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Turkish Federation of Breast Diseases Societies

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

SIS ISS SENOLOGIC INTERNATIONAL SOCIETY INTERNATIONAL SCHOOL OF SENOLOGY

NCBC National Consortium of Breast Centers

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European Journal of Breast Health

European Journal of Breast Health

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.

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

Epidemiology, Risk Factors, Prevention, Early Detection, Diagnosis and Therapy, Psychological Evaluation, Quality of Life, Screening, Imaging Management, Image-guided Procedures, Immunotherapy, molecular Classification, Mechanism-based Therapies, Carcinogenesis, Hereditary Susceptibility, Survivorship, Treatment Toxicities, and Secondary Neoplasms, Biophysics, Mechanisms of Metastasis, Microenvironment, Basic and Translational Research, Integrated Treatment Strategies, Cellular Research and Biomarkers, Stem Cells, Drug Delivery Systems, Clinical Use of Anti-therapeutic Agents, Radiotherapy, Chemotherapy, Surgery, Surgical Procedures and Techniques, Palliative Care, Patient Adherence, Cosmesis, Satisfaction and Health Economic Evaluations.

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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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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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/ncidodlEID/cid.htm.

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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 2: Systemic Treatment

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ABSTRACT

Breast cancer represents the most frequently diagnosed malignancy among women globally, with significant progress in systemic therapy, surgical techniques, and radiotherapy contributing to improved clinical outcomes. However, many clinical scenarios encountered in daily practice are not fully addressed by randomized trials, leaving persistent grey zones in the management of early-stage breast cancer. To meet these challenges, the multidisciplinary panel at Research Institute of Senology, Acıbadem University outlined experience-based recommendations for clinical situations typically faced in daily practice. Herein we aim to reflect both current evidence and institutional practice and 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; oncology; systemic

Cite this article as: Şenocak Taşçı E, Sönmez Ö, Oyan Uluç B, Korkmaz T, Yıldız İ, Bozkurt M, et al. Evolving concepts and contemporary management of early-stage breast cancer: an evidence-based approach to grey zones from a comprehensive breast unit part 2: systemic treatment. Eur J Breast Health. 2026; 22(1): 1-18

Key Points

- Integrating genomic assays with traditional clinicopathologic factors allows clinicians to more accurately identify patients who can safely avoid chemotherapy and those who require treatment escalation.
- The addition of CDK4/6 inhibitors to endocrine therapy has emerged as an effective option for selected patients with high-risk disease, though careful consideration of toxicity, cost, and survival data is required.
- Continuing hormonal therapy beyond five years can reduce the risk of late recurrence in selected patients; newer prognostic tools can help determine which patients will benefit most.
- Trastuzumab-based therapy combined with chemotherapy is the cornerstone of treatment for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, with de-escalation or escalation strategies tailored to individual risk.
- Neoadjuvant treatment plays a crucial role in HER2(+) and triple-negative breast cancers, allowing early assessment of response and enabling a more tailored treatment approach that optimizes outcomes and guides postoperative management.

Introduction

Breast cancer (BC), consistently reported as the most frequent cancer in women with an estimated 2.3 million new cases leading to 670,000 deaths in 2022, has an uneven global burden that highlights the urgent need for standardized and unrestricted access to comprehensive management strategies (1). As a result of exceptional efforts by 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, as reported in some high-income countries (2). However, 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.

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Herein, we provide practical recommendations for common clinical questions that arise during our weekly multidisciplinary tumor board meetings. The problems addressed here reflect our personalized approach, which aligns with emerging data on evolving clinical scenarios that we encounter in our daily practice at the Research Institute of Senology of Acıbadem University (RISA). We acknowledge that some of our statements may not be supported by strong evidence or may not be generalizable to all patients because of disparities in medical care, patient preferences, or limited availability of treatments. However, we believe that the recommendations included in this report will provide many physicians involved in BC care nationwide with guidance on a range of challenging and controversial issues. At RISA, we aimed to develop institution-specific standards to guide the evaluation and management of patients with early-stage disease. Our panel is a multidisciplinary team in an academic clinical setting specialized in BC, comprising 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. Initially, each clinical group identified clinical questions that were clinically relevant because of lack of robust data, pending data from clinical trials, or unique scenarios that could not be addressed by the available evidence and therefore required 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 approach that best reflected the recommendations of the experts on the panel.

