypical ductal hyperplasia, lobular neoplasia (LN), papillary lesions with atypia, particularly when imaging findings suggested possible underestimation or sampling was deemed insufficient, were preferentially referred for SE. For epithelial proliferative lesions MDT decisions incorporated lesion extent, residual imaging abnormalities following biopsy, patient-specific risk factors, and published upgrade rates. Although no single variable independently predicted MDT allocation, management decisions reflected an integrated evaluation of radiological and pathological factors, rather than subjective judgment. The primary aim of this structured, guideline-based MDT process was to reduce unnecessary surgery while maintaining diagnostic accuracy.

Surgical Excision

SE was performed using wire guidance following mammographic localization. The tip of the guidewire was placed within the residual lesion, or, in cases of complete removal of the target lesion during VABB, within the post-biopsy hematoma; in other cases, it was positioned adjacent to the non-migrated marking

Table 1. The relationship between radiological and pathological morphological characteristics of the lesions and MDT recommendations

	Lesions with or without atypia			MDT recommendation			
	Lesions without atypia	Lesions with atypia	p-value	Monitoring	SE	VAE	p-value
Age							
≤60	9	34	0.282	6	16	21	0.158
>60	7	14		4	12	5	
Initial mammography BI-RADS							
0	8	28	0.300	8	15	13	0.507
2	1	0		0	0	1	
3	1	1		0	0	2	
4	6	16		2	11	9	
5	0	3		0	2	1	
Magnification BI-RADS							
0	0	1	0.566	0	1	0	0.468
3	1	1		0	0	2	
4	12	38		10	22	18	
5	0	3		0	2	1	
ACR							
A	3	0	0.012	1	1	1	0.949
B	4	22		4	11	8	
C	8	20		3	11	12	
D	1	6		1	3	2	
MDT recommendation							
Monitoring	4	6	0.365				
SE	5	23					
VAE	7	19					

SE: Surgical excision; VAE: Vacuum assisted excision; BI-RADS: Breast imaging reporting and data system; MDT: Multidisciplinary team; ACR: American College of Radiology

clip. Intraoperative mammographic imaging of the excised specimen was carried out to confirm complete inclusion of the target lesion. If incomplete resection was identified, immediate re-excision was undertaken.

In the management of borderline and benign breast lesions, surgical margins are generally not of clinical significance. The primary objective in these cases is complete excision of the lesion to enable accurate histopathological assessment, rather than achieving tumor-free margins, given the minimal risk of recurrence or progression. Emphasis on surgical margins may result in overtreatment and the unnecessary removal of healthy breast tissue.

Final histopathological assessment of specimens obtained via SE or VAE served as the gold standard. An upgrade was defined as the histological detection of DCIS or invasive carcinoma within the excised specimen. The upgrade risk was subsequently assessed for each subset of B3 lesions.

Statistical Analysis

Statistical analyses were performed with MedCalc for Windows, version 23.0.2 (MedCalc Software, Ostend, Belgium) and the program Statistica Software Package for Windows 10, 14 (StatSoft, Inc., Tulsa, OK, USA). Descriptive statistics were used to characterize the study population. Upgrade rates from B3 lesions to higher pathological categories were compared between patients who underwent vacuum-assisted needle excision VAE and those who were treated with SE. Differences in categorical variables were analysed using the pearson chi-square test.

Duration of follow-up was compared for patients who underwent VAE, surgical biopsy or surveillance using Student's t-test for independent variables. Duration of follow-up was assessed

for both the VAE and SE groups and was calculated in months from the time of diagnosis of the B3 lesion to the diagnosis of breast cancer or the last recorded follow-up. The occurrence of breast cancer during follow-up and its association with clinical and pathological parameters were evaluated using descriptive statistics.

All statistical values were considered significant if the *p*-value (*p*) was <0.05.

Results

Between January 2018 and January 2024, 64 B3 lesions were diagnosed at the Clinical Hospital Centre Rijeka using tomosynthesis-guided VABB. The final study group consisted of these 64 patients with a mean age of 56.7±9.2 years (range 41–80 years). Of the 64 patients enrolled in the study, i.e. those who underwent VABB, SE was recommended for 28 patients and VAE for 26 patients. Ultimately, 26 (40.6%) patients opted for SE, while 22 (34.4%) patients chose VAE. Follow-up after VABB was recommended for 16 patients (25%) (Figure 1).

On mammography, the majority of lesions were identified as clusters of microcalcifications (59 cases, 92%). A smaller number presented as architectural distortions (4 cases, 6%), while only one lesion (2%) appeared as a mass.

The initial BI-RADS assessments included 36 lesions (56.2%) classified as BI-RADS 0, 22 lesions (34.4%) classified as BI-RADS 4, three lesions (4.7%) classified as BI-RADS 5, two lesions (3.1%) classified as BI-RADS 3, and one lesion (1.6%) classified as BI-RADS 2. Magnification views were obtained in 56 patients (87.5%). In this subgroup, the most common BI-RADS category was BI-RADS 4 (89.2%), followed by BI-RADS 5 (5.4%), BI-RADS 3 (3.6%), and BI-RADS 0 (1.8%).

Breast density was assessed according to the ACR classification. Twenty-eight patients (43.7%) had heterogeneously dense breasts (ACR C), 26 patients (40.6%) had scattered density (ACR B), seven patients (10.9%) had extremely dense breasts (ACR D), and three patients (4.7%) had entirely fatty breasts (ACR A).

Histopathological analysis revealed that the most common diagnosis was atypical intraductal epithelial proliferation (AIDEP) in 24 cases (37.5%). This was followed by LN in 16 cases (25%), papillary lesions without atypia in 12 cases (18.8%), flat epithelial atypia in eight cases (12.5%), radial scars in three cases (4.7%), and epithelial proliferation without atypia in one case (1.6%). A representative VABB sample demonstrating AIDEP and LN2 is shown in Figure 2.

No significant correlation was observed between BI-RADS classification on mammography and histological subtype (p = 0.300) or between BI-RADS classification on magnification views and histological subtype (p = 0.566). However, a statistically significant association was found between dense breast tissue (ACR categories C and D) and the presence of atypia (p = 0.012).

The majority of B3 lesions managed with VAE appeared as clusters of calcifications on mammography (94%), with only one lesion presenting as parenchymal distortion. Lesion size ranged from 3 mm to 21 mm, with a mean size of 6.7±5.4 mm.

SE was recommended in 28 cases. Ultimately, 26 patients (40%) underwent SE. VAE was recommended in 26 cases, and 22 patients (34%) underwent the procedure, while three converted to SE and 1 declined further intervention. Follow-up without further intervention after VABB was recommended in 16 patients (25%).

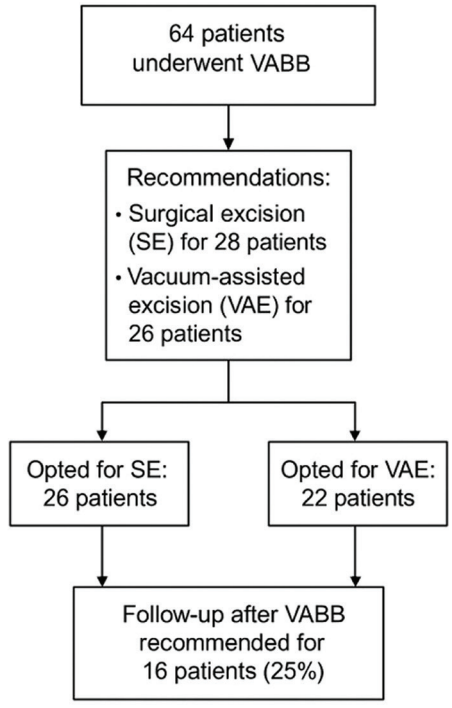

Figure 1. Patient management algorithm following VABB in our study

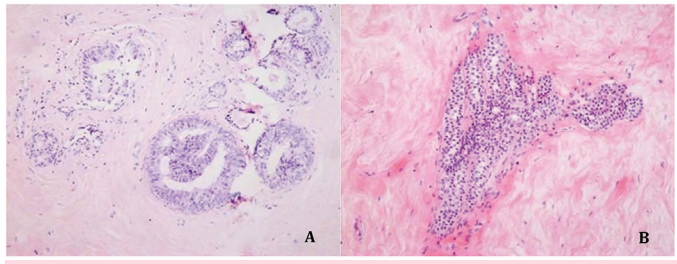

Figure 2. A) Atypical intraductal epithelial proliferation in the vacuum-assisted breast biopsy (VABB) sample. B) Lobular neoplasia 2 in VABB sample. Magnification 100x. Clinical Department of Pathology and Cytology, Clinical Hospital Centre Rijeka

The decision to recommend SE versus VAE was not significantly influenced by patient age ($p = 0.158$), breast density ($p = 0.949$), or the presence of atypia ($p = 0.365$) (Table 1). Similarly, the histological subtype diagnosed by VABB did not significantly predict MDT recommendations ($p = 0.223$). Among patients with AIDEP, however, SE was more frequently recommended (14 cases), compared with VAE (9 cases) or follow-up alone (1 case).

All malignant upgrades occurred in the SE group. Specifically, 8 of 26 SE-treated lesions (30.8%) were upgraded to DCIS or invasive carcinoma. In contrast, no malignant upgrades were identified in the VAE group (0%), representing a statistically significant difference ($p = 0.007$). Although upgraded lesions were more frequently classified as BI-RADS 4 on mammography, this association did not reach statistical significance ($p = 0.149$). When histological subtypes were analyzed, AIDEP accounted for the majority of upgrades (6 of 8 cases), followed by papillary lesions and flat epithelial atypia, although this association was not significant ($p = 0.201$). However, this finding was statistically significant when AIDEP was analyzed separately ($p = 0.040$).

Follow-up duration differed between groups, with a longer mean follow-up in the SE group compared with the VAE group (42 *vs.* 21 months, $p = 0.036$). During follow-up, invasive carcinoma was identified in one patient in the SE group, occurring 48 months after the initial biopsy. This patient had an initial diagnosis of LN grade 2, and the subsequent lesion was classified as classic invasive lobular carcinoma. No carcinomas were detected within the first 36 months of follow-up in either group.

Discussion and Conclusion

VAE is increasingly recommended for the treatment of B3 breast lesions without atypia, according to the third consensus of the European Society of Breast Imaging (18). However, SE is still favored in the current literature, despite concerns about potential overtreatment due to the low overall risk of malignant progression (5, 11, 12).

The aim of this study was to evaluate the safety and efficacy of diagnostic VAE in the removal of breast lesions of uncertain malignant potential, focusing on lesions identified by VABB and occult on ultrasound. To our knowledge, this is the first longitudinal study directly comparing VAE and SE in B3 lesions initially sampled by VABB.

The distribution of B3 lesions in our study was influenced by the inclusion criteria, which were limited to mammographically detected lesions, most of which appeared as calcifications (Figure 3). Other studies generally included all B3 lesions, some even B2 lesions (10, 12, 19, 20).

In our cohort, the most common lesion types were AIDEP (37.5%) and LN (25%), with 75% of all lesions categorized as high-risk

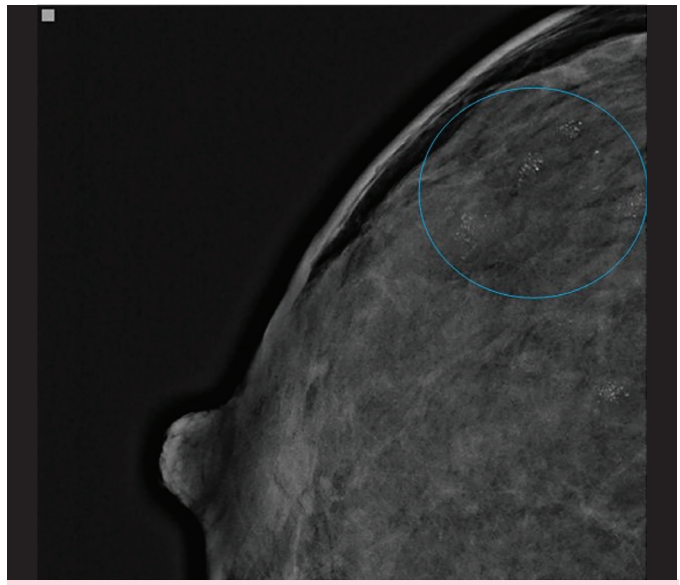

Figure 3. The mammographic view of the lateral part of the right breast shows a small cluster (blue circle) of calcifications in a 63-year-old female participant. A vacuum-assisted biopsy was performed, which revealed a flat epithelial atypia in the form of a cluster of microcalcifications. Department of Diagnostic and Interventional Radiology, Clinical Hospital Centre Rijeka

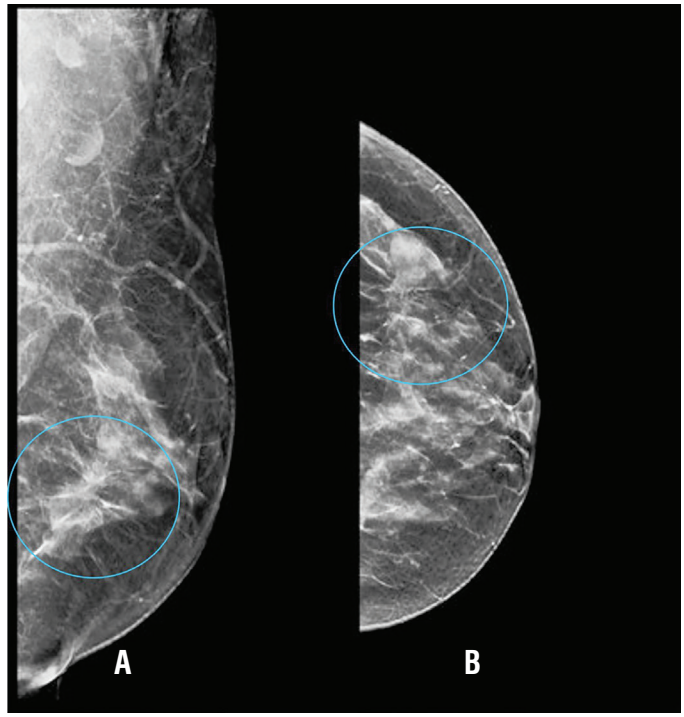

Figure 4. Mediolateral oblique (A) and craniocaudal (B) standard projections of the left breast of a 59-year-old female participant. The radial scar appears on mammography as an architectural distortion (blue circle). Department of Diagnostic and Interventional Radiology, Clinical Hospital Centre Rijeka

lesions. We observed no phyllodes tumors (PT) and only a few radial scars (Figure 4). The distribution of AIDEP was consistent with other studies (20–39%), while LN was slightly more common (10-21%) and other types of lesions were underrepresented (21-24).

Our results showed that no immediate upgrade to DCIS or invasive carcinoma occurred after VAE, while 30.8% of lesions treated with SE underwent an upgrade. Upgrade rates reported in the literature range from 3.6% to 21.5% overall (20-22, 24-28) and from 2.5% to 8.6% for VAE alone (29, 30). For B3 lesions with atypia after VAE, one study reported an upgrade rate of 20% (20).

The absence of upgrades in our VAE group may be explained by several factors. The exclusive use of tomosynthesis-guided VABB as the initial biopsy technique likely played a role, as it permits the retrieval of larger tissue volumes compared with CNB. Other published series that reported upgrades after VAE often used CNB or a combination of CNB and VABB for initial diagnosis, resulting in smaller tissue samples and a potentially higher risk of underestimation. However, the use of VABB alone does not fully account for the absence of upgrades in our VAE cohort, as lesions that were ultimately upgraded following SE had also been initially sampled with VABB. Importantly, baseline lesion characteristics differed between treatment groups. A higher proportion of atypical lesions was present in the SE group compared with the VAE group, reflecting differences in pre-procedural risk profiles. Therefore, the difference in upgrade rates cannot be attributed solely to the biopsy technique. Rather, it is more plausibly explained by the MDT-driven selection process: lesions referred for VAE generally demonstrated imaging-pathology concordance, limited extent of calcifications, and lower radiologic suspicion, whereas lesions triaged to SE more often exhibited features raising concern for potential underestimation despite adequate VABB sampling. Consequently, the absence of upgrades in the VAE group likely reflects careful MDT risk stratification and patient selection rather than differences in diagnostic sampling alone.

Our results support the view that VAE can safely replace SE in a subset of B3 lesions. In our study, VAE avoided open surgery in 34.4% of patients. Although this rate is lower than the 62% reported by Strachan et al. (30), with no adverse outcomes over a three-year follow-up, both studies support the role of VAE as a safe alternative to SE in appropriately selected cases.

The findings of our study should also be interpreted in the context of evidence indicating that follow-up after VABB may be sufficient for selected B3 lesions. In the study by Strachan et al. (30), VABB was performed after core biopsy in cases with B3 lesions, providing larger tissue samples, and no upgrades were observed during follow-up. Their results therefore support the safety of follow-up after VABB rather than indicating a specific need for VAE. In our cohort, no malignant upgrades occurred in patients for whom the MDT did not recommend SE, suggesting that these cases might also have been safely monitored without proceeding to VAE. Consequently, our data indicate that in carefully selected patients, particularly those for whom MDT consensus does not favor SE, follow-up based on high-quality VABB results may represent an appropriate and safe management strategy. In such scenarios, VAE may not be essential, and its use should be considered on an individualized basis rather than routinely applied. This interpretation reinforces the importance of MDT-guided stratification and supports a tailored approach to the management of B3 lesions. As the rate of malignant enhancement after VAE was low in our series, the majority of women can be diagnosed as benign without the need for further treatment.

Furthermore, B3 lesions are traditionally treated by SE, which is likely overtreatment given the low rate of malignant upgrades also demonstrated in this study. Importantly, even when VAE fails to completely resolve a lesion or when malignancy is subsequently identified, it offers the advantage of consolidating diagnosis and therapy into a single surgical procedure. This contrasts with the traditional two-step pathway of diagnostic excision followed by therapeutic surgery.

Of note, almost all upgrades were AIDEP lesions (6/8), which is consistent with recommendations in the literature that these lesions should be surgically removed. Our overall upgrade rate for AIDEP was 26.5%, and this rate includes all AIDEP lesions, regardless of whether they were managed with SE or VAE. As all upgrades occurred in the SE group, calculating the upgrade rate only within SE-treated AIDEP lesions yields a higher, selective upgrade rate of 40%, which is consistent with previously reported rates of 20.6 to 41% (21, 24, 28-32).

During follow-up, we observed progression of malignancy in one lesion treated with SE (6%), but no progression in B3 lesions treated with VAE. In previous studies, no progression of malignancy was observed in VAE-treated lesions during follow-up (29-31), with the exception of one group that reported a progression rate of 9.2% (16). In SE-treated lesions, progression rates range from 0% to 9.2% (20, 24, 32). The patient in our cohort developed breast cancer in the ipsilateral breast after four years of follow-up.

In the earlier years of our research, SE was predominantly recommended for almost all B3 lesions. In the last two years, VAE has become the preferred treatment (62%), with fewer cases treated with SE (28%) or retreatment (10%). This shift explains the shorter follow-up time for lesions treated with VAE, which may have influenced our results. However, the median follow-up time of 21 months is still remarkable.

Bianchi et al. (22) similarly analyzed B3 lesions detected by VABB that presented as calcifications directly removed by SE to

determine whether VABB alone was sufficient. Our study builds on this by including VAE as a second line for larger excisions, comparing it with SE, and including follow-up data. Bellini et al. (20) retrospectively compared SE and VAE, but included both mammographic and ultrasonographic lesions and had an unequal distribution of treatment modalities, with nearly 90% of patients undergoing SE. Furthermore, the immediate upgrade rates between VAE and SE were not compared. Strachan et al. (30) demonstrated that VAE safely prevented SE in 62% of cases, with no adverse events reported during a median follow-up of three years.

The main limitations of our study include the small overall sample size of only 64 patients, which limits the generalizability of the results, as well as the relatively small number of patients treated with VAE, which restricts the statistical power to detect rare adverse outcomes and precludes definitive conclusions regarding long-term safety and upgrade risk. In addition, the single-center design may introduce bias and limit the transferability of the results to other institutions with different resources or expertise. Finally, the shorter follow-up duration for patients treated with VAE, with a median follow-up of only 21 months, may lead to an underestimation of late complication or long-term outcomes.

In addition, some concerns about the generalizability of our results may paradoxically be due to the greater experience of the dedicated radiologists and pathologists at our institution, where all cases were collected. In other words, the specific subspecialities of the surgeons involved in this study may limit the generalizability of these results to centers with similar characteristics and likely explain the lower upgrade rates in our series compared to those reported in more recent summaries of the available literature.