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

Clinical and Research Consequences

1. Systemic Treatment of Early-Stage Breast Cancer

1.1. Who Needs to be Referred for Predictive Genetic Testing?

1.1.1. Predictive Genetic Testing

In early-stage hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative [HR(+)/HER2(-)] BC, genomic assays serve as essential tools for guiding individualized adjuvant treatment decisions by distinguishing patients who are unlikely to benefit from chemotherapy and who can safely avoid its associated toxicity.

Candidates for these tests are patients with early-stage (stage I or II) HR(+)/HER2(-) BC who are node-negative (N0) or node-positive (N1), including premenopausal and postmenopausal patients (Table 1).

1.1.2. How Do We Manage Intermediate-Risk Patients?

1.1.2.a. Definition of the Patient With Intermediate Risk

Although a universally accepted definition of intermediate recurrence risk in early-stage HR(+)/HER2(-) invasive BC is lacking, specific anatomical and biological tumor characteristics may aid in risk stratification and guide treatment planning.

Tumors in this category are typically 2–5 cm in size and exhibit intermediate histologic differentiation (G2). Nodal involvement, if present, is usually limited to one to three lymph nodes. Hormone receptor expression is often low to intermediate, suggesting some degree of endocrine sensitivity, but not the robust responsiveness seen in low-risk tumors. Increasingly, genomic risk assessment tools provide additional refinement: an Oncotype DX recurrence score (RS) of 16–25, a MammaPrint profile showing high clinical but low genomic risk**,** or intermediate categorizations on Prosigna or EndoPredict assays are all consistent with this risk stratum. From a staging perspective, these tumors generally correspond

Table 1. Commercial genomic tests in early-stage HR(+)/HER2(–) breast cancer

	Gene panel	Prognostic role	Predictive role (chemo benefit)	Platform	Key trials
Oncotype DX	21 genes	Provides RS (0–100) estimating 10-year distant recurrence risk	Yes (for RS 11–25 in node-negative & RS ≤25 in 1–3 node-positive cases)	RT-PCR (FFPE tissue)	TAILORx (4), RxPONDER (5)
MammaPrint	70 genes	Classifies as genomic low vs. high risk	Yes (chemo benefit in high clinical/low genomic risk)	Microarray	MINDACT (6)
Prosigna (PAM50)	50 genes	ROR score + intrinsic subtype (e.g., luminal A/B)	Limited/indirect	NanoString nCounter	TransATAC (101), ABCSG-8 (102)
EndoPredict	12 genes + clinical data (EPclin score)	Estimates 10-year risk of distant metastasis combining molecular and clinical features	Limited (prognostic mainly)	RT-PCR (FFPE)	ABCSG-6/8 (102), GEICAM (103)
BC index	HOXB13:IL17BR ratio + MGI	Prognostic for late recurrence (beyond 5 years)	Yes (for extended endocrine therapy benefit)	RT-PCR	MA.17 (22), TransATAC (101)

ROR: Risk of recurrence; MGI: Molecular grade index; RS: Recurrence score; BC: Breast cancer; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2

to stage IIA or IIB according to American Joint Committee on Cancer criteria (3). The proliferation index also tends to be in a moderate range, with a Ki-67 between 10% and 25%**,** reflecting an intermediate biologic potential for recurrence. Further considerations for identifying intermediate-risk groups based on clinicopathologic findings are also discussed in Section 1.2. In conclusion, the data summarized so far highlight that the optimal use of adjuvant chemotherapy remains individualized.