Future larger prospective studies with a longer and consistent follow-up period are needed to more accurately assess the risk of malignant progression in B3 lesions treated with VAE. In addition, performing detailed analyses of different B3 subtypes would help to refine treatment strategies for specific lesion types. Nonetheless, current evidence favors a broader application of VAE to reduce the incidence of SE, which is associated with higher complication rates, scarring, and a greater economic burden.

In conclusion, VAE represents a minimally invasive procedure that can be safely performed in the outpatient setting under local anesthesia. Compared with SE, VAE is associated with smaller incisions, minimal scarring, and faster recovery. It provides sufficient tissue for accurate histopathological analysis and, in selected cases, enables complete removal of small benign and borderline breast lesions.

Based on our findings, VAE appears to be a safe and effective alternative to open surgery for carefully selected B3 lesions, particularly those without atypia and with imaging–pathology concordance, potentially reducing overtreatment. Nevertheless, appropriate patient selection remains crucial, and management decisions should be made within a multidisciplinary framework, taking into account lesion characteristics, patient factors, and institutional expertise.

Ethics

Ethics Committee Approval: This retrospective, single-centre study was approved by the Ethical Committee of Clinical Hospital Centre Rijeka, Croatia (date: 24 June 2020; approval number: 003-05/20-1/92).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.V.Z., A.C.P.; Concept: P.V.Z., N.B., A.C.P.; Design: P.V.Z., N.B.; Data Collection or Processing: J.R., L.V., M.M., M.A., A.C.P.; Analysis or Interpretation: J.R., L.V., M.M., M.A., A.C.P.; Literature Search: N.B., M.M.; Writing: P.V.Z., N.B., A.C.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Pittsburgh Classification and Treatment Algorithm for Idiopathic Granulomatous Mastitis: A Multicenter Cohort Study

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ABSTRACT

Objective: Idiopathic granulomatous mastitis (IGM) is a rare inflammatory breast condition lacking standardized treatment and with unpredictable outcomes. To address these issues, using clinical and ultrasound findings from an initial subset, we created the Pittsburgh Classification to stratify severity and developed a corresponding treatment algorithm for IGM, then evaluated its effectiveness in a larger cohort of IGM patients.

Materials and Methods: This retrospective multicenter study reviewed clinical and sonographic findings and outcomes of women with biopsy-proven IGM treated at multiple breast centers between 2020 and 2025. The Pittsburgh clinical classification ranges from Type 1 (minimal skin irritation) to Type 5 (widespread involvement); ultrasound classification spans Type A (localized mass ≤2 cm) to Type D (diffuse disease). Treatments were assessed utilizing the Pittsburgh algorithm, with responses classified as full response (CR), near-complete response (nCR), or no response (NR). Chi-square tests assessed associations ($p<0.05$).

Results: Of 522 patients included (mean age 37.0±8.8 years), 86.4% ($n = 451$) received algorithm-concordant treatment, achieving CR in 68.7% ($n = 310$), nCR in 35.3% ($n = 159$) and NR in 11.8% ($n = 53$). Among these, 65.4% (295/451) of patients with CR were concordant with the Pittsburgh treatment algorithm, whereas 13.6% ($n = 71$) patients received discordant treatments, with a significantly lower CR rate of 21.1% (15/71) ($p<0.001$). Multifocal disease was significantly more prevalent in NR (83.0%, 44/53) and nCR (70.4%; 112/159) patients compared to CR (20.6%; 64/310) ($p<0.001$), although lesion-based response rates were similar (CR 56.8%, nCR 57.0%, NR 56.6%). Regarding concordance with treatment algorithm, clinical Type 4 IGM was more prevalent in NR (67.9%; 36/53) and nCR (72.9%, 116/159), whereas in clinical Type 1 IGM, NR, nCR, and CR were 1.8% (1/53), 4.4% (7/159), and 30.6% (95/310), respectively ($p<0.001$). Surgery at presentation was preferred in 16.9% ($n = 88$) of patients, with 6% ($n = 30$) requiring subsequent surgical treatments to treat residual disease.

Conclusion: Concordance with the proposed IGM treatment algorithm based on clinical and ultrasound findings resulted in significantly higher CR rates. Multiple foci and stratified clinical types correlated with outcomes. Prospective global research is needed to validate these findings.

Keywords: Idiopathic; granulomatous; mastitis; classification; algorithm

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KEY POINT

- Concordance with the proposed idiopathic granulomatous mastitis treatment algorithm based on clinical and ultrasound findings resulted in significantly higher complete response rates. Multiple foci and stratified clinical types correlated with outcomes.

Introduction

Despite ambiguous incidence and prevalence data, the number of referrals for idiopathic granulomatous mastitis (IGM) to breast clinics has been increasing. Breast care providers may be challenged by IGM, an inflammatory breast disease, from diagnosis to treatment. Although the exact cause of the condition is unknown, unusual genetic variations, autoimmune reactions, infections, and hormone imbalances are thought to be contributing factors (1-5).

IGM clinical presentation ranges from mild parenchymal changes to severe inflammation with fistulae, often mimicking malignancy (6). Although IGM commonly occurs in peripheral areas of the breast, like periductal mastitis IGM may also present in the central breast. Ultrasonography (US), which can identify hypoechoic masses, ductal extension, and abscess collections, remains the recommended imaging method. Histological confirmation is necessary for the diagnosis of IGM once secondary granulomatosis has been ruled out following investigation of hormonal, microbiological, and autoimmune marker tests. As clinical and imaging features of IGM may overlap with malignancy, clinics with less experience commonly order magnetic resonance imaging (MRI) for IGM patients (7), but MRI has little impact on management.

The lack of established classification of IGM leads to inconsistent treatment choices, which range from observation to repeated aspiration of collections, intralesional steroid (ILS) injections, systemic therapies, and surgical operations alone or in combination (8-10). In contrast to the severe side effects of systemic therapy, ILS injections typically heal the lesion with minimal morbidity (10, 11).

Globally, IGM challenges healthcare systems, particularly in low-resource settings where advanced diagnostics are limited (6). It would be widely beneficial for patients and clinicians if a validated consensus treatment algorithm based on standardized clinical and imaging classifications was available. A treatment regimen has not been established because of the absence of agreed-upon clinical and radiological classification for IGM, and IGM treatments described in the literature have been devised based solely on clinical presentation. While some researchers have suggested that IGM classification and grading methods integrate clinical presentation with images, no recommended therapeutic algorithms have been evaluated in a large patient population (12-14).

Our multidisciplinary IGM group developed the Pittsburgh classifications and standardized treatment algorithm for histologically proven IGM management by integrating clinical and radiologic findings; we have presented this approach in scientific meetings (15). In this ambidirectional study, we sought to evaluate alignment of treatment with the Pittsburgh clinical and US classification with outcomes.

Materials and Methods

Study Design and Participants

Ethical Approval

The study was approved by the University of Health Sciences Türkiye, Bağcılar Training and Research Hospital Non-Interventional Clinical Research Ethics Committee Ethical Board of the lead center (date: 12.07.2024, protocol number: 2024/07/12/065) and all participating centers adhered to ethical standards in accordance with the Declaration of Helsinki.

This ambidirectional cohort study analyzed data from a large cohort of women with biopsy-proven IGM treated at multiple breast centers (from January 2020 to January 2025) including university hospitals, state/public/community hospitals, and stand-alone breast centers. Inclusion criteria were female sex, age ≥18 years, histologically confirmed IGM, and complete medical electronic records. Medical record data included age, follow-up, details of skin inflammation [erythema, mild skin thickening, skin discoloration, symptoms/signs of abscess (fever, pain, drainage, fluctuation)], skin ulcers, fistulae, number of IGM foci, and other ultrasound finding such as vascularity, surrounding tissue inflammation, skin thickening, and presence of any mass. Treatment of IGM was classified based on the choice of observation, oral systemic therapy, ILS injection, and/or surgery.

IGM was diagnosed based on histopathological examination of ultrasound-guided ≥14-g core needle or excisional biopsy samples. The diagnostic criteria included the presence of non-caseating granulomas, composed of epithelioid histiocytes, multinucleated giant cells, and lymphocytes, within the breast parenchyma, in the absence of identifiable infectious or systemic causes (2). Special stains, including Ziehl-Neelsen for acid-fast bacilli and periodic acid-Schiff for fungi, were routinely performed to rule out infectious etiologies, such as tuberculosis or fungal infections. In addition, other differential diagnoses, including malignancy and systemic autoimmune diseases, were excluded through

clinical evaluation, imaging, and histopathological analysis to confirm the idiopathic nature of the disease, ensuring diagnostic accuracy and consistency across all participating centers.

Exclusion criteria included incomplete data, secondary granulomatous mastitis, malignancy, or prior IGM treatment elsewhere. Data were extracted from electronic records, including demographics, clinical findings, US images, treatments, follow-up and outcomes.

Single-focus IGM was defined as a single, localized lesion or abscess within the breast, confirmed by ultrasound and histopathology, with no additional foci of disease. Multifocal IGM was characterized by the presence of two or more distinct lesions or abscesses, either within the same breast or bilaterally, as identified by ultrasound imaging. In this study, the numbers of multiple foci were recorded (i.e., 2, 3, or 4 foci) to assess the impact of variation in foci count on treatment outcomes. This distinction guided treatment decisions, with multiple foci often requiring more aggressive intervention, such as systemic steroids or surgical excision, due to their association with poorer response rates.

Pittsburgh Classifications

The Pittsburgh Classifications were developed through a collaborative effort involving breast surgeons, radiologists, and histopathologists to standardize the assessment and management of IGM.

Clinical classification Types 1–5 were established based on the severity and extent of clinical manifestations. These are defined as: No or minimal skin irritation (Type 1); minimal and solitary skin inflammation associated with abscess symptoms/signs, skin ulcers or fistulae (Type 2); palpable mass(es) with skin inflammation, without symptom/signs of abscess, skin ulcers or fistulae (Type 3); evident skin inflammation with or without symptom/signs of abscess, skin ulcers or fistulae (Type 4); and widespread involvement with fistulae and necrosis (Type 5) (Table 1). These categories were defined by consensus, based on clinical presentations observed in a preliminary cohort of IGM patients, with input from multidisciplinary team discussions.

Radiologic classification Types A-D were created based on sonographic findings, categorizing lesions from localized mass ≤2 cm with discrete boundaries (Type A), localized mass >2 cm with discrete boundaries (Type B), regional type with a mass >2 cm, duct extension and lacking discrete margins (Type C), and diffuse disease with extensive parenchymal involvement (Type D) (Table 2). The classifications were designed to integrate clinical and radiologic features to guide treatment decisions, ensuring consistency and reproducibility across different healthcare settings. These classifications were evaluated retrospectively, and the patient responses to treatments were documented.

Treatments

Proposed treatment recommendations (Table 3) were aligned with clinical and sonographic classifications. Less aggressive clinical Type 1 and US Type A treatment recommendation is observation, but, for clinical Type 5 or US Type D, treatment is more aggressive and ranges from oral steroid treatment to total mastectomy.

The standardized ILS protocol was 40 mg triamcinolone acetonide (diluted with 10 cc saline) per 2 cm lesion every 28–30 days with US guidance until resolution. For multiple lesions, 40 mg triamcinolone acetonide was injected per lesion up to 200 mg total dosage. Patients were monitored for injection site pain, skin atrophy, acne-like skin lesions, and allergic reactions.

Topical steroid protocol was 0.01% topical triamcinolone twice a day, starting the day after ILS until the ILS treatment was completed. Patients were again monitored for skin atrophy, acne-like skin lesion, and allergic reactions.

When methotrexate was chosen as the steroid for intralesional treatment, the IL methotrexate protocol was 12.5 mg for lesion ≤2 cm and 25 mg for a lesion >2 cm every 4 weeks until complete responce. Patients were monitored for injection site pain, allergic reactions, renal and hepatic failure.

The systemic steroid starting dose was 0.5–1 mg/kg/day of oral prednisone (maximum 60 mg/day), tapered over 4–8 weeks based on clinical response. Treatment duration varied depending on

Table 1. Idiopathic granulomatous mastitis Pittsburgh clinical classification

Type 1	No or minimal and solitary skin inflammation (erythema, mild skin thickening, limited skin discoloration (≤2 cm) without abscess symptoms/signs (i.e., fever, pain, drainage, fluctuation), skin ulcers and fistulae. No palpable mass(es)
Type 2	Minimal and solitary skin inflammation (erythema, mild skin thickening, limited skin discoloration (≤2 cm) associated with abscess symptoms/signs (i.e., fever, pain, drainage, fluctuation), skin ulcers and fistulae. No palpable mass(es)
Type 3	Palpable mass(es) with skin inflammation (any degree), without abscess (i.e., fever, pain, drainage, fluctuation), skin ulcers and fistulae symptoms/signs
Type 4	Evident skin inflammation (>2 cm area but less than half the breast or multiple erythema, moderate skin thickening) with or without abscess symptoms/signs (i.e. fever, pain, drainage, fluctuation), skin ulcers and fistulae. With or without mass(es)
Type 5	Widespread involvement (more than half of the breast) or recurrence after any treatment modality or progressive disease

symptom resolution, with a median duration of 6 weeks (range: 4–12 weeks). Patients were monitored for side effects, including weight gain, hyperglycemia, and mood changes, with dose adjustments made accordingly. In cases of inadequate response, second-line immunosuppressants, such as methotrexate, were considered.

Surgical excision was defined as the complete removal of IGM-affected breast tissue, including granulomatous lesions or abscesses. This procedure was reserved for refractory or recurrent cases of Type 3–4 IGM with radiologic Type C or D findings or Type 4–5 with Type D findings, as specified in the treatment algorithm. Excision typically involved wide local excision to achieve clear margins, minimizing residual disease. In severe cases, mastectomy was performed. To reduce the risk of recurrence, surgical excision of the residual disease was done in certain cases following a course of ILS injections.

Treatment Protocol Adherence and Outcome Measures

All treatments were performed following a consensus decision among breast surgeons and radiologists at each center. Furthermore, all treatment choices were retrospectively compared with the Pittsburgh IGM treatment algorithm recommendations.

Clinical response to treatment was categorized as follows:

• Complete response (CR): Resolution of all clinical and sonographic findings

• Near-complete response (nCR): Sonographic findings persist, but clinical symptoms resolved

• No response (NR): Persistent or worsening symptoms or emergence of new disease foci

Statistical Analysis

All statistical analyses were conducted using SPSS version 25.0 (IBM Inc., Armonk, NY, USA). Descriptive statistics were used for demographic and clinical data. The chi-square test was used to compare categorical variables. A p-value <0.05 was considered statistically significant.

Results

Among the 522 women included, with a mean age of 37.0±8.8 years (range 21–71) and a mean follow-up of 15.3±10.8 months, 491 (94.1%) had unilateral and 31 (5.9%) had bilateral IGM, yielding a total of 872 lesions. Single-focus disease was present in 302 patients (57.8%), whereas 220 (42.2%) had multifocal disease (124 with 2 foci, 62 with 3 foci, and 34 with 4 foci).

Based on the most severe lesion presentin each patient, 103/522 women had Type 1 (19.7%), 109 Type 2 (20.9%), 147 Type 3 (28.2%), 152 Type 4 (29.1%), and 11 Type 5 (2.1%) IGM (Table 4).

When considering all lesions (n = 872), the distribution was Type 1 (14.6%, n = 127), Type 2 (15.3%, n = 133), Type 3 (26.5%, n =

Table 2. Idiopathic granulomatous mastitis Pittsburgh ultrasound classification

Type A	Localized Mass(es): solid ± collection(s)	**Size: ≤2 cm** **Findings:** Single or multiple mass(es) with discrete boundaries. **Vascularity:** Internal vascularity on Doppler (solid); or no vascularity (suggesting collection). **Surrounding tissue:** Inflammation (increased echogenicity due to edema, ± dilated lymphatics, increased vascularity). **Skin:** No thickening (>2 mm) or fistula formation.
Type B		**Size: >2 cm** **Findings:** Single or multiple mass(es) with discrete boundaries. **Vascularity:** Internal vascularity on Doppler (solid); or no vascularity (suggesting collection). **Surrounding tissue:** Inflammation (increased echogenicity due to edema, ± dilated lymphatics, increased vascularity). **Skin:** No thickening (>2 mm) or fistula formation.
Type C	Regional type	**Size: >2 cm** **Findings:** Mass(es), duct extension, lacking discrete margins. **Vascularity:** Internal vascularity on Doppler (solid); or no vascularity (suggesting collection). **Surrounding tissue:** Increased echogenicity due to edema, ± dilated lymphatics, increased vascularity. **Skin:** No thickening (>2 mm) ± fistula formation.
Type D	Diffuse type	**Size:** Involves multiple quadrants. **Findings:** Mass(es), duct extension. **Vascularity:** Internal vascularity on Doppler (solid); or no vascularity (suggesting collection). **Surrounding tissue:** Increased echogenicity due to edema, ± dilated lymphatics, increased vascularity. **Skin:** Skin involvement (>2 mm, intradermal collection, direct extension of mass to involve overlying skin) ± irregular sinus tract.

231), Type 4 (38.1%, *n* = 332), and Type 5 (5.6%, *n* = 49) (Table 4A). Ultrasound types included Type A (22.4%, *n* = 195), Type B (17.3%, *n* = 151), Type C (33.3%, *n* = 290), and Type D (27.1%, *n* = 236) (Table 4B). Erythema nodosum was seen in 10 patients (1.9%).

Of the treatments given to the 522 women, 451 (86.4%) were concordant with the Pittsburgh Classifications algorithm and 71 (13.6%) were discordant. Among the 310 women who experienced CR, treatments included aspiration + ILS (46.1%, *n* = 143), observation (21.6%, *n* = 67), surgical excision alone (9.4%, *n* = 29), aspiration + systemic steroids (6.5%, *n* = 20), aspiration alone (6.1%, *n* = 19), surgical excision + ILS (3.9%, *n* = 12), ILS alone (2.6%, *n* = 8), systemic steroids alone (2.3%, *n* = 7), and surgical drainage + ILS (1.6%, *n* = 5). Overall, ILS (alone or combined) was used in 168/310 (54.2%) and systemic steroids in 27/310 (8.7%) of CR patients (Table 5). Pittsburgh treatment algorithm concordance and CR rates differed significantly by clinical type (both $p<0.001$). Patients with clinical Type 4 disease had the lowest concordance rate (67.1%) whereas ultrasound type had no significant impact on either Pittsburgh treatment algorithm concordance ($p = 0.42$) or CR ($p = 0.18$).

Topical steroids were used in 28.2% (*n* = 147) patients, independent of the algorithm, and erythema nodosum occurred in 1.9% (*n* = 10).

Treatment concordant with the Pittsburgh algorithm was strongly associated with response ($p<0.001$, Table 6). Among the 451 women with concordant treatment, 65.2% (295/451) achieved CR, 25.9% (117/451) nCR, and only 8.6% (39/451) exhibited NR. In contrast, among the 71 patients with discordant treatment, CR dropped to only 21.1% (15/71), while 59.2% (42/71) had nCR and 19.7% (14/71) were NR.

Compared to women receiving discordant treatment, algorithm-concordant patients had half the NR rate (8.6% *vs.* 19.7%) and a three-fold greater CR rate (65.2% *vs.* 21.1%) ($p<0.001$).

Topical steroids were applied in 28.2% (*n* = 147) of all patients. Primary surgery was performed in 16.9% (*n* = 88) patients; 15.3% (*n* = 69) in the algorithm-concordant group and 26.8% (*n* = 19) in the discordant group. An additional 30 procedures (27 wide local excisions, 3 mastectomies) were performed for residual or recurrent disease.

Multifocal disease (≥2 foci) was significantly more frequent in nCR (70.4%, 112/159), and NR (83%, 44/53) patients than in CR patients (20.6%, 64/310) ($p<0.001$).

All 31 bilateral cases were managed concordant with the algorithm, with CR in 51.6% (*n* = 16), nCR in 29 (*n* = 9), and NR in 19.4% (*n* = 6). None of the patients in this cohort received oral or intralesional methotrexate or other immunosuppressants.