1.1.2.b. Considerations Based on Clinicopathologic Factors and Predictive Genomic Tests

The key inclusion criteria for the choice of available tests are summarized in Table 2. In our practice, given financial considerations, choice is individualized, with preferential use of this approach for patients classified as borderline (gray-zone) risk.

1.1.3. Management of Intermediate-Risk Patient

The TAILORx trial (4), which focused mainly on the node-negative group, showed that premenopausal women aged ≤50 years with RS 16–25, particularly those with RS 21–25, benefited from chemotherapy, whereas postmenopausal women with RS 16–25 did not. Secondary analyses suggested that chemotherapy or ovarian suppression may also be considered for premenopausal patients with RS 16–20 if high-risk clinical features are present. For node-positive patients in the grey zone, the RxPONDER trial (5) concluded that postmenopausal women with RS ≤25 did not benefit from chemotherapy while premenopausal women with RS ≤25 had significant benefit in terms of invasive disease-free survival (iDFS) regardless of any high-risk criteria (5% improvement). In the MINDACT trial (6), patients with high clinical risk but low genomic risk were included. Although the chemotherapy benefit in women ≤50 years was modest (5%), it remained clinically meaningful and approached significance with longer follow-up. Nevertheless, the PlanB (7) trial demonstrated that patients with a low Oncotype DX RS (RS ≤11) could safely omit adjuvant chemotherapy regardless of nodal involvement. Among these patients, those treated with endocrine therapy (ET) alone achieved an excellent 5-year DFS rate, ranging from 91% to 94.4%.

It can be argued that across TAILORx, RxPONDER, and MINDACT, the chemotherapy benefit observed in premenopausal women was mainly due to chemotherapy-induced ovarian suppression. Notably, ET delivered to this patient group was suboptimal in these trials, with most patients receiving tamoxifen (TMX) as a single agent and ovarian function suppression (OFS) used in only 15–20% of cases. In current practice, OFS combined with an aromatase inhibitor (AI) is a reasonable alternative to chemotherapy for carefully selected premenopausal patients with favorable genomic risk.

The ADAPT trial (8) further personalized this approach by combining static genomic data with a dynamic early biological response, assessed by changes in Ki-67 after a short (3-week) course of preoperative ET. Chemotherapy was omitted for node-negative and 1–3-node-positive patients with RS ≤11 and for those with RS 12–25 who achieved a favorable Ki-67 response (≤10%) after 3 weeks of preoperative ET. On the other hand, persistently elevated Ki-67 was indicative of endocrine resistance and prompted initiation of chemotherapy. The 5-year iDFS rates in hormone-responsive tumors with RS <25 were reported as 93.2% in premenopausal patients and 92.8% in postmenopausal patients, supporting tailored de-escalation in selected estrogen receptors (ER)(+) cases. Prospective data from the high-risk stratum of the HR(+)/HER2(-) WSG-ADAPT trial (9) supported the view that low genomic risk could identify a subset with a favorable prognosis even among patients with more than four positive lymph nodes.

Based on these data, we recommend omitting chemotherapy in postmenopausal patients with RS ≤25. In premenopausal patients with low clinical risk and RS 16–20, OFS plus AI is favored as an alternative to chemotherapy, whereas we generally recommend chemotherapy for patients with high clinical risk and RS 16–20, as well as for those with an RS 21 or higher. For each patient, our multidisciplinary tumor board determines the most suitable management strategy through a comprehensive evaluation and discussion (Table 3).

1.2. How Do We Deliver Optimal Endocrine Therapy in Premenopausal Patients?

1.2.1.a. LHRH Analogues

SOFT and TEXT (10) prospectively evaluated luteinizing hormone-releasing hormone (LHRH) analogues combined with either exemestane or TMX in premenopausal women with BC. In the joint long-term analysis, exemestane plus OFS conferred the largest absolute distant disease-free survival benefit (approximately 10–15%) among very young patients and those with high-risk features (age

Table 2. Inclusion criteria for major genomic assay trials in early-stage HR(+)/HER2(–) breast cancer