Table 3. Idiopathic granulomatous mastitis Pittsburgh treatment algorithm

Clinical	Ultrasound	Recommended treatment
Type 1	**Type A** (no collection)	Observation
	Type B, C (no collection)	ILS or surgical removal of lesion with intraoperative ILS
Type 2	**Type A, B, C**	US-guided aspiration (possible I&D), then continue with ILS
Type 3	**Type A, B, C** (no collection)	ILS or Surgical removal of lesion with intraoperative ILS
	Type A, B, C (with collection)	US-guided aspiration + ILS where applicable
Type 4	**Type B, C** (no collection)	ILS + Low dose systemic therapy
	Type B, C (with collection)	US-guided aspiration (possible surgical I&D), then continue with ILS + Low dose systemic therapy
Any	**Type D**	Wide-spread involvement (more than half of the breast) or uncontrolled recurrence after any treatment modality; High dose systemic treatment + ILS if applicable, possible surgery (partial or total mastectomy), consider oral low dose or intralesional methotrexate injection
Type 5	**Any**	

If clinical inflammation seen, topical steroid should be added; ILS: Intralesional steroid injection; Uncontrolled refers to any disease that failed previous treatment; I&D: Incision and drainage

Table 4. Distribution of Pittsburgh clinical and ultrasound types

Clinical type	Patients (*n* = 522)	%	Lesions (*n* = 872)	%	Ultrasound type	Lesions (*n* = 872)	%
Type 1	103	19.7%	127	14.6%	Type A	195	22.4%
Type 2	109	20.9%	133	15.3%	Type B	151	17.3%
Type 3	147	28.2%	231	26.5%	Type C	290	33.3%
Type 4	152	29.1%	332	38.1%	Type D	236	27.1%
Type 5	11	2.1%	49	5.6%	-	-	-
Total	**522**	**100%**	**872**	**100%**	**Total**	**872**	**100%**

Table 4A. Pittsburgh clinical classification (patient-based *n* = 522, lesion-based *n* = 872), concordance with treatment algorithm, and response distribution

Clinical type	Patients (*n* = 522)	Lesions (*n* = 872)	Concordant treatment n (%)	CR patients n (%)	nCR patients n (%)	NR patients n (%)	CR lesions n (%)
Type 1	103	127	98 (95.1%)	95 (92.2%)	7 (6.8%)	1 (1.0%)	118 (92.9%)
Type 2	109	133	102 (93.6%)	100 (91.7%)	8 (7.3%)	1 (0.9%)	122 (91.7%)
Type 3	147	231	138 (93.9%)	115 (78.2%)	28 (19.0%)	4 (2.7%)	178 (77.1%)
Type 4	152	332	102 (67.1%)	0 (0%)	116 (76.3%)	36 (23.7%)	0 (0%)
Type 5	11	49	11 (100%)	0 (0%)	0 (0%)	11 (100%)	0 (0%)
Total	**522**	**872**	**451 (86.4%)**	**310 (59.4%)**	**159 (30.5%)**	**53 (10.1%)**	**418 (47.9%)**

CR: Complete response; nCR: Near-complete response; NR: No response

Table 4B. Pittsburgh ultrasound classification (patient-based *n* = 522, lesion-based *n* = 872), concordance with treatment algorithm, and response distribution

US type	Patients (*n* = 522)	Lesions (*n* = 872)	Concordance with treatment, n (%)	CR patients n (%)	nCR patients n (%)	NR patients n (%)
Type A	118	195	110 (93.2%)	98 (83.1%)	16 (13.6%)	4 (3.4%)
Type B	98	151	90 (91.8%)	84 (85.7%)	12 (12.2%)	2 (2.0%)
Type C	176	290	156 (88.6%)	134 (76.1%)	36 (20.5%)	6 (3.4%)
Type D	130	236	115 (88.5%)	104 (80.0%)	22 (16.9%)	4 (3.1%)
Total	**522**	**872**	**451 (86.4%)**	**310 (59.4%)**	**159 (30.5%)**	**53 (10.1%)**

CR: Complete response; nCR: Near-complete response; NR: No response

Table 5. Treatment modalities and treatment algorithm discordance

Treatment modality	CR (*n* = 310)	nCR (*n* = 159)	NR (*n* = 53)
Observation only	*67 (21.6%) **(0%)	7 (4.4%) 2 (28.6%)	0 (0%) (N/A)
Aspiration only	19 (6.1%) (0%)	20 (12.6%) 2 (10%)	10 (18.9%) 9 (90.0%)
Intralesional steroid (ILS) injection only	8 (2.6%) (0%)	3 (1.9%) (0%)	6 (11.3%) 3 (50.0%)
Aspiration + ILS	143 (46.1%) (0%)	51 (32.1%) 13 (25.5%)	5 (9.4%) (0%)
Systemic steroids only	7 (2.3%) 2 (28.6%)	20 (12.6%) 5 (25.0%)	2 (3.8%) 1 (50.0%)
Aspiration + systemic steroids	20 (6.5%) 2 (10.0%)	31 (19.5%) 2 (6.5%)	15 (28.3%) (0%)
Surgical drainage + ILS	5 (1.6%) (0%)	11 (6.9%) 6 (54.5%)	4 (7.5%) (0%)
Surgical excision + ILS	12 (3.9%) (0%)	2 (1.3%) (0%)	2 (3.8%) (0%)
Surgical excision only	29 (9.4%) 11 (37.9%)	14 (8.8%) 1 (7.1%)	9 (17.0%) 1 (11.1%)
Overall algorithm concordance	295/310 (95.2%)	117/159 (73.6%)	39/53 (73.6%)
Topical steroid use*	No	375 (71.8%)	
	Yes	147 (28.2%)	

CR: Complete response; nCR; Near complete response; NR: No response

*Numbers and percentages indicate the proportion of patients receiving each treatment.

**Numbers and percentages indicate discordance with the Pittsburgh algorithm.

N/A indicates that no patients received the treatment. Topical steroid use is reported for the entire cohort and is independent of specific treatment modalities

Table 6. Clinical, treatment, and response characteristics of IGM patients (*n* = 522)					
Characteristic	**Overall (*n* = 522)**	**CR (*n* = 310)**	**nCR (*n* = 159)**	**NR (*n* = 53)**	***p*-value**
					0.212
Unilateral breast IGM	491 (94.1%)	294 (94.8%)	150 (94.3%)	47 (88.7%)	
Bilateral breast IGM	31 (5.9%)	16 (5.2%)	9 (5.7%)	6 (11.3%)	
Number of Foci					<0.001
1	302 (57.9%)	246 (79.4%)	47 (29.6%)	9 (17.0%)	
2	124 (23.8%)	49 (15.8%)	55 (34.6%)	20 (37.7%)	
3	62 (11.9%)	9 (2.9%)	35 (22.0%)	18 (34.0%)	
4	34 (6.5%)	6 (1.9%)	22 (13.8%)	6 (11.3%)	
Multiple foci (≥2)	220 (42.1%)	64 (20.6%)	112 (70.4%)	44 (83.0%)	
Concordance with Pittsburgh treatment algorithm					<0.001
No	71 (13.6%)	15 (4.8%)	42 (26.4%)	14 (26.4%)	
Yes	451 (86.4%)	295 (95.2%)	117 (73.6%)	39 (73.6%)	
CR: Complete response, nCR; Near complete response, NR: No response; IGM: Idiopathic granulomatous mastitis					

Discussion and Conclusion

IGM is a rare, chronic inflammatory condition that primarily affects women between the ages of 30 and 45 years (1, 2, 16). In our cohort of 522 women, the mean age was 37.0 years. The unclear etiology of IGM, potentially involving hormonal, microbiological, rare genetic variants and autoimmune factors continues to challenge the standardization of treatment protocols (1, 2, 16-18). The broader age range observed in our cohort (21–71 years), including both younger and postmenopausal patients, highlights the heterogeneous nature of the clinical presentation of IGM. The autoimmune etiology of this disease is currently being discussed, as IGM patients respond well to immunosuppressive medications. This hypothesis may explain why IGM occurs in pre- and post-menopausal women (19).

Although microbiological agents such as Corynebacterium species have been proposed as an etiological mechanism, the histopathological analyses in our cohort, which used specific stains to rule out infectious etiologies, suggest that such microbiological agents may be present in the process only once the main trigger for IGM has occurred or infectious agents contribute to the progression of IGM (1, 17). Multifactorial etiology complicates treatment decisions.

In our series, patients with multiple foci (42.0% of our cohort) or severe clinical types (Type 4: 37.9%, Type 5: 5.6%) exhibited poorer response rates, potentially reflecting more aggressive inflammatory processes driven by a combination of these factors, though those with bilateral disease did not have worse outcomes. This variability underscores the value of a standardized approach, such as the Pittsburgh classifications, which integrates clinical and sonographic features to tailor interventions, addressing the challenge of heterogeneous disease presentations. For instance, the greater frequency of Type 4 disease in non-responders (67.9%) suggests that in order to improve outcomes, severe cases might need to be escalated to systemic therapy or surgery earlier. Future studies should explore biomarkers, such as cytokine profiles or hormonal receptor expression, to elucidate the relative contributions of these etiological factors and guide personalized treatment strategies (18).

Multiple classification and grading proposals are available in the literature but none of them have been adopted extensively worldwide. One of the reasons for this is that there is no commonly accepted IGM classification because of a lack of radiologic uniformity of diagnosis. The most common imaging modalities are US, mammography, and MRI. Radiological characteristics of IGM are non-specific and can overlap with those of malignant tumors. Irregular masses and focal asymmetry are common mammographic findings, but mammography can cause severe discomfort and pain, especially in patients with extensive swelling, infection, or abscesses. Ultrasound is considered the first-line imaging modality in IGM patients, and MRI in selected patients, especially to distinguish from malignancy (20-24).

The first proposed management algorithm based on imaging modalities was reported in 2017, but there was no detailed clinical and imaging characterization of lesions, such as size, abscess formation, or number of lesions in the same breast (8). Later, scoring and staging systems were developed to predict recurrence and steroid response. In this study, patients received corticosteroid treatment for three months and then the dose was tapered in three days. Surgical excision of IGM was the treatment approach in patients with incomplete response, recurrence and in patients who were non-complaint with the corticosteroid treatment. The authors created a prediction score for recurrence, taking statistically significant variables into consideration including number of births, duration of lactation, body mass index, presence of fistulae, abscess formation detected on US examination and luminal inflammation. The presence of each

risk factor was given 1 point and then a total risk score was then calculated for each patient. The mean IGM score was significantly different in with and without recurrence patients (5.1 *vs.* 1.9, respectively; $p<0.001$) (14).

Another study considered US-based staging and the estimate of ILS injection response (25). These authors used their own classification and graded from I to IV. Grade I was irregular mass, grade II with tubular extensions and skin thickening, grade III with extensive fistula/sinus tracts draining to the skin and grade IV A sequela of any grade mostly characterized by hypoechoic foci. They compared 40 and 80 mg methylprednisolone sodium injection dosage in 230 patients. ILS injections were done every three weeks. It was concluded that high-dose of ILS injection was effective in grades II and III and also hypothesized that observation for management of grade I should be considered.

Four clinical patterns (A, B, C, D) were proposed in 68 patients in another study (12). Clinical patterns were classified as A: painless breast mass, B; painful breast mass with gross inflammation, C; a breast abscess-like presentation and D: a subacute presentation with ulceration, sinus, or fistula formation. In this study the patients in pattern A received no steroid treatment and although the median follow-up time was not given, the authors stated that patients in this pattern who had wide local excision had zero recurrence. Oral prednisolone was given in 49% of patients in patterns B, C and D and overall recurrence rate was 32%. This study did not provide a treatment algorithm based on clinical patterns but gives information of the high recurrence risk in severe clinical patterns.

In another study the authors classified IGM as diffuse type, sheet hypoechoic type, localized abscess type and localized hypoechoic mass type in 30 patients (26). Their treatment was initial dosage of methylprednisolone was 20 mg/day, which was reduced to 16, 12, 8, 4 mg/day every 1–2 weeks until the drug was stopped. They performed minimally invasive rotary cutting surgery in patients with no obvious acute inflammation and the mass remained stable and localized after glucocorticoid therapy, or when the diameter of the newly diagnosed lesion was less than 2 cm, or there were contraindications for glucocorticoid use or the patient refused to use glucocorticoid. The median follow-up was 12 (4–42) months. Recurrence was seen in 3 cases (10.00%) and they were all in the sheet hypoechoic type. Although this alternative minimally invasive approach for treatment of IGM showed promising results, US classification made no mention of multiple IGM lesions and clinical correlation was missing.

Recently a consensus report and Turkish Clinical classification was published (13). This consensus report for treatment and follow-up was reached with 62 medical professionals experienced in managing IGM. Type 1 to Type 4 clinical variables were size, skin inflammation, skin ulcers/sinus, presence of systemic findings, multiple foci, recurrence and treatment resistance. The majority of this consensus voted for observation of 81% in Type 1 and 85% patients in pregnancy/lactation. For Type 2 disease, ILS injection (66%), observation ± drainage (62%), and topical steroids (60%) were similarly favored as first-line treatments, and for Type 3 disease, systemic steroids achieved consensus as the first-line treatment (84%). For Type 4 resistant cases, consensus was reached on combination therapies (82%). This paper provided a clinical classification that did not include combination with imaging. Data-driven prospective research should be used to test survey-based studies.

The Pittsburgh Classification offers a comprehensive framework by integrating clinical (Types 1–5) and radiological (A-D) features to guide treatment strategies. In the present study we tested our classification and treatment algorithm in a cohort of 522 patients with histopathologically confirmed IGM. In this analysis, 86.4% of patients received treatment in accordance with this algorithm, yielding a CR rate of 65.4% among compliant patients compared to only 21.1% in the non-compliant group ($p<0.001$). Notably, all bilateral cases (5.9% of the cohort) were managed according to the algorithm. In a subgroup analysis, patients with multifocal disease ($n = 220$) had significantly lower CR (29.1%, $n = 64$) compared to those with single-focus disease (81.4%, $n = 246$) ($p<0.001$, Table 6).

Regarding treatment methods, the combination of aspiration and ILS injections emerged as the most often used and effective technique among patients who achieved CR (46.1%; 143/310). Corticosteroid phobia, which is defined as fear of the side effects of corticosteroids, is one of the primary causes (80%) of poor treatment compliance, even though oral steroid treatment was previously advised as a first-line treatment for IGM (27). In contrast, ILS injections have a great healing rate and few side effects, and it is well-accepted by patients as well as physicians (10,11). In the literature it has been reported that high dose systemic corticosteroids and immunosuppressants were reserved for severe or recurrent cases (28-30). In our study, no patient received oral or IL methotrexate and azathioprine.

Primary surgical intervention was performed in 16.9% (88/522) of patients overall and was significantly less frequent among algorithm-compliant patients (15.3%, 69/451) compared to the non-compliant group (26.8%, 19/71). An additional 30 surgical procedures were required for residual or recurrent diseases. Our findings support current recommendations that surgical intervention should be considered only after failure or intolerance of conservative approaches (31-34).

Our study outcomes support the view that for effective management and to prevent needless procedures, an accurate diagnosis of IGM is essential. Clinical, radiological, and histological findings must be integrated using a multidisciplinary team approach.

Study Limitations

The ambidirectional design of the study limits our ability to establish causal relationships. The median follow-up duration of 15.3 months may not fully capture long-term recurrence rates. In certain subgroup analyses, direct chi-square comparisons were limited. Minor discrepancies in the initial classification of clinical types were corrected following data review. In this study we did not evaluate the complications of each treatment. Although the literature suggests using MRI as a tool in differential diagnosis and disease assessment (21, 35), our study did not include MRI data in addition to US. Finally, the relatively small number of bilateral cases (n = 31) limits the generalizability of subgroup-specific conclusions.

IGM requires a multidisciplinary, tailored therapeutic approach due to its heterogeneous clinical presentation. The Pittsburgh Classification and treatment algorithm have demonstrated clinical efficacy in standardizing treatment decisions and significantly improved CR rates (65.4% *vs.* 21.1%, $p<0.001$). In particular, patients with multifocal disease and more severe clinical types (Type 4–5) are more likely to experience poor treatment outcomes if not managed according to algorithmic guidance. Early consideration of systemic therapies or surgical intervention may enhance outcomes in this subgroup. Prospective and long-term studies are needed to confirm these findings and assess recurrence rates.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Bağcılar Training and Research Hospital Non-Interventional Clinical Research Ethics Committee Ethical Board of the lead center (date: 12.07.2024, protocol number: 2024/07/12/065) and all participating centers adhered to ethical standards in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.S., M.T., H.Ö.A., M.A.N., S.Ö., B.Y., E.B.M., W.A.B.; Design: A.S., M.T., H.Ö.A., M.A.N., S.Ö., B.Y., E.B.M., W.A.B.; Data Collection or Processing: A.S., M.T., H.Ö.A., M.A.N., S.Ö., B.Y.; Analysis or Interpretation: A.S., M.T., H.Ö.A., M.A.N., S.Ö., B.Y., E.B.M., W.A.B.; Literature Search: A.S., M.T., H.Ö.A., M.A.N., S.Ö., B.Y., E.B.M., W.A.B.; Writing: A.S., M.T., H.Ö.A., M.A.N., S.Ö., B.Y., E.B.M., W.A.B.

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ORIGINAL ARTICLE

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A Comparative Analysis of Complications and Patient-Reported Outcomes in Implant-Based Breast Reconstruction with Polytetrafluoroethylene (PTFE) versus Allogeneic Dura Mater (DM)

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ABSTRACT

Objective: Mastectomy with immediate reconstruction is a primary surgical treatment for breast cancer. While both synthetic meshes and biological grafts are used in these procedures, their comparative effectiveness requires further investigation. This study evaluates the use of polytetrafluoroethylene (PTFE) mesh versus allogeneic dura mater (DM) in direct-to-implant breast reconstruction for reinforcing the inframammary fold (IMF) and stabilizing the implant.

Materials and Methods: A prospective, randomized, open-label trial enrolled 116 patients (192 breasts) who underwent subcutaneous or skin-sparing mastectomies or subtotal radical resections, all followed by immediate subpectoral implant-based reconstruction. Participants were randomized to receive either a PTFE mesh (60 patients; 96 breasts) or a DM graft (56 patients; 96 breasts) for implant support. Outcomes were assessed through radiological imaging for complications, anthropometric measurements for IMF and implant stability, and the breast evaluation questionnaire version 2.0© (reconstruction module) for quality of life.

Results: The PTFE group demonstrated a lower rate of major complications (3 vs. 7, respectively), while minor complications were comparable (23 vs. 28, respectively). Anthropometric analysis demonstrated that PTFE mesh provided superior stabilization of the IMF and the implant position postoperatively. Quality of life scores were comparable between the two groups.

Conclusion: The use of PTFE mesh in immediate subpectoral breast reconstruction provides reliable anti-gravitational stabilization of the IMF and implant, and is associated with a favorable complication profile and high patient-reported quality of life.

Keywords: Breast reconstruction; dura mater; inframammary fold; polytetrafluoroethylene; quality of life

KEY POINTS

- Implant-based breast reconstruction utilizing either polytetrafluoroethylene (PTFE) mesh or dura mater allografts resulted in similarly favorable complication profiles.
- The synthetic PTFE mesh demonstrated significant advantages in maintaining both implant position and inframammary fold definition.
- Patient-reported outcomes measured by quality of life assessment tools confirmed high satisfaction rates with both reconstruction materials.

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Introduction

Breast cancer constitutes a major global health challenge, exerting a profound medical, social, and psychological burden on populations worldwide (1). Radical mastectomy remains the most frequent operation in the surgical treatment of breast cancer; however, it is usually associated with significant psychological trauma due to loss of the breast (2, 3). Immediate breast reconstruction has thus gained significant importance, as it enables the restoration of natural breast contours concurrently with the oncological operation (4). This approach has proven effective in reducing psychological distress, improving overall quality of life (5-7), and offering economic advantages over delayed reconstruction by minimizing the number of surgical interventions and reducing the time to adjuvant therapy (8). Nevertheless, immediate reconstruction demonstrates oncological safety comparable to that of mastectomy alone, without increasing the risk of local recurrence or distant metastasis (9).

The inframammary fold (IMF) is a critical anatomical structure for achieving a stable aesthetic outcome in implant-based breast reconstruction. Its integrity is often compromised during mastectomy or resection, necessitating specific surgical techniques for restoration. While numerous methods for IMF reconstruction have been described in the literature, none has yet emerged as an optimal solution or a universally accepted "gold standard" (10).

Current literature on implant-based breast reconstruction indicates a shift in focus from biological matrices, such as acellular dermal matrices, to synthetic alternatives (11).

Our study investigates the application of a polytetrafluoroethylene (PTFE) mesh for IMF retention and implant stabilization in direct-to-implant breast reconstruction. The selected material has a well-established safety and efficacy profile in various surgical fields, including hernioplasty (12, 13), neurosurgery (14), cardiovascular surgery (15, 16), and blepharoplasty (17). The control group underwent IMF stabilization using lyophilized autologous dura mater (DM), an established technique with documented clinical applications in ophthalmologic practice (18), maxillofacial practice (19), and neurosurgical practice (20), which has been previously investigated for breast reconstruction (21).

Materials and Methods

Study Population

The study was a prospective, randomized, open-label, controlled, comparative, parallel-group trial designed as a test for equality. The study employed simple (unstratified) randomization, which was a deliberate methodological choice for this pragmatic comparative trial. Patient enrollment and data collection were conducted between December 2022 and May 2025. The primary evaluation endpoints included the analysis of postoperative complications, quality-of-life assessment via the breast evaluation questionnaire (BREAST-Q) version 2.0© reconstruction module, and controlled anthropometric measurements of principal breast landmarks. The study enrolled 116 patients (192 breasts) who underwent subcutaneous or skin-sparing mastectomies or wide local excision (removing up to 90% of the glandular tissue and was performed for multiple benign lesions), followed by immediate implant-based subpectoral breast reconstruction using a reinforcing material. Patients were pre-randomized into two groups: the PTFE group (study group, 60 patients, 96 breasts) and the DM group (control group, 56 patients, 96 breasts). Inclusion criteria for the study were: female sex, Caucasian ethnicity, age ≥18 years, and a subcutaneous adipose tissue thickness of ≤2 cm. Demographic characteristics and pathologies for both groups are presented in Table 1. The data are reported per breast rather than per patient, as the breast was the primary unit of analysis in this study.

The study was approved by the Local Ethics Committee of Federal Scientific and Clinical Center for Specialized Types of Medical Assistance and Medical Technologies of the Federal Medical-Biological Agency (FGBU FNKTS FMBA of Russia) (approval no: 5_2022, date: 07.06.2022) and was registered on ClinicalTrials.gov under the identifier NCT06931548. Informed consent for participation in the study and for pre- and postoperative surveys was obtained in the presence of the investigating physicians prior to surgery and again at 6 months postoperatively.

Polytetrafluoroethylene Mesh

The PTFE mesh (Ecoflon Scientific and Production Complex, Russia) utilized in this study was a non-resorbable, porous, perforated membrane with a thickness of 0.2 mm and perforation diameters of 2.5 mm. The PTFE mesh was supplied in a dome configuration with a diameter of 14 cm and a radius (arc width) of 7 cm. PTFE is approved by the United States Food and Drug Administration (FDA) for applications including cardiovascular grafts and sutures, and its use complies with European regulatory standards. The material pyrogen-free, non-toxic, chemically inert, and biocompatible. The porous architecture of the PTFE mesh is hypothesized to facilitate host tissue integration, while the perforations allow for effective drainage of the breast implant pocket.

Dura Mater Graft

The acellular lyophilized DM allograft (Lyoplast®, Russia) was crescent-shaped, with a thickness of up to 2.5 mm. The DM graft had dimensions of 13–4 cm long and 7–8 cm wide, as provided by the manufacturer. This graft is FDA-approved for

neurosurgical applications and is a biodegradable and bioinert material. It is capable of mimicking native tissue without initiating inflammatory or adhesive processes. Despite the long-standing clinical use of DM, the precise timeline for its complete resorption and biodegradation in soft tissues is not well-defined in the literature. However, a fundamental study from 2014 demonstrated that vascular ingrowth into the DM thickness is evident by day 30, and that by day 70, although the connective tissue framework becomes more fragmented, it does not lose its barrier function (22).

Complications

Postoperative complications were defined as the primary endpoint of this pragmatic trial, as they represent the most objective measure for comparing the materials, thereby minimizing the confounding effects of non-standardized surgical techniques. They were monitored over a 6-month period following surgery and categorized as either having general surgical or aesthetic complications. The general surgical complications included seromas persisting for more than one month, hematomas, marginal necrosis, and infectious complications. Aesthetic complications included prosthesis dislocation and animation deformity.

Additionally, complications were classified as major if they required surgical revision and minor if they resolved with conservative outpatient management (23). Capsular contractures were evaluated separately, as they did not demonstrate clinical significance within the scope of this study.

BREAST-Q

The BREAST-Q version 2.0© (reconstruction module) is a validated, patient-reported outcome instrument designed to assess quality of life. All participants completed the questionnaire preoperatively and at 6 months postoperatively, specifically, the psychosocial well-being, sexual well-being, and satisfaction

Table 1. Patient and breast surgery characteristics

	DTI breast reconstruction with PTFE mesh (n = 96)	DTI breast reconstruction with dura mater graft (n = 96)	p-value
Age, mean ± SD	48±9.18 year	52.5±9.83 year	0.06[a]
BMI, mean ± SD	22.9±2.52 kg/m^2	22.95±2.33 kg/m^2	0.85[a]
Smoking, n (%)	12 (12.5)	9 (20.8)	0.65[b]
Breast cancer, n (%)	68 (70.8)	73 (76)	0.41[b]
pTis (DCIS) N0 M0 (stage 0), n	9	5	0.6[c]
pT1 N0 M0 (stage I), n	28	35	
T0-1 N1 M0/T2 N0 M0 (stage IIA), n	20	20	
T2 N1 M0/T3 N0 M0 (stage IIB), n	11	13	
Fibroadenomas and other nodular mastopathies, n (%)	22 (22.9)	18 (18.8)	0.48[b]
Genetic predisposition, n (%)	6 (6.6)	5 (5.2)	1[c]
Type of breast surgery			
Subcutaneous mastectomy, n (%)	69 (71.9)	74 (77.1)	0.74[c]
Skin-sparing mastectomy, n (%)	5 (5.2)	4 (4.2)	
Wide local excision, n (%)	22 (22.9)	18 (18.8)	
Type of lymphnode surgery			
SLNB, n (%)	51 (53.1)	57 (59.4)	0.71[c]
ALNB, n (%)	17 (17.7)	15 (15.6)	
Neoadjuvant CHT, n (%)	37 (38.5)	28 (29.2)	0.22[b]
Adjuvant CHT, n (%)	41 (42.7)	28 (29.2)	0.07[b]
Radiotherapy, n (%)	17 (17.7)	15 (15.6)	0.7[b]
Implant volume			
200–300 cc, n (%)	25 (26)	25 (26)	0.62[a]
310–400 cc, n (%)	46 (47.9)	51 (53.1)	
410–525 cc, n (%)	25 (26)	20 (20.8)	

DTI: Direct-to-implant; PTFE: Polytetrafluoroethylene; BMI: Body mass index; CHT: Chemotherapy; SLNB: Sentinel lymph node biopsy; ALNB: Axillary lymph node biopsy; ALND: Axillary lymph node dissection; DCIS: Ductal carcinoma *in situ*; [a]: Mann-Whitney U test; [b]: Pearson's chi-square test; [c]: Fisher's exact test; SD: Standard deviation

with breast domains. Data from the physical well-being: chest domain were also collected but excluded from the final analysis because they were deemed non-informative. Patient responses for each domain were converted into scores on a 100-point scale using the official BREAST-Q conversion tables, where higher scores indicate better quality of life.

Anthropometric Measurements

To assess the positions of the IMF and the breast implant, standardized measurements were taken from the nipple to each of the following landmarks: the IMF, the anterior midline, the midclavicular point, and the jugular notch. These measurements were performed intraoperatively at the conclusion of the procedure and at the 6-month postoperative follow-up. The resulting changes in distances were analyzed to evaluate the efficacy of the PTFE and DM stabilization techniques.

Patient-reported quality of life and anthropometric measurements were analyzed as secondary endpoints, acknowledging that these outcomes could be influenced by factors beyond the material type, such as individual patient variables and surgical technique.

Surgical Technique

Preoperative lymphoscintigraphy with technetium-99 identified the sentinel lymph nodes. All procedures were performed under general anesthesia. Surgery commenced with a separate axillary incision for sentinel node biopsy, guided by gamma detection. If the frozen section confirmed metastases, level I–II lymph node dissection was performed.

The type of breast surgical procedure performed (subcutaneous mastectomy, skin-sparing mastectomy, or wide local excision) was selected based on clinical and anatomical factors. Surgical access was via an IMF incision, an inverted-T incision, or an S-shaped incision. Retroareolar tissue was submitted for frozen-section analysis to assess involvement of the nipple-areolar complex.

Following tumor resection, reconstruction began. After hemostasis, a subpectoral pocket was created. A crescent-shaped PTFE mesh was sutured to the inferior border of the pectoralis major and to the projected neo-IMF using continuous Vicryl 3–0 sutures, thereby forming a hammock-like implant pocket. Thus, the upper pole of the implant was covered by the muscle, while the lower pole was supported by the PTFE mesh. A drain was placed prior to layered closure (Figure 1).

Reconstruction using allogeneic DM was performed according to the PTFE technique. Prior to application, the lyophilized DM was rehydrated intraoperatively by immersion in 0.9% normal saline containing a broad-spectrum antibiotic for 3 minutes, in accordance with the manufacturer's instructions. The graft was then fixed identically using a continuous absorbable suture (Figure 2).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 23 and Microsoft Excel 2016. We employed descriptive statistics (mean, median, frequency), correlation analysis, and both parametric and non-parametric tests. Group comparisons utilized the Mann-Whitney U test for quantitative variables and the chi-square or Fisher's exact test for categorical data. Results were visualized through contingency tables and diagrams.

Results

A total of 192 cases of immediate implant-based breast reconstruction using additional coverage materials (PTFE or DM) in 116 patients were analyzed. Key patient and surgical data are summarized in Table 1. The groups were comparable in demographic characteristics and treatment methods. The median follow-up period was 14±5 months, with a minimum required follow-up of 6 months.

Among the malignant neoplasms, invasive ductal carcinoma was the most prevalent, identified in 47 cases in the PTFE group and 52 cases in the DM group. Based on molecular genetic typing, the luminal A subtype was the most frequently observed, found in 26 and 41 cases in the PTFE and DM groups, respectively. In 11 cases, prophylactic mastectomies were performed after somatic mutations in the *BRCA1, BRCA2*, or *CHEK2* genes had been identified prior to surgery.

In the PTFE group, postoperative complications were recorded in 26 cases (27.1%): 21 general surgical complications (21.9%) and 7 aesthetic complications (7.3%). Two cases presented with combined general surgical and aesthetic complications.

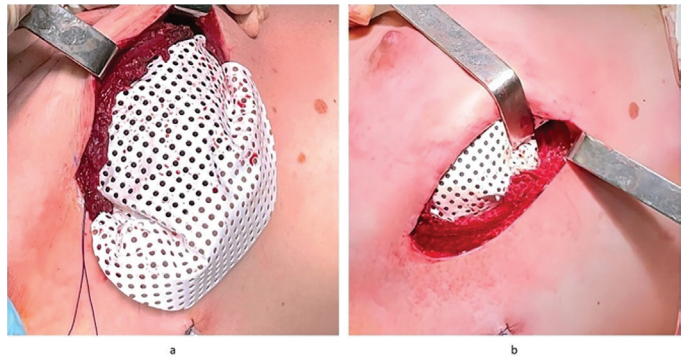

Figure 1. a. Fixation of the perforated porous PTFE mesh to the inferior border of the mobilized pectoralis major muscle, b. fixation of the perforated porous PTFE mesh to the projected neo-inframammary fold

PTFE: Polytetrafluoroethylene

Three cases required surgical revision. Other complications were successfully managed conservatively. The six-month postoperative outcome of breast reconstruction using PTFE is presented in Figure 3.

The DM group experienced complications in 34 cases (35.4%), including 24 general surgical complications (25%) and 15 aesthetic complications (15.6%). Five cases showed combined complications, and seven required reoperation.

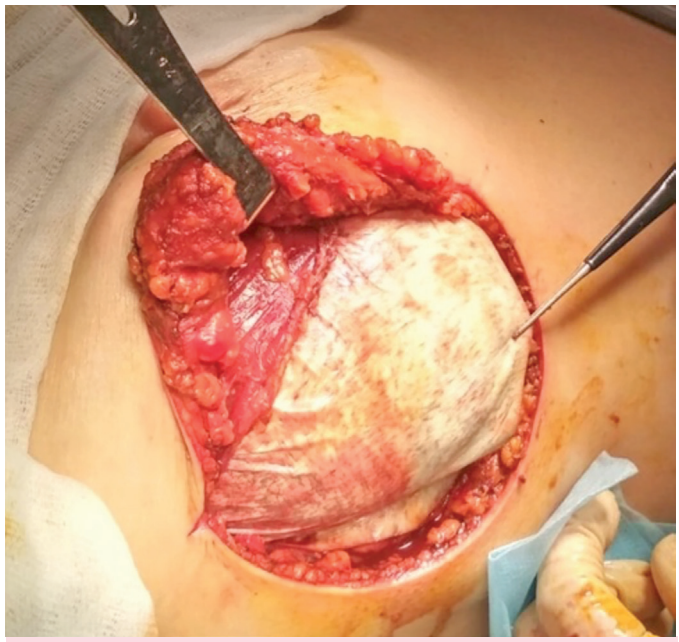

Figure 2. Stage of creating a subpectoral implant pocket using dura mater graft

In seven implant displacement cases, surgical correction was declined. The complete list of complications, with a detailed frequency analysis, is presented in Table 2.

Capsular contractures graded 0–II on the Baker classification were recorded separately because they were clinically insignificant. However, patients who underwent radiotherapy demonstrated significantly greater capsular severity ($p<0.05$).

Despite comparable overall complication rates between the study groups, statistical analysis revealed a significant association ($p<0.05$) between marginal skin necrosis and smoking history. Specifically, 9 out of 11 necrosis cases (81.8%) occurred in smokers.

Anthropometric Measurements

The positions of the IMF and the implant were assessed by measuring distances between anatomical landmarks immediately after surgery and at 6 months postoperatively. Evaluation of these topographic changes identified significant implant displacement (defined as a change >1 cm in any measured distance) in 4.2% ($n = 4$) of the PTFE group and in 10.4% ($n = 10$) of the DM group (Table 3).

Postoperative analysis identified several patient factors influencing reconstruction stability. A significant age-dependent effect was observed, with older patients exhibiting a pronounced tendency toward greater displacement of both the implant and the IMF.

A statistically significant correlation was found between larger implant volumes and increased displacement of the prosthesis

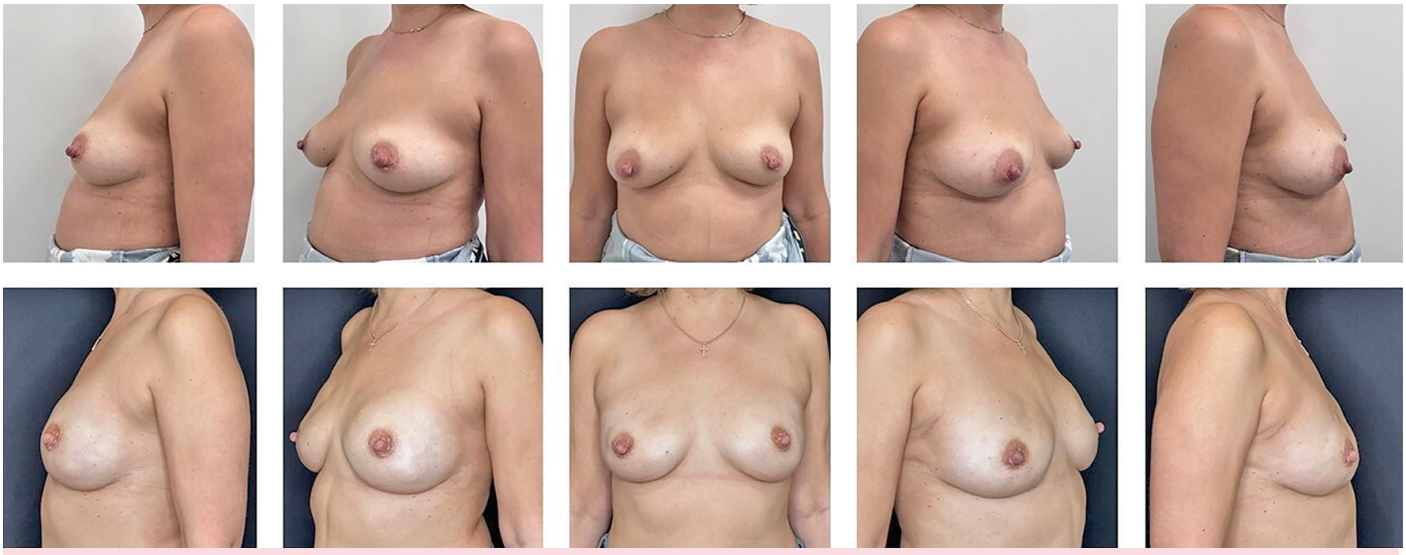

Figure 3. Clinical photographs of a 52-year-old patient with bilateral breast cancer. Above: preoperative appearance. Below: 6-month postoperative outcome following bilateral subcutaneous mastectomy with immediate subpectoral reconstruction using 325 cc implants and polytetrafluoroethylene mesh

and IMF. Furthermore, higher body mass index (BMI) was associated with reduced implant stability, indicating increased implant mobility postoperatively.

BREAST-Q

Patient-reported quality of life was assessed using the BREAST-Q version 2.0© (reconstruction module) preoperatively and at 6 months postoperatively. The two study groups had nearly identical quality of life scores at both time points (Table 4). A trend toward a decline in psychosocial and sexual well-being was observed following reconstruction in both cohorts, although these changes did not reach statistical significance, as noted previously.

Bilateral breast reconstruction was performed on 76 patients (36 in the PTFE group and 40 in the DM group). A comparative analysis of postoperative BREAST-Q scores revealed no statistically significant differences in outcomes between these patients and those who underwent unilateral surgery.

The sexual well-being questionnaire was completed by 41 patients in the PTFE group and 34 in the DM group. In total, 19 (31.7%) and 22 (39.3%) patients in the respective groups declined to complete this module, citing the absence of sexual activity at the time of the study.

Notably, statistical analysis of the "satisfaction with breasts" module revealed similar scores before and after surgery. This finding can be attributed to a subset of patients reporting higher satisfaction with their breasts postoperatively than preoperatively.

A more detailed analysis confirmed a sustained age-related correlation, with older patients exhibiting statistically significantly lower scores in both sexual well-being (assessed pre- and postoperatively) and preoperative satisfaction with breasts.

Discussion and Conclusion

Breast cancer remains a significant medical and social problem requiring comprehensive treatment and rehabilitation. Although breast-conserving techniques are widely used (70–80% of cases), mastectomy remains indicated for 20–30% of patients.

Table 2. Incidence and spectrum of complications across the study groups

	DTI breast reconstruction with PTFE mesh (*n* = 96)	DTI breast reconstruction with dura mater graft (*n* = 96)	*p*-value
Major complications, n breasts (%)*	3 (3.13)	7 (7.29)	0.33[b]
Minor complications, n breasts (%)*	23 (23.96)	28 (29.17)	0.51[a]
General surgical complications, n breasts (%)*	21 (21.9)	24 (25)	0.55[a]
Seroma, n (%)	13 (13.5)	17 (17.7)	0.55[a]
Hematoma, n (%)	3 (3.1)	2 (2.1)	1[b]
Infections, n (%)	1 (1)	3 (3.1)	0.62[b]
Marginal necrosis, n (%)	5 (5.2)	6 (6.3)	1[b]
Aesthetic complications, n breasts (%)*	7 (7.3)	15 (15.6)	19[a]
Prosthesis dislocation, n (%)	4 (4.2)	10 (10.4)	0.16[b]
Animation deformity, n (%)	4 (4.2)	9 (9.4)	0.25[b]
Capsular contractures			
Grade I, n (%)	41 (42.7)	54 (56.3)	0.83[a]
Grade II, n (%)	8 (8.3)	14 (14.6)	0.26[b]

*: Complications were recorded as binary events (present/absent) for each type, regardless of co-occurrence of multiple complication types in a single breast; [a]: Pearson's chi-square test; [b]: Fisher's exact test; DTI: Direct-to-implant; PTFE: Polytetrafluoroethylene

Table 3. Topographic changes in breast landmarks: 6-month postoperative assessment

	DTI breast reconstruction with PTFE mesh (*n* = 96)	DTI breast reconstruction with dura mater graft (*n* = 96)	*p*-value
Nipple to inframammary fold (cm), mean ± SD	0.3±0.1	0.6±0.3	<0.05[a]
Nipple to mid-clavicular point (cm), mean ± SD	0.3±0.1	0.5±0.3	<0.05[a]
Nipple to jugular notch (cm), mean ± SD	0.3±0.2	0.6±0.3	<0.05[a]
Nipple to anterior midline (cm), mean ± SD	0.2±0.2	0.3±0.2	<0.05[a]

[a]: Mann-Whitney U test; DTI: Direct-to-implant; PTFE: Polytetrafluoroethylene; SD: Standard deviation

Table 4. BREAST-Q assessment of quality of life: preoperative and postoperative comparison

	DTI breast reconstruction with PTFE mesh (n = 60)	DTI breast reconstruction with dura mater graft (n = 56)	p-value
Psychosocial well-being preoperative (scores), mean ± SD	80±6.4	80±6.3	0.49[a]
Psychosocial well-being postoperative (scores), mean ± SD	70±5	71±5.8	0.44[a]
Satisfaction with breasts preoperative (scores), mean ± SD	64±9.9	64±11.4	0.13[a]
Satisfaction with breasts postoperative (scores), mean ± SD	64±7	62±6.9	0.1[a]
	DTI breast reconstruction with PTFE mesh (n = 41)	**DTI breast reconstruction with dura mater graft (n = 34)**	**p-value**
Sexual well-being preoperative (scores), mean ± SD	74±8.6	74±7.5	0.63[a]
Sexual well-being postoperative (scores), mean ± SD	62±5.7	66±6.3	0.84[a]

[a]: Mann-Whitney U test; DTI: Direct-to-implant; PTFE: Polytetrafluoroethylene; SD: Standard deviation; BREAST-Q: Breast evaluation questionnaire

The psychosocial consequences of mastectomy necessitate reconstructive interventions as an essential component of comprehensive treatment (5-7). Implant-based reconstruction is the most common method worldwide (4). This trend is associated with the introduction of subcutaneous and skin-sparing mastectomies into clinical practice.