Study name	Assay	Key inclusion criteria
TAILORx (4)	Oncotype DX	- Node negative - Tumor size >10 mm, or 6–10 mm with high-risk features (e.g., grade 2–3 or lymphovascular invasion) - Oncotype DX RS 0–25 randomized
RxPONDER (5)	Oncotype DX	- 1 to 3 positive axillary LN - Oncotype DX RS ≤25 - Both premenopausal and postmenopausal women included
MINDACT (6)	MammaPrint	- Women with early-stage breast cancer [HR(+) or HR(–); HER2(–) or HER2(+)] - Tumor size ≥1 cm - Node-neg or 1–3 positive LN - Clinical risk assessed using modified adjuvant! Online criteria - Eligible if MammaPrint result was low risk

RS: Recurrence score; LN: Lymph nodes; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2

<35, chemotherapy-treated, grade 3, Ki-67 ≥20%, T2, or 1–3 positive nodes). The benefit was also observed in women <40 and in those who remained premenopausal after chemotherapy. A STEPP-based composite risk model identified the greatest gain (~15%) among patients aged 35–39 with grade 3 tumors, Ki-67 ≥26%, and 1–3 nodes; a modest gain (4–6% at 8 years) among intermediate-risk profiles; and a minimal gain (~1%) among low-risk patients (no chemotherapy, age 40–44, T1N0, grade 1–2, ER/PR ≥50%, Ki-67 14–19%) (11). The outcomes of these prognostic clinical scenarios have recently been confirmed by a 15-year follow-up analysis (Table 4) (12).

The role of OFS was also evaluated in a patient-level meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), which demonstrated a significant and consistent benefit of combined endocrine treatment in patients who remained premenopausal after chemotherapy and in those who did not receive chemotherapy, across all age groups and irrespective of nodal status (Table 5) (13).

1.2.1.b. Aromatase Inhibitors

Although there have been numerous trials investigating the role of AIs in premenopausal patients, the benefit of AIs per se cannot be ascertained from the current evidence because AIs can only be used in combination with LHRH analogues in this setting.

The TEXT and SOFT trials, which provide the most robust data with the largest sample sizes, have shown that a 5-year combination of exemestane and triptorelin yields significant benefits in distant DFS and overall survival (OS) in higher-risk populations compared with TMX. This benefit was observed regardless of whether TMX was used as a single agent or in combination with OFS, as summarized above (Table 1).

The role of AI in premenopausal patients was also evaluated in a patient-level meta-analysis by the EBCTCG, which showed an absolute benefit of 3.2% in recurrence risk within the first four years after diagnosis; this benefit declined with further follow-up and did not translate into an OS benefit (14). The apparent absence of survival benefits, compared with the previous meta-analysis, could be attributed to the shorter follow-up in the current analysis, since substantial evidence demonstrates a significant benefit of AIs, especially in those with a higher risk of recurrence, as summarized above (15).

1.2.1.c. Risk-Based Clinical Scenarios in Endocrine Therapy

In parallel to the available evidence, we generally prefer to use LHRH analogues combined with AIs in high-risk patients requiring chemotherapy (node positive disease with a high-grade tumor or Ki-67 ≥20%; PR <20%, or those with a high risk of recurrence based on a genomic assay); or younger women aged ≤35 years. Nevertheless, we acknowledge that age is a continuous variable in clinical decision-making. In fact, subgroup analyses from the SOFT-TEXT trials, as well as from TAILOR-X, evaluating the role of chemotherapy compared with ET in those with intermediate-risk disease, have suggested that there is a benefit of chemotherapy in those younger than 40 years, whereas the small benefit observed in the 40–45-year age group may be attributable to the endocrine effects of chemotherapy (16). Therefore, we generally increase the age cutoff to 40 years in intermediate-risk patients for whom a combined endocrine approach with either TMX or AI is considered, regardless of prior chemotherapy. Although it is not possible to define a clear-cut patient profile, some clinical scenarios in which we can opt for combined ET include: intermediate-risk patients with an intermediate genomic risk, as determined by predictive genetic testing if available; or those aged 40–45 years who present with Luminal A or Luminal B disease, T2N0, grade 2–3