Recent years have seen active investigation into biological and synthetic meshes in breast reconstruction, aimed at strengthening the IMF and providing additional implant stabilization, although their use remains controversial. The lack of large-scale randomized studies that objectively compare clinical outcomes of reconstructions that use different supplemental covering materials makes it difficult to draw definitive conclusions. Consequently, the choice of a specific technique and type of material is determined primarily by the surgeon's experience and clinical circumstances.

Our study investigated a PTFE-based synthetic mesh for IMF reinforcement and additional implant coverage in immediate subpectoral breast reconstruction. This material is widely used in various surgical fields due to its biocompatibility, chemical inertness, and low friction coefficient (12-17). We also used allogeneic DM as a control in breast reconstruction (21).

This study was not designed to demonstrate the superiority of one technique over the other. In our view, different methodologies, when applied by experienced practitioners, can yield comparable outcomes. Indeed, our findings showed no significant differences between the PTFE and DM groups with respect to postoperative complications or impact on quality of life. The obtained results are consistent with existing literature data (24).

However, attention should be paid to postoperative changes in key anatomical landmarks of the breast. Although the differences did not reach clinical significance, the synthetic PTFE mesh provided a more predictable and stable reconstructive outcome than the biological DM graft.

Data analysis confirmed that older age and higher BMI were associated with an increased likelihood of implant and IMF displacement. This correlation is anatomically plausible: aging leads to decreased skin elasticity due to both reduced synthesis and degradation of collagen and elastin fibers (25), while a higher BMI contributes to chronic mechanical stress on tissues and to the replacement of damaged structural fibers with scar tissue (26).

Study Limitations

While we strived for a comprehensive study design, certain limitations must be acknowledged. Specifically, the 6-month follow-up period, while adequate for assessing primary aesthetic and early complication endpoints, may not fully capture late-onset events. These include seromas (with incidence variably reported, up to 2%) (27) and infections, often associated with secondary bacteremia or invasive procedures unrelated to the initial breast surgery (28). We acknowledge this limitation and will continue prospective monitoring to document any late occurrences.

A key limitation is the non-randomized selection of the surgical incision, which was clinically determined. The approach (inframammary, inverted-T, or S-shaped) depended on tumor location, breast volume, excess skin, and ptosis. While this reflects real-world practice, it introduces a potential confounding factor. In particular, for larger implants (>300 cc), the vertical component of an inverted-T/S incision provides additional lower-pole support, which may independently influence implant stability, complication rates, and the assessment of postoperative quality of life. Although our primary comparison focused on the materials, the effect of the incision itself could not be fully isolated.

The proposed technique of using a synthetic PTFE mesh for supplemental lower-pole coverage in immediate, one-stage, subpectoral implant-based breast reconstruction is an effective approach and is associated with a low complication rate.

Furthermore, the method demonstrates satisfactory support for the IMF and implant position, and produces favorable patient-reported quality-of-life outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Federal Scientific and Clinical Center for Specialized Types of Medical Assistance and Medical Technologies of the Federal Medical-Biological Agency (FGBU FNKTS FMBA of Russia) (approval no: 5_2022, date: 07.06.2022).

Informed Consent: Informed consent for participation in the study and for pre- and postoperative surveys was obtained in the presence of the investigating physicians prior to surgery and again at 6 months postoperatively.

Footnotes

Authorship Contributions

Surgical and Medical Pracites: A.K., A.M., V.O., M.S.; Concept: A.K., A.M., S.G., I.G.; Design: A.K., S.G., I.G.; Data Collection and/or Processing: A.M., V.O., M.S.; Analysis and/or Interpretation: A.K., A.M., S.G., I.G.; Literature Search: A.M., M.S.; Writing: A.K., A.M., V.O.

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ORIGINAL ARTICLE

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Imaging-Based Prediction of Key Breast Cancer Biomarkers Using Deep Learning on Digital Breast Tomosynthesis

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ABSTRACT

Objective: To evaluate the feasibility of using deep learning models applied to digital breast tomosynthesis (DBT) images for non-invasive prediction of breast cancer biomarkers, including estrogen receptor (ER), progesterone receptor (PR), human epithelial growth factor receptor 2 (HER2), Ki-67 proliferation index, and triple-negative breast cancer (TNBC).

Materials and Methods: In this retrospective study, patients with histopathologically-confirmed, invasive breast cancer were included. Furthermore, all included patients had complete, immunohistochemically-assessed biomarker data available. For each case, a representative DBT slice showing the tumor was selected and preprocessed using histogram equalization. Two pretrained convolutional neural networks (VGG19 and ResNet50) were fine-tuned for binary classification of each biomarker. Model performance was evaluated using accuracy, area under the curve (AUC), F1 score, and Matthews correlation coefficient.

Results: The study sample included 43 anonymized female patients. Deep learning models achieved strong predictive performance for ER (AUC = 0.81) and TNBC (AUC = 0.93). HER2 (AUC = 0.74) and Ki-67 index (AUC = 0.70) were predicted with moderate accuracy. PR results varied, with VGG19 reaching AUC = 0.76 while ResNet50 performed poorly (AUC = 0.24).

Conclusion: Deep learning models applied to DBT images enabled non-invasive prediction of some key breast cancer biomarkers, especially ER status and TNBC type. This approach may function as a virtual biopsy to complement histopathology, guide biopsy targeting, and support treatment planning. Although preliminary, the findings highlight the potential of artificial intelligence-enhanced DBT assessment and warrant validation in larger, multi-center prospective studies.

Keywords: Breast neoplasms; machine learning; mammography; digital breast tomosynthesis; biomarkers; artificial intelligence

KEY POINTS

- Breast cancer
- Digital breast tomosynthesis
- Deep learning
- Receptor status
- Artificial intelligence

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Introduction

Breast cancer remains a significant global health burden and continues to be the most frequently diagnosed cancer in women. As reported by GLOBOCAN 2022, there were an estimated 2.31 million new breast cancer cases globally, accounting for 23.8% of all female cancers. Furthermore, breast cancer led to approximately 662,000 deaths worldwide, making up 15.4% of all female cancer-related deaths and 6.9% of total cancer mortality across both sexes (1).

Early diagnosis is essential for improving clinical outcomes. Digital breast tomosynthesis (DBT), a quasi-3D imaging modality, has been shown to improve lesion detection and diagnostic performance compared with conventional digital mammography (2, 3). Large screening studies have also demonstrated that DBT reduces recall rates, particularly in women with dense breast tissue (4-6). Tissue-based biomarker assessment may be affected by sampling variability and limited representation of tumor heterogeneity, while imaging-based approaches may offer complementary information to support pathological evaluation (7-9).

Beyond its role in early detection, the full potential of DBT may be realized when combined with artificial intelligence (AI) and deep learning (DL) approaches. Recent evidence suggests that convolutional neural networks (CNNs) applied to DBT images can enhance lesion characterization, support cancer detection, and deliver reproducible diagnostic outputs (7). These findings suggest that DBT-based imaging tools may be clinically useful beyond diagnostic applications by providing imaging-derived information relevant to prognostic assessment.

In routine oncology practice biomarkers, such as estrogen receptor (ER), progesterone receptor (PR), human epithelial growth factor receptor 2 (HER2), and Ki-67 play a central role in risk stratification, therapeutic decision-making, and individualized treatment planning. These markers are typically assessed through immunohistochemistry (IHC), guiding the use of endocrine therapies, HER2-targeted agents, and chemotherapy (10). Incorporating molecular profiling into imaging analysis will provide an opportunity to combine diagnostic imaging with precision oncology, supporting more informed and individualized treatment strategies.

To the best of our knowledge, this study is among the first to combine DBT slice data with CNNs for imaging-derived prediction of multiple breast cancer biomarkers, representing a novel step toward molecular profiling and precision oncology.

Materials and Methods

Dataset and Study Design

This retrospective, single-center study was conducted at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital with approval from the local ethics committee (approval number: KAEK/2023.04.134, date: 05.04.2023). The cohort included anonymized female patients with histopathologically-confirmed breast cancer, diagnosed between January 2020 and December 2021. DBT scans were acquired using the Giotto Class 3000 DBT System (IMS Giotto S.p.A., Via Toscanini 56, 40055 Budrio, Bologna, Italy) in the Mediolateral Oblique (MLO) view, with each volume consisting of 60 to 80 slices. Due to the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived by the local ethics committee.

Inclusion criteria were:

- Histopathological confirmation of breast cancer prior to treatment
- Availability of complete biomarker data based on IHC analysis (ER, PR, HER2, Ki-67)
- Lesions clearly visible on DBT

Exclusion criteria were:

- T0-stage tumors or ductal carcinoma *in situ*
- Lesions not detectable on DBT
- DBT images of inadequate quality for analysis
- Incomplete histopathology or imaging data

The dataset was divided into training (70%) and testing (30%) sets using stratified sampling to preserve the distribution of biomarker subtypes.

Pathological Evaluation Criteria

The following prognostic biomarkers were evaluated (10-12):

- ER: considered positive when ≥1% of tumor cell nuclei exhibited IHC staining.
- PR: considered positive when ≥1% of tumor cell nuclei stained with IHC.
- HER2: defined as positive when IHC scored 3+ or when gene amplification was confirmed by fluorescence *in situ* hybridization, as per American Society of Clinical Oncology/College of American Pathologists guidelines (11).
- A Ki-67 cut-off value of ≥20% was used in accordance with widely accepted clinical guidelines (10).
- Triple-negative breast cancer (TNBC): defined as the absence of ER, PR, and HER2 expression.

For patients with multifocal or multicentric disease, lesion selection was performed by a breast radiologist with 10 years of experience according to a predefined protocol. The largest lesion

was preferentially selected for analysis; however, if it was not clearly visualized on DBT, the lesion demonstrating the highest morphological conspicuity was chosen as the representative lesion.

DBT Image Preprocessing

DBT scans were acquired in right mediolateral oblique and left mediolateral oblique views. For each patient, the affected breast was selected for analysis. Each DBT study consisted of 60–80 slices stored as DICOM files. The representative DBT slice was selected by a breast radiologist with 10 years of experience according to a predefined protocol that prioritized slices demonstrating clear lesion visualization, well-defined lesion margins, and maximal lesion conspicuity within the DBT stack. To ensure compatibility with DL workflows, images were converted from DICOM to PNG format while preserving the original spatial resolution and pixel dimensions. Histogram equalization was then applied to improve contrast and emphasize structural differences between dense and fatty tissues. This preprocessing step enhanced visualization of lesion margins and improved overall parenchymal contrast (Figure 1). Histogram equalization was applied uniformly to all images across both training and testing datasets.

The preprocessing pipeline included:

• Grayscale conversion: reduced input complexity by representing each pixel with a single channel.

• Histogram equalization: increased contrast to better highlight tumor structures.

The normalized image histogram was defined as follows: let a digital image be represented by f, with pixel intensity values ranging from 0 to L-1L-1L-1. For grayscale images, L = 256L = 256L = 256, representing the total number of possible intensity levels. The normalized histogram is given by Equation (1), and contrast enhancement was achieved using the transformation function in Equation (2), which redistributes intensity values across the image, particularly improving visibility in low-contrast regions (13-17).

Equation (1): $pf(f\kappa) = n\kappa / n$

Equation (2): $T(fk)=(L-1) \times j=0\sum kpf(fj)$

These preprocessing steps enhanced both anatomical and pathological feature visibility, which is critical for extracting meaningful patterns during DL model training. Images were then manually labeled according to five biomarker categories: ER status, PR status, HER2 status, TN molecular subgroup, and Ki-67 proliferation index.

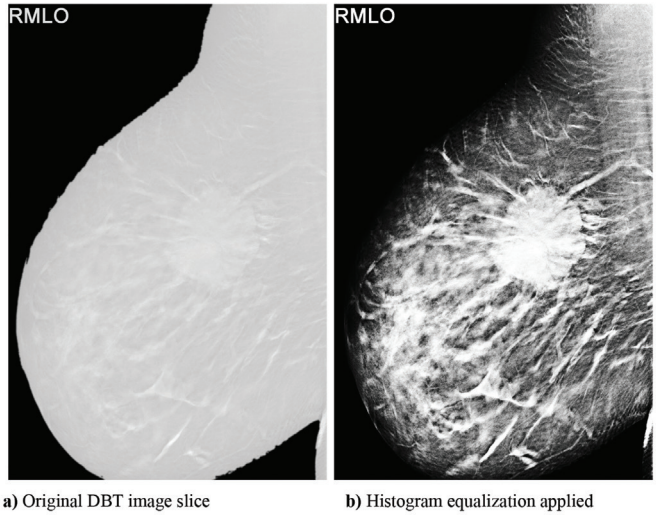

Figure 1. Representative DBT slice before (a) and after (b) histogram equalization. Enhanced contrast improves lesion visibility and delineation of margins

DBT: Digital breast tomosynthesis

Data Augmentation Techniques

To reduce the risk of overfitting and enhance the model's ability to generalize to unseen data, several data augmentation strategies were applied to the training set. These techniques introduced controlled variability while maintaining the integrity of lesion morphology.

The following augmentations were performed:

• Random rotations (±15 °)

• Horizontal and vertical translations (up to 10%)

• Zooming in or out (±10%)

• Horizontal flipping

Deep Learning Architecture and Visualization

The most representative slice showing the tumor was selected from the DBT stack. This deliberate choice mirrors histopathology practice, where biomarker assessment is typically performed on the most informative or aggressive field. Selecting the slice with maximal lesion conspicuity reduced background noise, highlighted biologically relevant features, and ensured computational feasibility for this proof-of-concept study. Histogram equalization was then applied to enhance lesion contrast and improve boundary definition, particularly in dense breast tissue. Histogram equalization was applied to enhance lesion contrast and improve boundary definition, particularly in dense breast tissue. The preprocessed, histogram-equalized slices were subsequently used to train and evaluate two CNN architectures.

The two machine learning AI applications used were the VGG19 and ResNet50 models. These architectures were selected for their established effectiveness in medical image

analysis and their ability to extract hierarchical features from high-resolution radiological data. Both VGG19 and ResNet50 architectures, illustrated in Figure 2, are composed of multiple stacked convolutional layers, max-pooling operations, and fully connected layers.

The VGG19 model (18, 19) network consisted of 16 convolutional layers followed by three fully connected layers. It employed ReLU activation, batch normalization, dropout (rate: 0.3), and max-pooling operations throughout the architecture. For binary classification, a final sigmoid activation function was applied. The model was optimized using the Adam algorithm (learning rate = 0.0001) with binary cross-entropy loss and was trained for 10 epochs with a batch size of 32 in TensorFlow 2.13.

The ResNet50 model (18, 19) is a modified ResNet50 pretrained on ImageNet and was used as the backbone for feature extraction. The original classification head was replaced with a GlobalMaxPooling2D layer, followed by fully connected dense layers with ReLU activations and a final sigmoid output. Residual blocks were preserved to maintain gradient flow and support deeper network training.

Statistical Analysis

To evaluate the robustness and generalizability of the classification models, a comprehensive statistical analysis was performed. For binary classification tasks, performance was quantified using sensitivity, specificity, precision, negative predictive value, false negative rate, false discovery rate, overall accuracy, F1 score, and Matthews correlation coefficient (MCC).

Probabilistic model performance was assessed using the area under the receiver operator characteristic (ROC) area under the curve (AUC) and log loss. Comparisons between models were conducted using DeLong's test to determine statistical differences in AUC, with significance defined as $p<0.05$.

To estimate uncertainty in model performance, 95% confidence intervals (CIs) for AUC values were calculated through stratified bootstrap resampling with 1,000 iterations. All statistical analyses were conducted in Python 3.11.4, using Scikit-learn, TensorFlow, NumPy, and associated packages for ROC curve analysis and bootstrap-based CI estimation (20, 21).

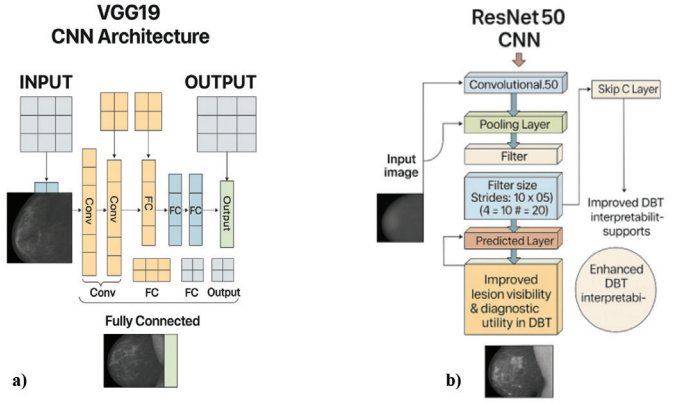

Figure 2. Workflow of image preprocessing, data augmentation, and deep learning model training using VGG19 and ResNet50 architectures. (a) Preprocessed grayscale DBT slices are provided as input to the convolutional neural network, followed by convolutional, pooling, and fully connected layers to generate the classification output. (b) Schematic representation of the ResNet50 architecture, highlighting convolutional blocks and residual (skip) connections that facilitate deeper feature learning

DBT: Digital breast tomosynthesis; CNN: Convolutional neural network

Results

This retrospective study included 43 patients diagnosed with breast cancer. From their DBT acquisitions, a total of 960 lesion-focused slices were selected. The dataset was split into 70% training and 30% testing cohorts, ensuring balanced distributions of prognostic markers (no statistically significant differences, $p>0.05$ by chi-square test).

Hormonal Receptor (ER, PR) Status

Model performance varied notably between ER and PR receptor classification tasks. Both VGG19 and ResNet50 demonstrated similar effectiveness for ER detection, achieving an AUC of 0.81 (95% CI: 0.78–0.84), with identical F1 scores (0.81) and MCC values (0.6194). No statistically significant difference was found between the models ($p = 0.83$), indicating consistent performance across architectures.

In contrast, PR classification revealed substantial discrepancies. VGG19 achieved an AUC of 0.76 (95% CI: 0.71–0.80), with an F1 score of 0.76 and MCC of 0.52, indicating moderate predictive strength. However, ResNet50 failed to generalize effectively for PR status, showing an AUC of only 0.24, suggesting performance below random chance. This significant performance gap ($p<0.001$ *vs.* VGG19) may indicate overfitting, architecture mismatch, or a lack of sensitivity to PR-specific morphological features in ResNet50. Among luminal tumors, there were no ER-positive/PR-negative cases in our cohort, which precluded meaningful subgroup discrimination and resulted in marked class imbalance. PR status was not evaluated as an independent primary predictive target in this study.

These results are summarized numerically in Table 1 and visually represented in Figure 3, which compares classification metrics (accuracy, AUC, F1 score, MCC) across both models for ER and PR tasks.