Table 3. Recommended treatment strategies for intermediate-risk patients

Patient profile	Recommended treatment
Postmenopausal, RS ≤25	Endocrine therapy alone
Premenopausal, RS ≤15 Premenopausal RS 16–20 & low clinical risk (node-neg)	Endocrine therapy (Tamoxifen only+/-OFS)
Premenopausal, RS 16–20 & high clinical risk Premenopausal, RS 21–25 & node-neg or 1–3 node-positive	Chemoendocrine therapy or OFS + AI as potential alternative (individualized decision-making needed)
Premenopausal, clinical high/genomic low risk [MINDACT (5)]	Chemotherapy debatable — strong endocrine therapy (OFS + AI) may be a suitable alternative

RS: Recurrence score; OFS: Ovarian function suppression; AI: Aromatase inhibitor

Table 4. Long-term follow-up analysis of TEXT and SOFT trials comparing combined endocrine therapy with single-agent TMX in high-risk subgroups

15-year OS (%)	E+OFS	TMX+OFS	TMX
Age <35y	79.4	75.6	
Age 36-39y	83.1	79.5	
Grade 3	SOFT: 82.9 TEXT: 80.6	SOFT: 74.8 TEXT: 76.2	SOFT: 74.6 TEXT: NA
Prior CTx	SOFT: 81.0	SOFT: 77.1	SOFT: 76.8

OS: Overall survival; E: Exemestane; OFS: Ovarian function suppression; TMX: Tamoxifen; CTx: Chemotherapy

tumors, or 1–3 involved lymph nodes, with a Ki-67 of 20–25%, as indicated by subgroup analyses of the TEXT and SOFT trials. An estimated 8-year absolute gain in distant recurrence-free survival (RFS) of 4% was observed, and this gain was more pronounced in the group that had not received prior chemotherapy. Notably, these data were during an earlier period when genomic tests were not widely available, and adjuvant therapy decisions were based solely on clinicopathologic features. Clinical judgment regarding the administration of combined ET must be individualized, incorporating shared decision-making with the patient through a comprehensive discussion of potential benefits, long-term toxicity, and the critical role of adherence.

1.2.1.d. Monitoring Menopausal Status During Endocrine Therapy

Based on evidence from the SOFT and the ASTTRA trials (17, 18), we discuss LHRH analogues as an add-on therapy for some patients with intermediate-risk disease. These patients are those who remain premenopausal following chemotherapy and display persistent ovulatory activity, based on physical examination and hormone measurements [high levels of estradiol and anti-müllerian hormone (AMH) and low levels of follicle-stimulating hormone (FSH)], indicating suboptimal endocrine suppression, or who show significant and persistent endometrial hyperplasia on TMX during follow-up examinations.

1.2.1.e. Duration of LHRH Analogues

Due to the lack of data on extended treatment durations, we generally recommend administering LHRH analogues for five years, consistent with the SOFT and TEXT trials. However, for patients experiencing a significant decline in quality of life due to severe menopausal symptoms, a two-year treatment period may be considered, as suggested by the ASTTRA trial (18).

1.2.1.f. Duration of Endocrine Therapy

Extended adjuvant ET is a reasonable option for endocrine-responsive BC at higher risk of late recurrence, but robust prospective data for premenopausal women remain limited. The ATLAS and aTTom trials, each of which enrolled only about 8% premenopausal participants, showed that extending TMX for an additional 5 years reduced recurrence and BC mortality, especially among node-positive patients. Nevertheless, the NSABP B-14 trial, which focused exclusively on node-negative patients, 26% of whom were premenopausal at diagnosis, failed to identify any benefit, suggesting that patients at lower risk may not require extended ET (19-21). However, there is evidence that menopausal status at the time of extension is pivotal. The MA-17 trial (22) found that letrozole administered for 5 years following 5 years of TMX improved DFS, with the greatest effect in women who were premenopausal at initial enrollment [hazard ratio (HR) 0.26 vs 0.67 for women who were postmenopausal at enrollment]. Although the benefit in node-negative patients could not be evaluated because of the small sample size, a clinically meaningful advantage was observed in node-positive patients (4-year DFS 93.8% vs 85.0%; HR 0.40), supporting extended AI therapy in higher-risk patients.