HER2 Receptor Expression

HER2 classification using the ResNet50 model resulted in moderate predictive performance, with an AUC of 0.74 (95% CI: 0.70–0.78), an F1 score of 0.74, and an MCC of 0.48. Comparative ROC analysis revealed that the ability of the model to discriminate HER2 status was significantly inferior to ER classification ($p = 0.047$). This reduced performance may stem from the heterogeneous imaging phenotypes characteristic of HER2-positive tumors, which often exhibit variable morphological and biological features. These results reflect the complexity of modeling HER2 expression using imaging data and underscore the challenges of non-invasive biomarker prediction in biologically diverse tumor subtypes.

Triple-Negative Subgroup

Classification of TNBC showed the highest predictive performance across all biomarker categories. Both CNN architectures (VGG19 and ResNet50) achieved an AUC of 0.92 (95% CI: 0.90–0.94), an F1 score of 0.92, and an MCC of 0.85. The narrow confidence intervals obtained through bootstrap analysis further confirmed the consistency and robustness of model performance. Pairwise ROC comparisons demonstrated that identification of TNBC by both CNN architectures significantly outperformed their performance for HER2, PR, and Ki-67 predictions ($p<0.001$ for all comparisons). These findings highlight the potential of DBT-based DL tools in accurately identifying TNBC. Performance metrics are provided in Table 2, and model trends are illustrated in Figure 4.

Ki-67 Proliferation Index

The predictive modeling of Ki-67 expression yielded moderate classification success. The VGG19 architecture slightly outperformed ResNet50, with accuracy scores of 68.9% and 68.5%, respectively. VGG19 produced an AUC of 0.70 (95% CI: 0.64–0.75), with balanced F1 and MCC values, suggesting improved generalizability. While these metrics were not high, the AUC values remained statistically superior to random guessing ($p<0.01$). These findings imply that while CNNs may capture certain proliferation-associated patterns from DBT images, further model refinement or multimodal approaches may be needed to improve the accuracy of non-invasive Ki-67 prediction.

Discussion and Conclusion

This study demonstrated the feasibility of imaging-based prediction of key prognostic biomarkers in breast cancer, ER, PR, HER2, Ki-67, and TNBC, using DBT images analyzed with two CNNs, VGG19 and ResNet50 architectures (11, 22). These models were capable of extracting morphological features from DBT images that reflected some of the underlying tumor biology.

Among the evaluated biomarkers, TNBC yielded the highest predictive performance (AUC: 0.92, F1-score: 0.93), followed by ER status (AUC: 0.81). Predictions for HER2 and Ki-67 achieved moderate accuracy, while substantial discordance was observed in PR classification between the two CNNs: VGG19 achieved 76% accuracy, whereas ResNet50 reached only 24%. This poor performance by ResNet50 may stem from insensitivity to fine texture-based features, class imbalance, or overfitting (20). Comparable findings have been reported in the literature using other imaging modalities. For instance, Dominique et al. (13) used images from contrast-enhanced spectral mammography (CEM) to predict ER and TN status with AUCs of 0.85 and 0.91, respectively. In contrast, the current study achieved comparable results without the use of contrast agents, offering a potential advantage in patients with contraindications for contrast administration.

Prior DBT-based studies have primarily focused on malignancy detection and lesion classification. Bevilacqua et al. (22) demonstrated the superiority of deep CNNs over shallow models, and El-Shazli et al. (23) proposed a 3D DBT-based DL diagnostic pipeline. Our study contributes to this body of work by extending the use of DL beyond binary lesion classification to derive biologically meaningful output that may contribute to personalized treatment planning.

Importantly, our study adopted a 2D slice-based approach rather than volumetric analysis. This deliberate choice was motivated by computational feasibility and the premise that a carefully selected, representative slice may sufficiently capture the biological aggressiveness of the tumor. In histopathology practice, biomarker evaluation is often performed on the most representative or biologically aggressive portion of the specimen (10), reflecting the area most relevant to clinical behavior. By analogy, selecting DBT slices with maximal lesion conspicuity

Table 1. Performance metrics of deep learning models (ResNet50 and VGG19) for classification of ER and PR status. Metrics reported include Accuracy, AUC, F1 Score, MCC

Marker	Model	Accuracy	AUC	F1 score	MCC
ER	ResNet50	0.8097	0.8097	0.8097	0.6194
ER	VGG19	0.8097	0.8097	0.8097	0.6194
PR	ResNet50	0.2422	0.2422	0.7543	0.5087
PR	VGG19	0.7578	0.7578	0.7578	0.5156

AUC: Area under the curve; MCC: Matthews correlation coefficient; ER: Estrogen receptor; PR: Progesterone receptor

may highlight biologically meaningful features while reducing background noise. Similar single-slice or representative-field strategies have been successfully applied in prior radiomics and AI studies in breast imaging and neuro-oncology, further supporting the validity of this approach. Nevertheless, future work should explore multi-slice fusion or 3D CNNs, which may provide incremental value by incorporating spatial context and capturing intratumoral heterogeneity (21-26). Consistent with this perspective, Zhang et al. (27) demonstrated that 2D CNNs applied to selected slices from 3D DBT volumes may achieve reliable classification performance, supporting the feasibility of slice-based DL strategies when volumetric analysis is computationally constrained.

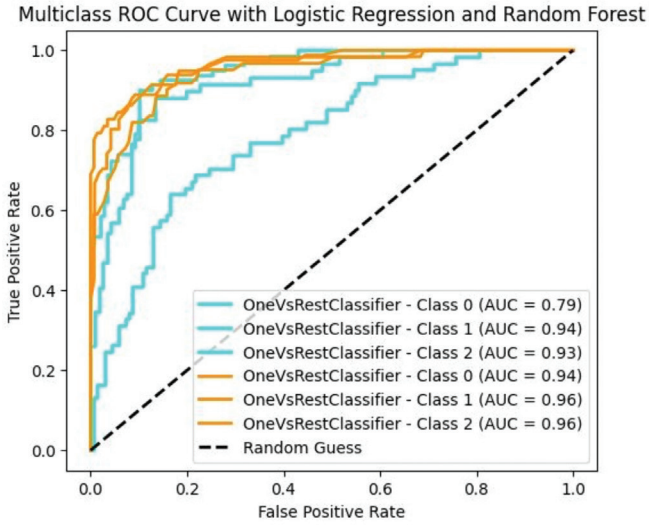

Figure 3. ROC curves show the performance of VGG19 and ResNet50 models for ER and PR status prediction. Both models demonstrated comparable performance for ER classification (AUC = 0.81). In contrast, PR classification showed a marked discrepancy, with VGG19 achieving moderate discrimination (AUC = 0.76) and ResNet50 performing below chance level (AUC = 0.24). The dashed diagonal line indicates chance-level performance

ER: Estrogen receptor; PR: Progesterone receptor; AUC: Area under the curve; ROC: Receiver operator characteristic

Table 2. Performance metrics for HER2, TNBC, Ki-67 index classification. Reported metrics include Accuracy, AUC, F1 score, and MCC. The table summarizes model performance for predicting HER2 and TNBC and Ki67 index status using deep learning

Marker	Accuracy	AUC	F1 score	MCC
HER2	0.7405	0.7405	0.7405	0.481
TNBC	0.9239	0.9239	0.9262	0.8523
Ki-67	0.8536	0.8536	0.8542	0.7056

AUC: Area under the curve; MCC: Matthews correlation coefficient; TNBC: Triple-negative breast cancer; HER2: Human epidermal growth factor receptor 2

The diagnostic potential of DBT has also been reported by Ricciardi et al. (28), who demonstrated high accuracy for malignancy detection, and by Shimokawa et al. (29), who used CNNs to predict stromal invasion based on DBT images. Collectively, these studies suggest that DBT captures rich morphological information extending beyond lesion presence or invasion status. In this context, the present study further broadens the scope of DBT by leveraging its morphological capacity for biological and molecular profiling. The high prediction accuracy observed for TNBC and ER status may be attributed to their distinct imaging characteristics. For instance, TNBC frequently appear as high-density masses with ill-defined margins on DBT, which may be readily captured by CNN models (3, 5). In contrast, the moderate performance for HER2 and Ki-67 may reflect their heterogeneous imaging appearance or features that fall below the spatial resolution of DBT. A meta-analysis by Yoon et al. (7) supported the use of DBT over digital mammography in AI applications, highlighting pooled AUCs up to 0.91 and improved performance with deeper architectures, such as ResNet and VGG (18). These findings are in line with our results, particularly the superior performance of VGG19 in PR and Ki-67 prediction. Prediction of the Ki-67 proliferation index yielded moderate success in this study (AUC = 0.70, 95% CI: 0.64–0.75), with balanced F1 and MCC scores indicating reasonable generalizability. These findings are consistent with previous literature. Dominique et al. (13) reported an AUC of approximately 0.72 for Ki-67 prediction in CEM images using DL models. Despite using contrast-based imaging, their results suggest that Ki-67 remains a challenging biomarker to predict via imaging modalities alone. Unlike biomarkers such as ER or TNBC status, Ki-67 does not consistently produce distinct radiological patterns, particularly in DBT, which may explain the moderate performance observed. Nevertheless, the AUC was statistically better than chance, supporting the hypothesis that certain morphological patterns associated with cellular proliferation are partially captured in DBT images and can be recognized by deep CNNs (13, 22, 23).

From a clinical perspective, imaging-based biomarker prediction aligns with the evolving concept of a "virtual biopsy". Such approaches may assist in biopsy targeting, inform therapeutic decision-making in scenarios with limited tissue availability, and enable non-invasive longitudinal monitoring (3, 7). Moreover, recent studies have provided complementary evidence supporting our DBT-CNNs framework for biologically meaningful prediction. do Nascimento et al. (30) identified members of the Pleckstrin Homology-Like Domain, Family B as prognostic and predictive biomarkers, highlighting the value of molecular signatures for treatment stratification. Mundinger and Mundinger (31) demonstrated that AI-assisted image analysis may reduce workload and recall rates in breast screening, reinforcing the practicality of integrating AI with DBT to generate clinically actionable outputs, consistent with our CNN-based approach for deriving molecular surrogates.

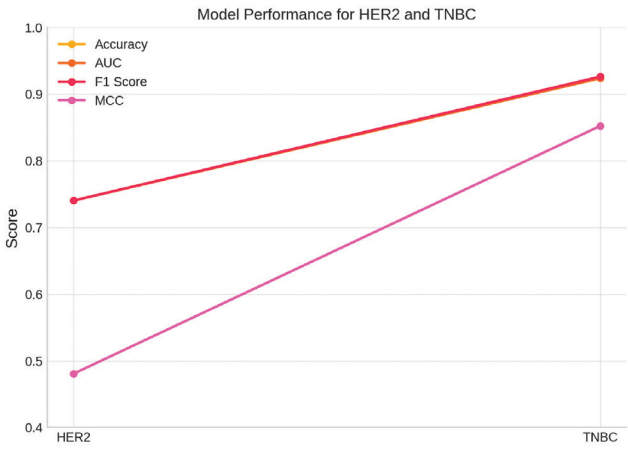

Figure 4. Line plot comparing the performance metrics of CNN-based classification for HER2-positive breast cancer and TNBC using DBT images. Across all evaluation metrics—including accuracy, AUC, F1 score, and MCC. TNBC demonstrated consistently superior discriminative performance compared with HER2 (AUC = 0.92 vs. 0.74; MCC = 0.85 vs. 0.48)

HER2: Human epithelial growth factor receptor 2; CNN: Convolutional neural network; DBT: Digital breast tomosynthesis; TNBC: Triple-negative breast cancer; AUC: Area under the curve; MCC: Matthews correlation coefficient

Collectively, these studies support the premise that imaging-derived biomarkers may be capable of extending precision oncology beyond histopathology and may serve as the foundation for future virtual-biopsy-driven clinical workflows. Future investigations should explore volumetric approaches, such as 3D CNNs or multi-slice fusion, that might better capture intratumoral heterogeneity and subtle architectural cues associated with proliferative activity, including Ki-67 expression. Moreover, integrating DBT with complementary imaging modalities, such as MRI or ultrasound, may further enhance predictive performance through multi-modal DL frameworks.

Study Limitations

This study has certain limitations that merit acknowledgment. Its retrospective, single-center design and relatively small sample size may affect the generalizability of the findings. The deliberate use of a single representative DBT slice per patient focused our analysis on the most morphologically informative regions and avoided the confounding impact of excessive heterogeneity or poorly defined areas. Supporting this strategy, Hossain et al. (32) demonstrated that automatic region of interest detection in histopathological imaging can significantly enhance accuracy by concentrating computational focus on relevant areas and reducing noise (33). Given the relatively small sample size, this study should be regarded as exploratory and proof-of-concept in nature. Although data augmentation was applied, the risk of model overfitting cannot be fully excluded, and the reported performance metrics should be interpreted with caution. Future ablation studies comparing histogram equalization, contrast-limited adaptive histogram equalization, and raw images are warranted.

This study demonstrated that imaging-based prediction of key prognostic biomarkers in breast cancer is feasible using CNNs (VGG19 and ResNet50) applied to selected DBT images. High accuracy in prediction was achieved for ER status and the TNBC type, and moderate precision was observed for HER2 and Ki-67 index. Notably, PR prediction substantially varied between CNN models. These findings suggest that DBT combined with DL may provide complementary imaging-based information to support clinical decision-making, rather than replacing tissue-based profiling. Clinical translation and integration into decision-support workflows will require confirmation in large-scale, multi-center, prospective studies.

Clinical Relevance Statement

The integration of selected DBT images with DL enabled the prediction of key histopathological biomarkers—such as ER, PR, HER2, TNBC and the Ki-67 index, to varying degrees of accuracy, which may be integrated into clinically guided workflows. Imaging-based biomarker prediction has the potential to improve biopsy targeting, guide therapy selection, and support treatment planning, particularly in cases with limited or unavailable tissue although more evidence is required before widespread acceptance. External validation in larger, multi-institutional cohorts is warranted, we believe, and our findings support the growing role of DBT image analysis using AI models to accelerate individualized care pathways and advance precision oncology in breast cancer.

Ethics

Ethics Committee Approval: This retrospective, single-center study was conducted at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital with approval from the local ethics committee (approval number: KAEK/2023.04.134, date: 05.04.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.A., M.A.N., M.B.; Design: E.A., M.A.N., M.B.; Data Collection or Processing: E.A., M.A.N., M.B.; Analysis or Interpretation: E.A., M.A.N., M.B.; Literature Search: E.A., M.A.N., M.B.; Writing: E.A., M.A.N., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Oncoplastic Approach to Juvenile Giant Fibroadenoma: A Case Series

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ABSTRACT

Juvenile giant fibroadenoma (GFA) is defined as a benign tumor larger than 5 cm, 500 grams, and/or involving at least 80% of the breast. It typically occurs in young patients and causes breast deformity and asymmetry. Surgical treatment involves resection of the tumor (enucleation), rearrangement of the skin envelope, and repositioning of the nipple-areola complex. However, the expected re-expansion of the breast following tumor removal, often managed through periareolar approaches, can be unpredictable and prolonged in certain cases. For this reason, oncoplastic surgery techniques have been developed, which allow for immediate partial reconstruction and are now among the available therapeutic options. This report describes three cases in which an oncoplastic approach was used for the treatment of GFA.

Keywords: Oncoplastic surgery; giant fibroadenoma; juvenile fibroadenoma; mammoplasty

KEY POINTS

- Juvenile giant fibroadenoma is a benign breast tumor >5 cm or >500 g, often causing deformity and asymmetry in young patients.
- Treatment involves tumor removal and breast reconstruction.
- Oncoplastic surgery allows immediate partial reconstruction with better cosmetic outcomes.
- Surgical approach depends on tumor size, asymmetry, and ptosis.

Introduction

Juvenile giant fibroadenoma (GFA) is defined as a lesion larger than 5 cm, 500 grams, or one that replaces at least 80% of the breast. It occurs in patients aged 9 to 25 years, with a prevalence of 2.2% in this age group (1). Accelerated growth is associated with increased levels of estrogen, progesterone, and prolactin (2), which leads to breast asymmetry and deformity. Surgical treatment is required; however, there is no consensus on the optimal surgical approach. Oncoplastic surgery techniques aim to allow for enucleation, remodeling of the skin envelope, preservation of breast tissue, and repositioning of the nipple-

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areola complex in cases of marked asymmetry (3). We present three cases treated with an oncoplastic approach in a hospital in Latin America.

Case Presentations

Case 1

A 12-year-old patient reported progressively growing palpable bilateral breast masses over the past year. On physical examination, multiple well-defined, mobile tumors were palpated in both the left and right breasts, without skin involvement. The largest tumor was located in the upper inner quadrant of the left breast, measuring 5.5 cm (Figure 1A). Breast ultrasound showed, in the left breast: ovoid, hypoechoic, heterogeneous lesions with circumscribed margins, parallel to the skin axis, located at: clock positions (r) 11, 12, and 1 (46x19 mm), r3 (15x8.6 mm and 11x6.6 mm), r6-r7 (51x12 mm); and in the right breast at r11-r12 (36.7x22.2x39.5 mm), r1-r2 (12x10 mm and 25x12 mm), r6 (20x12 mm and 15x10 mm), r8-9 (44x22.5 mm), suggestive of bilateral GFA, Breast Imaging Reporting and Data System (BIRADS 3).

Core needle biopsies were performed on the largest lesions in both breasts, showing fibroepithelial neoplasms with moderate stromal cellularity and mild atypia, suggestive of fibroadenomas. Two oncoplastic treatment options were considered: crescent mammoplasty and inframammary fold approach (inferolateral incision), with the latter performed.

The pathology report confirmed fibroadenoma in both breasts, with the largest surgical specimen measuring 6.2 cm in the left breast and 4.9 cm in the right. The patient had a favorable postoperative outcome with no asymmetry observed at the 12-month follow-up (Figure 1B).