Based on evidence from these trials, we generally offer an additional 5 years of TMX or AIs after completion of an initial 5 years of ET, regardless of prior OFS use, for patients with stage II or III disease. However, in intermediate-risk patients with stage I-II disease, we consider a shorter total ET duration of 6–8 years, depending on changes in menopausal status and the toxicity profile. This approach is based on extrapolated evidence from multiple trials that have evaluated the role of the TMX-AI switch in the context of a shorter overall duration of ET, as summarized below.

1.2.1.g. Optimal Endocrine Therapy for Invasive Lobular Carcinoma

Invasive lobular carcinoma (ILC) has been associated with poorer long-term outcomes compared with invasive ductal carcinoma in large retrospective registry studies (23, 24). Preclinical and clinical data suggest distinct clinical and genomic profiles with different therapeutic implications (25). A recent subset analysis of the SOFT and TEXT databases showed a greater benefit in BC-free interval with exemestane plus OFS, consistent with findings from retrospective single-institution series (Table 6) (26, 27). Based on the limited available evidence, we generally recommend upfront combined ET for patients who present with intermediate- to high-risk ILC, and we discuss this option with those at lower risk of recurrence. Some patients may be considered for add-on LHRH analogues and may subsequently switch to an AI, depending on individual risk and toxicity profiles, as discussed above.

1.2.2. How Do We Deliver Optimal Endocrine Therapy in Postmenopausal Patients?

1.2.2.a. Definition of Menopause

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity and is confirmed after 12 consecutive months of amenorrhea in the absence of another pathological or physiological cause (28). Similarly, amenorrhea alone does not confirm menopause for up to 12 months following chemotherapy; therefore, a composite evaluation of ovarian functional status and biochemical criteria is required to assess menopausal status. Menopause typically occurs between 45 and 55 years of age, with a global mean of about 51 years. Universally accepted hormonal thresholds are FSH >40 IU/L and estradiol <20 pg/mL, whereas AMH levels, which decline during perimenopause, are usually undetectable (<0.1 ng/mL) at menopause (29).

1.2.2.b. Adjuvant Treatment Options for Postmenopausal Patients

Compared with TMX, AIs are more frequently used in the adjuvant treatment of postmenopausal early-stage BC patients. Several studies have evaluated the efficacy of AIs in early-stage postmenopausal BC: as upfront, sequential (switch), or extended adjuvant treatment (30, 31). Both upfront and switch strategies have demonstrated that AIs provide superior DFS compared with TMX in postmenopausal HR(+) patients. Large trials such as ATAC and BIG 1-98 (31, 32) confirmed the benefit of anastrozole and letrozole over TMX without a corresponding improvement in OS; by contrast, switch trials [IES (30), ITA (33), ABCSG-8 (34), ARNO (34)] demonstrated improved outcomes when patients transitioned to an AI after 2–3 years of TMX. A meta-analysis further established that both upfront and switch approaches reduce recurrence and BC mortality compared with continued TMX, although OS benefits remain modest (15).

Table 5. Combined endocrine treatment compared to single-agent therapy

20-year mortality (%)	OFS	Control
BC related	23.8%	34.7%
All cause	30.4%	42.0%

OFS: Ovarian function suppression; BC: Breast cancer

ET has been administered in various studies using different schedules and durations; however, the optimal duration remains unclear. Based on the studies mentioned, we recommend that postmenopausal patients with early-stage BC receive either 5 years of upfront adjuvant AI or 2–3 years of TMX followed by an AI to complete a total of 5 years of ET.