Case 2

A 15-year-old patient presented with a progressively growing mass for the past two years in the right breast. Upon examination, there was a well-defined, multilobulated, mobile tumor in the right breast affecting all four quadrants and causing grade 3 ptosis,

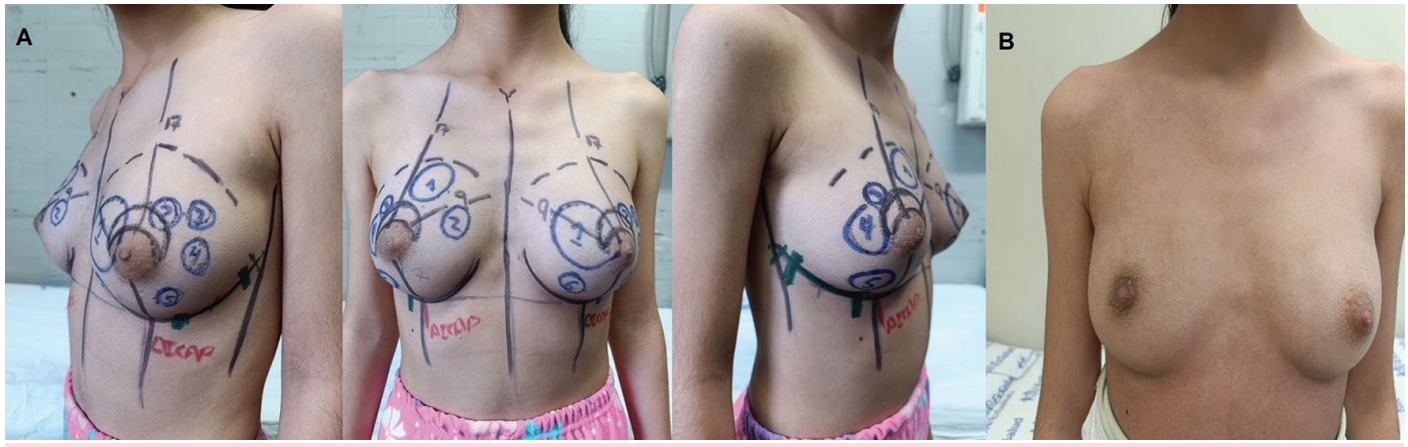

Figure 1. Case 1; (A) Preoperative image showing multiple bilateral fibroadenomas and a giant juvenile fibroadenoma in the left breast. Planned oncoplastic approaches included crescent mammoplasty and a submammary fold incision. (B) Postoperative image of the submammary fold approach at 12-month follow-up

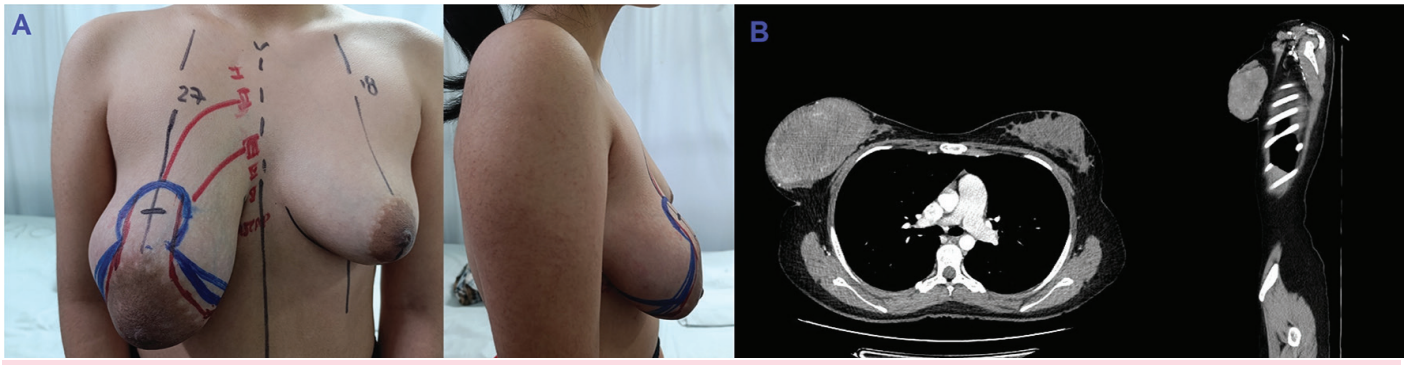

Figure 2. Case 2; (A) Preoperative image of the right breast showing the tumor and marked asymmetry. (B) Computed tomography image demonstrating the interface of the extensive tumor with the pectoralis major fascia

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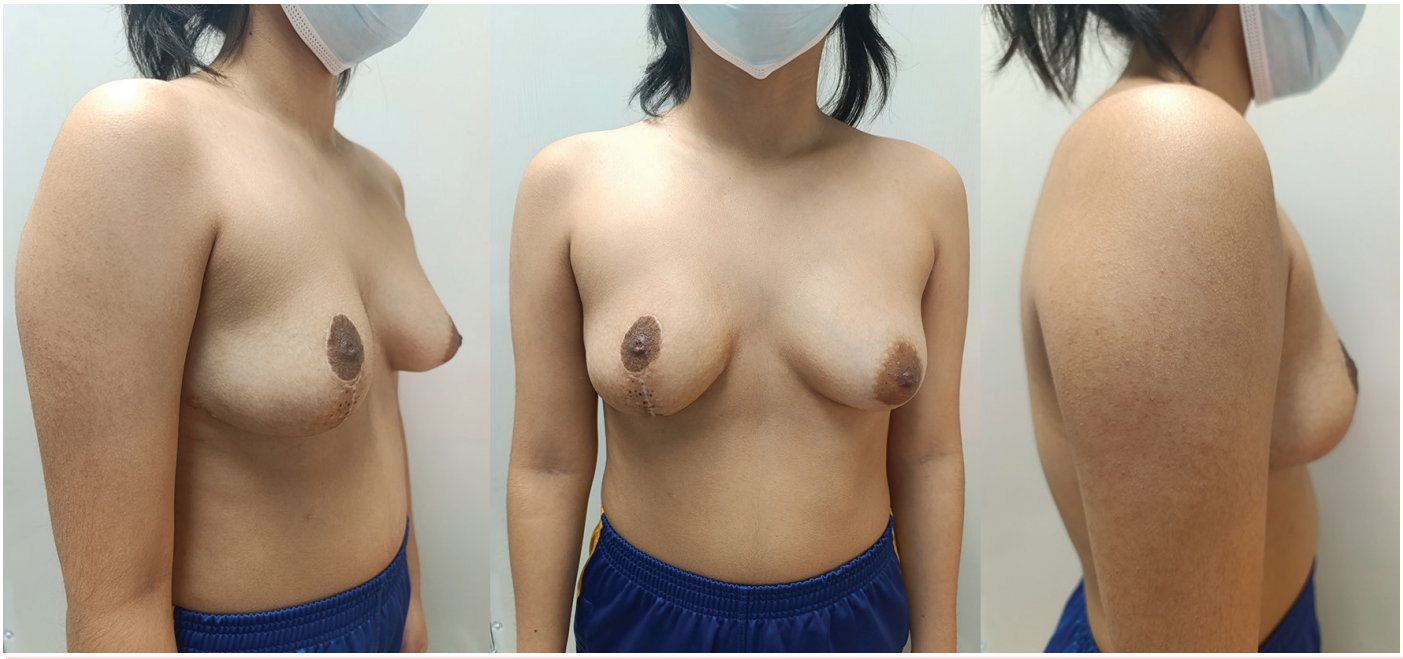

Figure 3. Case 2; postoperative image at 12-month follow-up

without skin edema (Figure 2A). An ultrasound was requested, showing a solid, hypoechoic lesion with well-defined borders measuring approximately 11x7 cm, occupying the entire right breast, with internal Doppler flow signal; categorized as BIRADS 4. A chest computed tomography scan revealed an enlarged right breast with a heterogeneous solid lesion measuring 10x8 cm, occupying a large portion of the breast (Figure 2B). A core needle biopsy showed a fibroepithelial proliferation with mild to moderate stromal cellularity, mild cellular pleomorphism, and a mitotic index of less than 1 per 10 high-power fields.

Treatment was performed using an inverted T mammoplasty (McKissock technique) and tumor enucleation by blunt dissection. The pathological report confirmed a GFA measuring 14.8x10.7x5.2 cm and weighing 720 grams. The patient had a favorable postoperative course with mild asymmetry at one-year follow-up (Figure 3). A 2 cm left breast fibroadenoma was resected and the tuberous breast was corrected using vertical mammoplasty (Lyacir R. Type I technique), resulting in an optimal outcome (Figure 4).

Case 3

A 20-year-old woman with a history of resection of two right breast fibroadenomas 2 years earlier presented with a progressively enlarging mass in the upper quadrants and a smaller mass in the lower pole of the right breast over the past 12 months. Physical examination revealed two periareolar scars; at 12 o'clock, an 8 cm well-defined, partially mobile mass without skin involvement, and at 6 o'clock, a 2 cm mass with similar characteristics (Figure 5A).

Ultrasound showed a solid, hypoechoic lesion at 12 o'clock measuring 7.6×5.8×4.6 cm and another at 6 o'clock measuring 2.2×1.9×1.8 cm, classified as BIRADS 4a. Core biopsy of the 12 o'clock lesion revealed fibroepithelial proliferation with moderate stromal cellularity, mild pleomorphism, and a mitotic index of 1/10 high-power fields, suggesting complete excision for definitive diagnosis.

The patient underwent round-block mammaplasty based on a medial pedicle, taking into account prior periareolar scars and absence of breast ptosis. Pathology confirmed a GFA (8 cm, 420 g) and a 2.2 cm fibroadenoma. Postoperatively, the patient had an uneventful course, with 10-month follow-up showing no asymmetry and only slight enlargement of the areolar diameter (Figure 5B).

Discussion and Conclusion

The management of a GFA presents a challenge due to its large dimensions, ranging from 5 to 60 cm (average 11 cm), and requires a differential diagnosis with phyllodes tumors, physiological glandular hypertrophy, and inflammatory processes before planning surgery. The most commonly used imaging methods are ultrasound (72%) and mammography (26%) (4). However, in young patients, the density of breast tissue limits the quality of mammographic images, as in the described cases where ultrasonography was used. Core needle biopsy is recommended for the evaluation of lesions larger than 3 cm and recurrent lesions; however, regression changes in GFA can mimic non-specific areas of hyalinization, making it difficult to differentiate from benign phyllodes tumors (5).

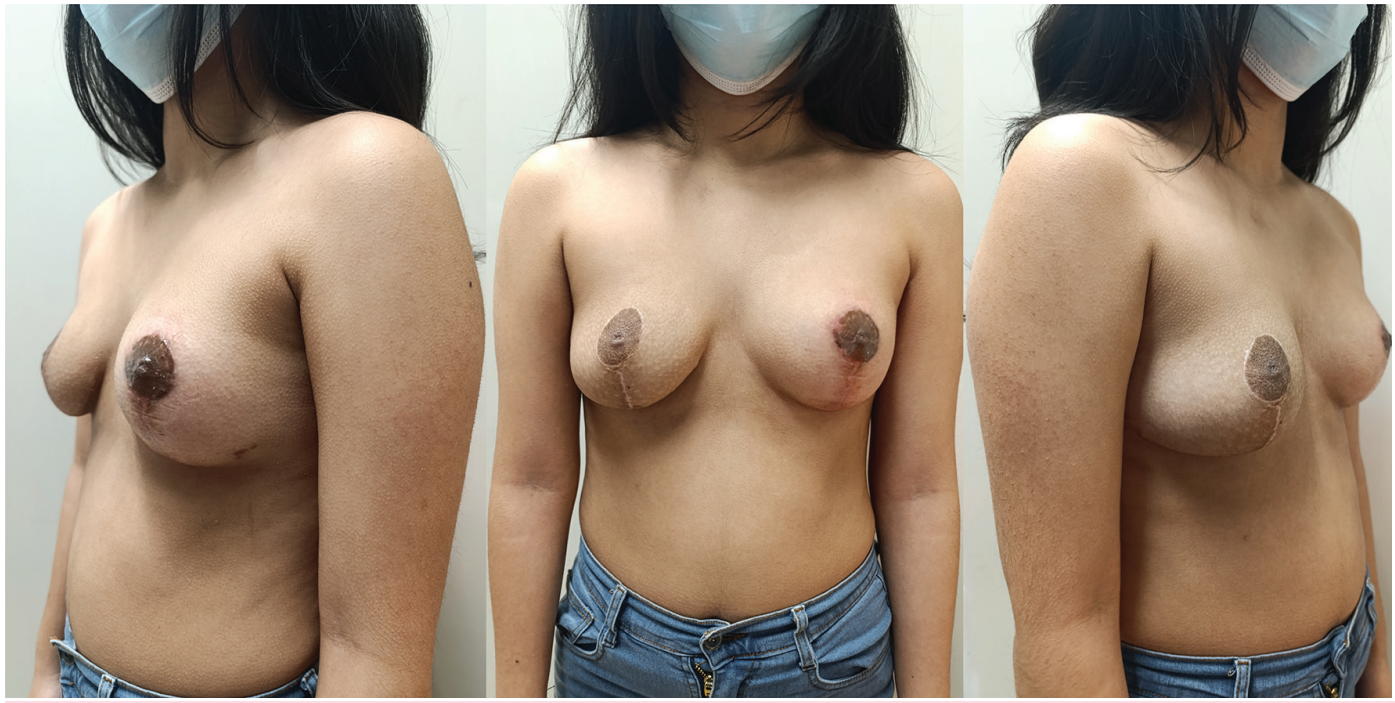

Figure 4. Case 2; postoperative image following vertical mammoplasty with breast symmetrization

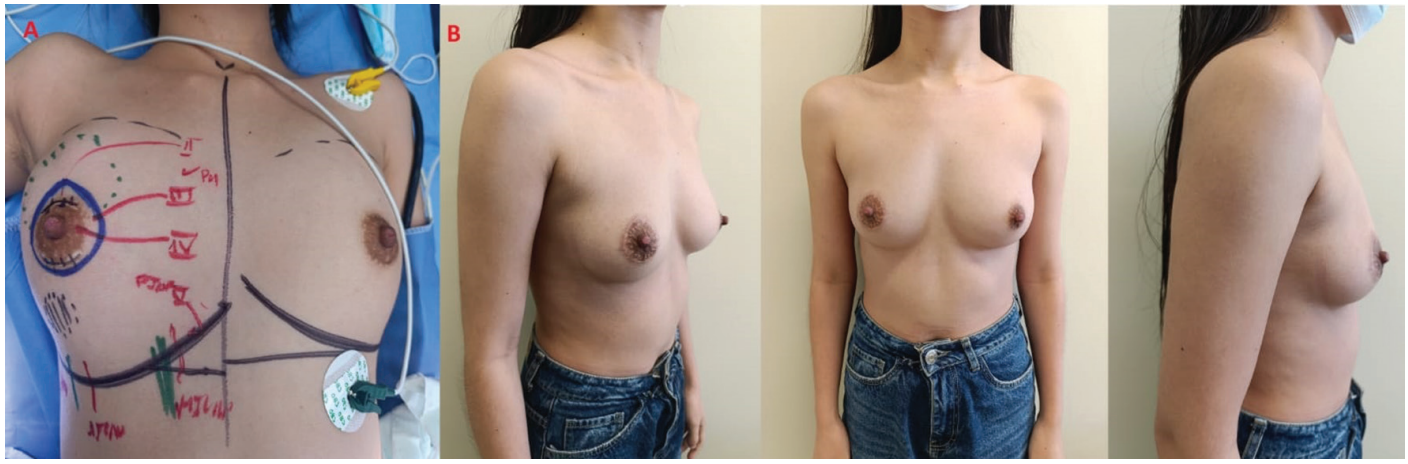

Figure 5. Case 3; (A) Preoperative image showing a giant fibroadenoma at 12 o'clock and a smaller fibroadenoma at 6 o'clock, with previous periareolar scars and round-block mammaplasty markings. (B) Postoperative follow-up at 10 months showing no asymmetry

The goal of surgical treatment is to remove the tumor with minimal dissection of ducts and lobules. The classic recommendation is a periareolar incision, given that GFAs compress healthy breast tissue, which will undergo re-expansion after resection, improving postoperative asymmetry over time (6). However, in cases where 20–50% of breast volume is lost during resection and there is grade 3 ptosis on the affected side, waiting for glandular re-expansion and adjustment of the skin envelope leads to unpredictable outcomes. Therefore, oncoplastic surgical techniques have been proposed, such as inframammary fold approach, reduction mammoplasty (inverted T technique, round block mammoplasty, crescent mammoplasty), displacement mammoplasty (horizontal mammoplasty), and in some cases, mastectomy with reconstruction (7).

In cases of mild to moderate asymmetry, an inframammary incision (low visibility) facilitates the removal of multiple lesions from different quadrants and, through blunt dissection, allows the tumors to be separated from the breast tissue while avoiding thermal, vascular, and nerve damage that could affect the nipple-areola complex (8), as in Case 1.

The recommendations for selecting a reduction mammoplasty technique such as the inverted T technique include cases of severe asymmetry, tumors averaging 15 cm in diameter, weighing over 1500 grams, and a 6 cm difference in the location of the nipple-areola complex compared to the unaffected side (9). In case 2, there was an extensive unilateral tumor that met these criteria, leading to the choice of an inverted T mammoplasty using the McKissock technique, ensuring bipedicle vascular support and appropriate surgical field exposure. Blunt dissection preserved the breast ducts, reduced the skin envelope, and repositioned the nipple-areola complex, similar to what was described by Chang and McGrath (10), with satisfactory results at twelve months of follow-up. In addition, the procedure of maintaining symmetry and correction of the contralateral tuberous breasts was performed, further improving the results obtained.

In cases with previous periareolar surgical scars, planning an oncoplastic technique must be done carefully to ensure adequate vascular supply to the nipple-areola complex, typically via a reliable vascular pedicle (such as medial or postero-inferior) (11). While the round-block technique may lead to some loss of breast projection, subsequent breast re-expansion after resection of a GFA allows preservation of breast contour and projection, as demonstrated in case 3.

GFAs are benign tumors that, due to their large size, can cause deformity, breast asymmetry, pain, discomfort, and anxiety. Surgical treatment should be selected based on the size of the lesion, the degree of asymmetry, and the level of ptosis. Oncoplastic surgery techniques for GFAs have been successfully used and are part of the currently available therapeutic options.

Ethics

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.C.D., G.D.l.C.K., C.C.C.L., M.d.R.C.P.; Concept: I M.C.D., G.D.l.C.K., C.C.C.L., M.d.R.C.P.; Design: M.C.D., G.D.l.C.K.; Data Collection or Processing: M.C.D., C.C.C.L., M.d.R.C.P.; Analysis or Interpretation: M.C.D., G.D.l.C.K., C.C.C.L., M.d.R.C.P.; Literature Search: M.C.D., G.D.l.C.K.; Writing: M.C.D., G.D.l.C.K., C.C.C.L., M.d.R.C.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

European Journal of BREAST HEALTH

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Eur J Breast Health 2026;22(2):231-233

Herpes Zoster of the Nipple: A Rare Diagnostic Challenge

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ABSTRACT

The breast constitutes an essential component of a woman's identity, body image, and self-esteem. The objective of this article is to present a rare case of breast skin pathology and to examine its differential diagnosis. A fifty-year-old woman consulted our department for a burning sensation in her right breast in combination with a rash involving the nipple-areola complex. The patient received treatment for evolving bacterial mastitis; however, a zosteriform vesicular rash subsequently developed over the right scapular region. The diagnosis of varicella zoster virus infection was confirmed, and oral medication was adjusted to antivirals, resulting in progressive reduction of the rash. To the best of our knowledge, reports on herpes zoster involving the nipple are scarce in the literature. This article presents such an atypical manifestation, underscoring the importance of including herpes zoster in the differential diagnosis of nipple-areolar complex lesions, and provides a brief review of the relevant literature.

Keywords: Herpes zoster; breast disease; nipple; diagnosis; differential

KEY POINTS

- Breast skin, areola, and nipple may present with malignant, inflammatory, infectious, or traumatic lesions.
- Varicella zoster virus may involve the nipple-areola complex mimicking inflammatory or malignant breast conditions and creating a diagnostic challenge.
- Awareness of this presentation prevents unnecessary invasive procedures and enables timely antiviral treatment.

Introduction

A wide spectrum of dermatological conditions can affect the skin of the breast, nipple, and areola. This article reports an uncommon case of herpes zoster involving the nipple-areola complex. Varicella zoster virus (VZV) establishes latency in the dorsal root ganglia of the spinal cord after primary infection in childhood. Its reactivation can manifest as a distressing blistering rash, typically involving one to three adjacent dermatomes, most often the thoracic segments (1). However, involvement of the nipple-areola complex has rarely been documented. Such presentations may be misinterpreted as inflammatory, infectious, or neoplastic breast conditions, potentially resulting to unnecessary interventions or delayed initiation of antiviral therapy.

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Eur J Breast Health
2026;22(2):231-233

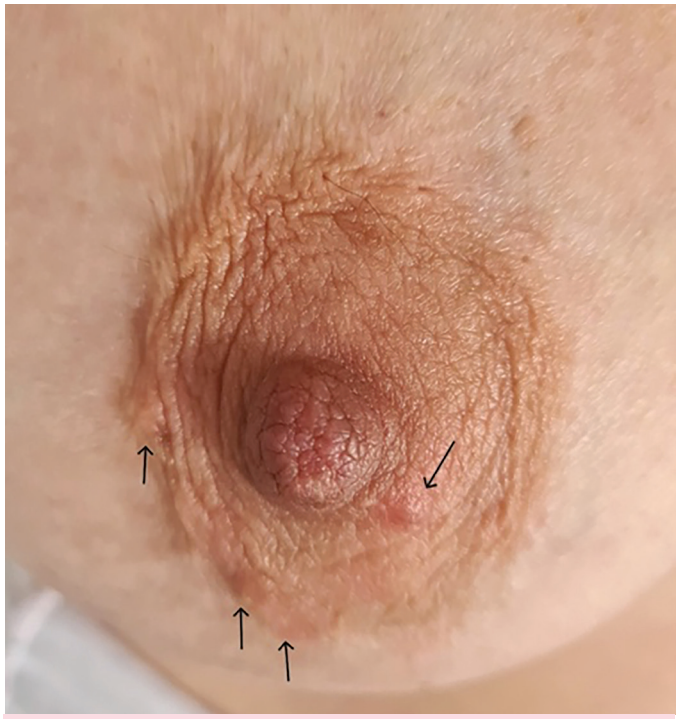

Figure 1. The patient presented with a painful, oedematous nipple. On examination, several evolving vesicles were noted near the nipple and along the lateral semicircular margin of the areola

Case Presentation

A nulliparous 50-year-old woman presented to our department with a burning sensation involving the right breast, which was more intense in the nipple-areola complex and was accompanied by distressing back pain. This clinical presentation commenced three days prior to consultation. The patient reported undergoing yearly breast checkups due to a family history of breast cancer and noted a personal history of mastitis two years earlier. The only chronic conditions mentioned were Hashimoto's thyroiditis and hypercholesterolemia, both managed with medication. The patient disclosed ongoing tobacco use. On clinical examination, the right breast was tender, and the nipple appeared oedematous. Several small vesicular lesions were observed in the areola (Figure 1). Breast ultrasonography revealed no abnormalities. Due to the clinical concern for evolving mastitis, and considering the patient's prior history of the condition and ongoing tobacco use, empirical antibiotic therapy was initiated. Two days later, a vesicular rash developed on the patient's back, following a zosteriform distribution that extended toward but did not involve the right breast (Figure 2). The patient reported childhood varicella infection and had not been vaccinated against herpes zoster. Initial antibiotic therapy was discontinued, and the treatment was altered to include oral valaciclovir for antiviral coverage and gabapentin for pain management. Both the scapular and breast lesions showed clinical improvement shortly after the initiation of antiviral therapy. The rash on the back resolved within ten days; however, the lesion on the breast (Figure 3) persisted for over thirty days before complete resolution.

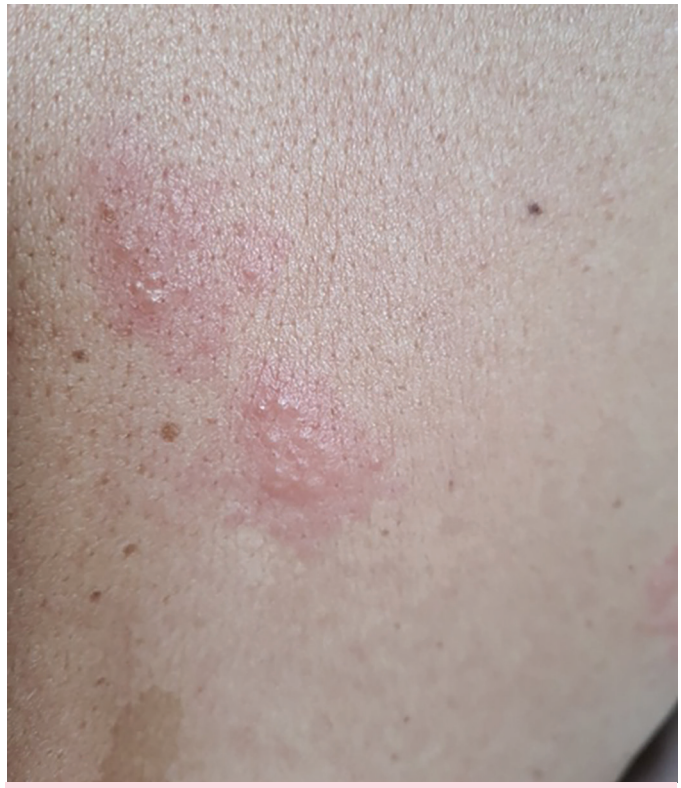

Figure 2. A few days after the initial presentation, the appearance of a vesicular rash on the right side of the back prompted a revision of the diagnosis

Informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion and Conclusion

Breast skin disorders encompass a spectrum of presentations, from localized dermatologic lesions to systemic manifestations. As defined by Deluca et al. (2), breast dermatosis may be classified as a proliferative disease, benign or malignant, or as an inflammatory condition, infectious or non-infectious. Considering this case, an appropriate differential diagnosis included bacterial or viral mastitis, contact dermatitis, and malignant conditions such as Paget's disease of the nipple which often mimics persistent eczematous changes of the nipple-areolar complex (3).

The presence of tender nipple oedema, in conjunction with the patient's medical history and tobacco use, supported the diagnosis of evolving bacterial mastitis. A concerning aspect was that the reported pain was disproportionate to the patient's clinical presentation. The subsequent appearance of the rash on the back provided a diagnostic clue suggestive of VZV infection; however, the characteristic progression along a continuous

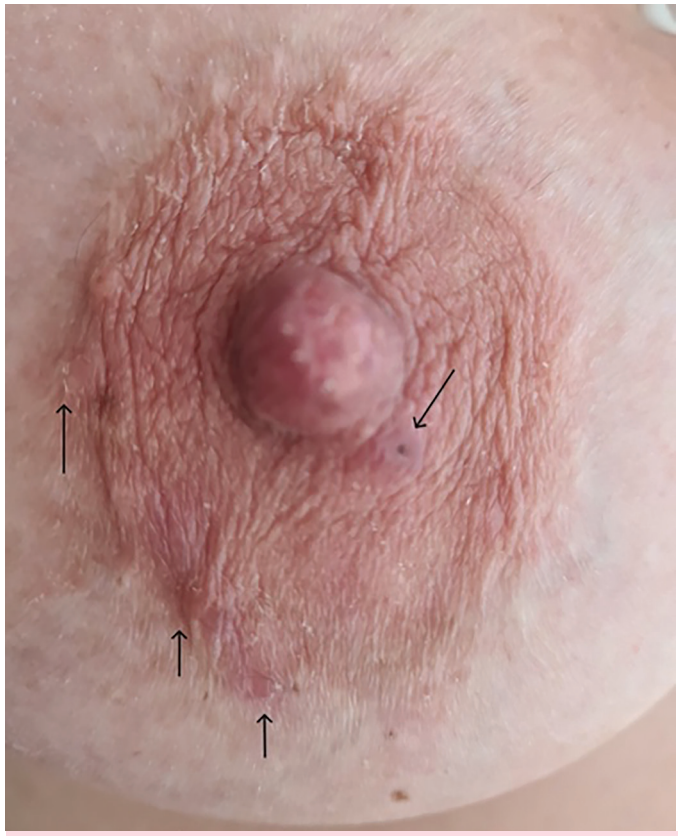

Figure 3. Two weeks later, following initiation of appropriate treatment, both nipple and back rashes followed the expected course of herpes zoster, accompanied by resolution of pain

dermatome was absent, as the rash did not extend to the breast. The clinical improvement of both lesions following initiation of antiviral medication corroborated the diagnosis of herpes zoster.

Regarding viral breast infections, herpes simplex virus can affect the nipple-areola complex (4), whereas VZV usually spares this site. A review of the literature identified only four reported cases of VZV infection of the breast with vesicular eruption involving the nipple-areola complex (5-8). Mathers et al. (5) described a case of herpes zoster presenting typically along the left T4 dermatome, extending from the back to the nipple, which was implicated in the onset of a breastfeeding strike. In contrast, Watanabe et al. (6) reported a case involving a young male patient with VZV infection localized exclusively to the nipple, notably occurring in the absence of the characteristic zosteriform rash. Sütcüoğlu and Özdemir (7) presented a case of a female patient undergoing chemotherapy for metastatic breast cancer, who developed herpes zoster with maculopapular and vesicular lesions involving the left breast and the nipple-areola complex. The diagnostic trajectory outlined by Alonso García et al. (8) closely parallels the present case, in which an initial clinical impression of bacterial mastitis was ultimately revised to be herpes zoster affecting the breast. Collectively, these cases underscore the potential for VZV to affect the nipple-areolar complex and impact related functional activities, such as breastfeeding.

In conclusion, the present report highlights the importance of considering herpes zoster in the differential diagnosis of localized nipple-areolar lesions, particularly when accompanied by neuropathic pain in a dermatomal pattern. Clinicians should remain mindful of the emotional, sexual, and aesthetic significance of the breast, areola, and nipple skin. Careful clinical evaluation and a sensitive approach are essential for the accurate diagnosis and effective management of conditions affecting this region.

Ethics

Informed Consent: Informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Pracites: E.L., G.,K., Z.A., D.V., T.P., M.G., M.K.A.; Concept: E E.L.; Design: E.L.; Data Collection and/or Processing: E.L., G.,K., Z.A., D.V., T.P., M.G., M.K.A.; Analysis and/or Interpretation: E.L., G.,K., Z.A., D.V., T.P., M.G., M.K.A.; Literature Search: E.L., G.,K., Z.A., D.V., T.P., M.G., M.K.A.; Writing: E.L., D.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Bilateral Oleogranuloma of the Breast Following Self-Injection of Baby Oil: A Clinical Image

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ABSTRACT

Self-injection of non-medical substances, such as mineral or baby oil, into the breast for augmentation is an unsafe practice and can lead to serious complications. Chronic granulomatous inflammation and fat necrosis may develop, and the imaging findings may mimic breast cancer, creating diagnostic and therapeutic challenges. We present the case of an 18-year-old woman who developed bilateral breast pain and masses after self-injection of baby oil. We highlight the radiological and histopathological features and remind clinicians to consider foreign-body granulomatous reactions in the differential diagnosis of suspicious breast lesions.

Keywords: Breast augmentation; baby oil; self-injection

KEY POINTS

- Breast injection of baby oil is a rare and non-medical cosmetic practice with significant clinical consequences.
- It can lead to foreign body reactions, fat necrosis, and chronic inflammation.
- Proper clinical history is crtical to avoid misdiagnosis and unnecessary interventions.

Introduction

Esthetic concerns play a significant role in the increasing demand for breast augmentation. Silicone implants are the most commonly used method. Hydrophilic gel-based fillers (such as Aquafilling®) have also been used as non-surgical alternatives; however, serious complications, including infection, migration, deformity, and inflammatory reactions, have been reported on long-term follow-up (1, 2). Historically, non-medical substances such as paraffin, mineral oil, and baby oil have been injected into the breast, but these procedures have been abandoned because they may lead to severe granulomatous reactions and radiological findings that mimic malignancy (3-6). Patients often conceal their history of injection, which may delay diagnosis. In cases where subcutaneous oleomas develop after oil injection, patients may repeatedly deny the use of foreign material. Therefore, this diagnosis should be considered, particularly in patients with atypical and unusual radiological findings. Treatment is usually surgical, and repeated operations may be required (3-6). Awareness of this rare, but important condition is essential for proper diagnosis and management.

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Case Presentation

An 18-year-old woman presented with pain and palpable masses in both breasts. She had no history of trauma or smoking. Physical examination revealed multiple firm masses and skin ulcers in both breasts (Figure 1a). Breast ultrasound revealed bilateral diffuse thickening of the skin and edematous subcutaneous tissue, along with increased echogenicity and numerous well-defined anechoic cystic lesions with surrounding hyperechoic halos (Figure 1b). Magnetic resonance imaging showed that these cystic areas demonstrated the same signal characteristics as fat, being hyperintense on T1- and T2-weighted sequences, with marked signal loss on fat-suppressed sequences (Figure 1c-d). In addition, the glandular tissue showed marked hyperintensity on T2-weighted images, a finding consistent with edema (Figure 1d). On contrast-enhanced fat-suppressed T1-weighted images, a thin rim-like enhancement was observed around these cystic structures (Figure 1e). These findings indicated cystic lesions containing fat with surrounding inflammatory changes, supporting a foreign-body reaction. Ultrasound-guided fine-needle aspiration followed by a tru-cut core biopsy was performed from the most prominent lesion under local anesthesia (Figure 1f). The core biopsy specimen revealed multinucleated giant cells, foamy histiocytes, fat necrosis, and lymphogranulomatous inflammation, consistent with a foreign-body granulomatous reaction.

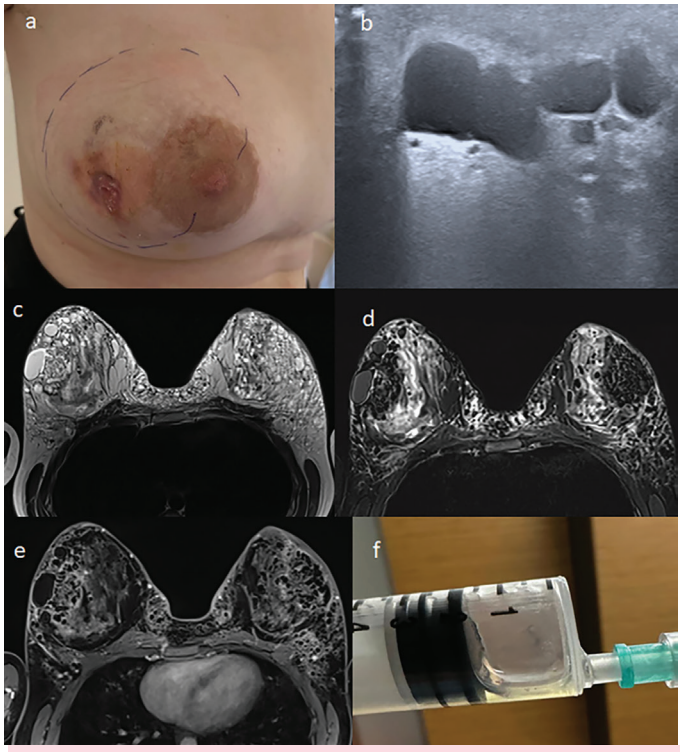

Figure 1. (a) Clinical appearance showing multiple skin ulcers and palpable masses in both breasts. (b) Ultrasound image demonstrating diffuse skin thickening, edematous subcutaneous tissue, and multiple well-defined anechoic cystic lesions with hyperechoic halos. (c-d) Magnetic resonance imaging showing cystic lesions with fat signal characteristics (hyperintense on T1- and T2-weighted images with signal loss on fat-suppressed sequences). (d) The glandular tissue shows marked T2 hyperintensity consistent with edema. (e) On contrast-enhanced fat-suppressed T1-weighted images, a thin rim-like enhancement is observed around these cystic structures. (f) Oily-appearing aspirated material obtained during ultrasound-guided aspiration

Follow-up

On further questioning, the patient admitted to having injected baby oil into both breasts for cosmetic purposes. The case was interpreted as bilateral oleogranuloma secondary to self-injection of baby oil. The patient was referred to a multidisciplinary team including breast surgeons and plastic surgeons. Surgical options, including wide debridement and even mastectomy with delayed reconstruction, were discussed in detail. However, given her young age, the extensive nature of the required surgery, and the patient's strong preference to avoid mutilating procedures at that time, a conservative approach with close clinical and radiological follow-up was chosen. Local wound care was initiated for the superficial skin ulcers, and the patient was scheduled for regular follow-up visits. During follow-up, the ulcers gradually improved, and no new suspicious masses or progressive radiological changes were observed. The patient remains under ongoing surveillance, and delayed surgical correction will be reconsidered if symptoms worsen or new complications develop.

Discussion and Conclusion

Oleogranuloma of the breast is a chronic foreign-body granulomatous reaction that may develop after injection of oily substances, such as paraffin, mineral oil, or baby oil (3-6). The clinical and radiological findings can closely mimic breast malignancy, leading to diagnostic uncertainty and sometimes unnecessary extensive surgery. Although surgical excision or mastectomy is often recommended, especially in symptomatic and extensive disease, a conservative approach with close follow-up may be considered in selected young patients after careful multidisciplinary evaluation (3-6).

In recent years, severe complications after injection of non-approved fillers and oils for breast augmentation have been increasingly reported, including chronic inflammation, infection, migration, and deformity, frequently requiring complex reconstructive surgery (3-6). In addition to the medical consequences, psychosocial factors such as body image dissatisfaction, social pressure, and misleading information shared on social media may drive young women to attempt self-injection with easily accessible substances rather than

seeking professional care (7). Increased public awareness and proper counseling are therefore essential to prevent avoidable harm and to promote safe, evidence-based options for breast augmentation.

Ethics

Informed Consent: Informed consent was obtained from the patient. All potentially identifying features have been removed from the clinical images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.Ç.K.; Concept: Y.K.; Design: Y.K.; Data Collection or Processing: P.Ç.K.; Analysis or Interpretation: P.Ç.K.; Literature Search: Y.K.; Writing: Y.K.

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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LETTER TO EDITOR

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Eur J Breast Health 2026;22(2):237-239

Lipid-Rich Carcinoma of the Breast: A Rare but Aggressive Mammary Malignancy

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Dear Editor,

Breast cancer is a complex and heterogeneous disease encompassing various morphologic and molecular subtypes (1). Invasive ductal carcinoma of no special type is the most common morphologic subtype of breast cancer. Within this subtype, the World Health Organization classification of breast cancers recognizes several rare morphologic patterns, including the lipid-rich variant of breast carcinoma (LRBC) (1). It is characterized by the neoplastic proliferation of cells enriched with neutral lipids in their cytoplasm, irregular nuclei exhibiting marked atypia, and frequent mitoses (1). LRBC appears to be extremely rare, with only around 100 cases published up to mid-2025 (2-4).

Based on the Surveillance, Epidemiology, and End Results (SEER) analysis up to 2021, we identified 15 new LRBCs among approximately three million breast cancer patients, corresponding to ~0.001% of all breast cancer cases. Table 1 summarizes the demographic features, tumor characteristics, treatment details, and survival outcomes of the LRBC cohort.

Notably, most patients were between 50-79 years of age, and 58% of those with available data had high-grade cancers. In line with its aggressive clinical behavior (2), lymph node involvement was also common (57%) (Table 1). The mean survival was 114.7 months, with 33% cancer-specific mortality among evaluable patients.

Our findings from the SEER cohort align with previously published case series and reviews, further underscoring the distinct clinical and pathologic profile of LRBC. A recent comprehensive review by Zhang et al. (2) analyzed 98 published cases and found that LRBC predominantly affected women in their 50s, consistent with the mean age of 62.2 years in our SEER cohort.

Hormone receptor status of LRBC has shown variability in the published literature (5, 6). Zhang et al. (2) reported estrogen receptor (ER) negativity in approximately 65%, progesterone receptor (PR) negativity in around 68%, and human epidermal growth factor receptor 2 (HER2) positivity in ~57% of cases. Shi et al. (7) also reported the predominant absence of ER and PR expression, with >70% exhibiting HER2 expression in LRBC. In contrast, our SEER data revealed 50% ER positivity, 25% PR positivity, while all cases lacked HER2 expression but it is important to note that data were available for only 4/15 patients (27%). This discrepancy, particularly the lack of HER2-positive cases in SEER, may reflect the small number of reported cases and limitations of registry-based data or regional/pathologic heterogeneity in diagnostic interpretation of HER2 expression. Still, it highlights the importance of recognizing the variability in receptor expression, which may impact therapeutic decision-making.

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Table 1. Demographic and clinicopathologic characteristics of the lipid-rich carcinoma cohort from the SEER database

Variable	Lipid-rich breast carcinoma n (%)
Age	
18–49	1 (6.7)
50–79	14 (93.3)
≥80	0 (0.0)
Age mean ± standard deviation	62.2±9.9
Race	
Black	2 (13.3)
White	11 (73.3)
Other	2 (13.3)
N/A	0 (0.0)
Tumor grade	
I	0 (0.0)
II	5 (41.7)
III	7 (58.3)
N/A	3
Tumor stage	
I	1 (14.3)
II	2 (28.6)
III	1 (14.3)
IV	2 (28.6)
N/A	9
Tumor size	
<2 cm	3 (42.9)
2–5 cm	3 (42.9)
>5 cm	1 (14.3)
N/A	8 (53.3)
Lymph node involvement	
Yes	4 (57.1)
No	3 (42.9)
Unknown	8
Distant metastases	
Yes	2 (28.6)
No	5 (71.4)
Unknown	8
Estrogen receptor	
Positive	2 (50.0)
Negative	2 (50.0)
N/A	11
Progesterone receptor	
Positive	1 (25.0)
Negative	3 (75.0)
N/A	11
Human epidermal growth factor receptor 2	
Positive	0 (0.0)
Negative	4 (100.0)
N/A	11
Surgery performed	
No	0 (0.0)
Yes	9 (100.0)
Unknown	6
Adjuvant chemotherapy	
No	4 (40.0)
Yes	6 (60.0)
Unknown	5
Radiotherapy	
No	4 (44.4)
Yes	5 (55.6)
Unknown	6
Survival months (mean ± standard deviation)	114.7 (105.4)
All-cause mortality (%)	
Alive	5 (55.6)
Dead	4 (44.4)
Unknown	6 (40.0)
Cancer-specific mortality (%)	
Dead	3 (33.3)
Alive or dead from another cause	6 (66.7)
Unknown	6 (40.0)

More than 50% of patients in our cohort received adjuvant chemo- and/or radiotherapy (Table 1), while neoadjuvant treatment status was not available in SEER. The data on chemo- and radiotherapy use for LRBC are comparable with those reported by Zhang et al. (2), who also reported neoadjuvant treatment in one patient. Finally, survival data from our SEER cohort suggest relatively prolonged outcomes, with a mean survival of 114.7±105.4 months, compared to the 26.5±46.8 months reported by Zhang et al. (2) in their pooled analysis. This substantial difference may reflect variations in data sources; SEER provides long-term, population-based survival tracking, while the review by Zhang et al. (2) was based primarily on case reports/case series, which often represent more aggressive or complex presentations and may have limited follow-up. Despite the longer mean survival in SEER, the observed 33% cancer-specific mortality and 44% overall mortality among patients with known outcomes underscore the aggressive nature of LRBC, consistent with prior reports.

While the small sample size and missing data in our cohort limit definitive conclusions, the findings collectively support the view that LRBC is a biologically aggressive morphological subtype of breast cancer that warrants early recognition and possibly intensified treatment strategies.

Footnotes

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

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