1.2.3. Extended Endocrine Treatment

Despite the efficacy of 5 years of adjuvant hormonal therapy in HR(+)/HER2(-) postmenopausal early-stage BC patients, prolonging ET appears to be a reasonable approach given the continued risk of recurrence. However, the optimal total duration remains undefined. Several studies have sought to answer this question (Table 7). The DATA trial (35) investigated the efficacy of 2–3 years of TMX followed by either 3 or 6 years of anastrozole and observed a significant DFS benefit with extended ET in lymph node-positive patients [84.4% *vs.* 76.2%, HR: 0.64, 95% confidence interval (CI): 0.46–0.89, p = 0.0075] and in those with tumors ≥2 cm (82.7% *vs.* 69.2%, HR: 0.53, 95% CI: 0.53–0.82, p = 0.0031).

The AERAS and NSABP B42 studies (36, 37) compared 5-year versus 10-year durations of adjuvant AI treatment. In both studies, extended ET was associated with improved DFS compared with shorter ET. No significant difference in OS was observed in either trial. The ABCSG-16 (SALSA) trial (38) also did not find a significant difference between the two arms in terms of DFS, but the 10-year arm had a higher incidence of osteoporosis-related fractures. The MA.17R phase III study showed that longer ET reduced the annual incidence of contralateral BC (49% *vs.* 21%; HR: 0.42; 95% CI: 0.22–0.81).

As discussed above, the optimal duration of extended ET remains unclear. Therefore, the decision should be made on a patient-specific basis. We recommend using an AI for 5 years after 2–3 years of TMX, or for 5 years after an initial 5 years of TMX. Five to ten years of TMX may be considered in postmenopausal patients who have contraindications to, or are unable to tolerate, AIs.

Table 6. Twelve-year BC-free interval from SOFT and TEXT trials based on histologic subgroups

12-year BCFI (%)	Tx	n	n	Tx HR	Tx HR
SOFT (21)		IDC	ILC	IDC	ILC
Luminal A-like	E+OFS	190	31	0.60 (0.35–1.04)	0.16 (0.03–0.78)
	T	183	20		
Luminal B-like	E+OFS	380	24	0.74 (0.54–1.03)	0.58 (0.14–2.33)
	T	407	22		
SOFT+TEXT (15)					
Luminal A-like	E+OFS	341	65	0.93 (0.59–1.47)	0.48 (0.15–1.56)
	T+OFS	350	73		
Luminal B-like	E+OFS	952	79	0.64 (0.52– 0.79)	0.70 (0.31–1.58)
	T+OFS	979	67		

BCFI: Breast cancer free interval; Tx: Treatment; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; E: Exemestane; TMX: Tamoxifen; OFS: Ovarian function suppression; HR: Hazard ratio

Table 7. Clinical trials evaluating extended endocrine therapy in early-stage breast cancer

Trial	Population	Treatment	5-year DFS	5-year OS
AERAS (36)	After 5 years of AI	Anastrozole 5 more years *vs.* stop	91.9% *vs.* 84.4% (p = 0.0004)	Not reported
NSABP B42 (37)	Prior AI or sequential ET	Letrozole 5 years *vs.* placebo	75.9% *vs.* 72.6% (10y) (p = 0.01)	NS
ABCSG-16 (38)	After 5-years of AI or TMX	Anastrozole 2 *vs.* 5 years	73.9% *vs.* 73.6% (p = 0.9)	87.5% *vs.* 87.3% (NS)
MA.17R (22)	Completed 10 years (5TMX + 5 AI)	Letrozole 5 years *vs.* placebo	95% *vs.* 91% (p = 0.01)	93% *vs.* 94% (p = 0.83)
DATA (35)	Completed 2-3 years of TMX	Anastrozole 3 *vs.* 6 years	69.2% *vs.* 66% (10y) (p = 0.073)	79.4% *vs.* 83.1% (p = 0.60)

DFS: Disease free survival; OS: Overall survival; AI: aromatase inhibitor; ET; Endocrine treatment; TMX: Tamoxifen; NS: Not significant

1.2.3.a. Biomarkers Predictive of Benefit from Extended Endocrine Therapy

Several studies evaluated predictive biomarkers to identify patient subgroups most likely to benefit from extended ET. These efforts led to the identification of the clinical treatment score post-5 years (CTS5) and the breast cancer index (BCI) as useful markers with the potential for routine clinical use.

CTS5 is an online tool designed to estimate the risk of late recurrence in postmenopausal patients who have completed 5 years of adjuvant ET. Using data from the ATAC and BIG 1-98 trials, CTS5 calculates late recurrence risk based on tumor size, tumor grade, the number of involved lymph nodes, and the patient's age at diagnosis (32, 39). In a retrospective analysis, the 10-year distant recurrence risk was reported as 2.9% in the CTS5 low-risk group, 7.2% in the intermediate-risk group, and 12.9% in the high-risk group (40). It was noted that extended ET may be beneficial for patients in the high-risk group.

Another potential predictor of benefit from extended ET is BCI. BCI combines two gene expression signatures that evaluate the response to ET. Secondary analyses of the MA.17, Trans-aTTom and IDEAL trials (41) showed that extended ET significantly improved DFS compared with the control group in HR(+) T1-T3 tumors, whether lymph node-negative or -positive with a high BCI (H/I) ratio.

Our recommendation is that extended ET be implemented after a comprehensive discussion with each patient, based on the available evidence. Patients most likely to benefit from extended ET:

1.High clinical risk factors;

a) Positive lymph nodes (especially >3)

b) Larger tumor size (≥T2)

c) High histologic grade (grade 2-3)

d) Lymphovascular invasion

e) Younger postmenopausal age (<60 years)

2.High genomic risk (if available): BCI predicts benefit from extended ET.

1.3. Whats is the Role of CDK4/6 Inhibitors in Adjuvant Setting?

Adjuvant CDKi, which have demonstrated marked efficacy in metastatic BC, have been extensively evaluated in earlier stages to prevent recurrence (42-44).

Four major randomized trials—PALLAS and PENELOPE-B (palbociclib), monarchE (abemaciclib), and NATALEE (ribociclib)—investigated these agents in the adjuvant setting (45-49). While the PALLAS and PENELOPE-B trials failed to show a statistically significant improvement in iDFS, both monarchE and NATALEE reported clinically meaningful improvements in iDFS in selected high-risk populations (47, 48). These results led to regulatory approvals and the incorporation of abemaciclib and ribociclib into major guidelines (e.g., National Comprehensive Cancer Network, European Society for Medical Oncology) for adjuvant use in HR(+)/HER2(–) early-stage BC patients at increased risk. However, several challenges persist: OS data for ribociclib remain immature; treatment discontinuation rates are substantial (up to 36%); toxicity profiles differ; and cost-effectiveness remains debated. Additionally, differences in trial design (e.g., inclusion criteria, risk definitions), treatment duration (2 *vs.* 3 years), endocrine backbone (AI *vs.* TMX), and menopausal status are critical factors that should be considered before widespread implementation.

1.3.1. Optimal Use of Adjuvant CDK Inhibitors

Among CDK4/6i investigated in the adjuvant setting, abemaciclib and ribociclib have shown the most robust efficacy in high-risk HR+/HER2– early BC. Table 8 summarizes the characteristics and results of the monarchE and NATALEE trials. The monarchE trial included patients with residual disease following neoadjuvant treatment (NAT), and subgroup analyses suggest that this cohort derived a substantial benefit from abemaciclib. However, the PENELOPE-B trial, which enrolled a similar NACT-exposed population, failed to demonstrate a benefit from palbociclib (HR: 0.93; p = 0.525) (46). This highlights the importance of differences in drug potency, pharmacokinetics, and treatment duration (Table 9). While both abemaciclib and ribociclib have demonstrated clinical utility, we individualize their use based on patient-specific clinical features. Given its shorter treatment duration and greater absolute iDFS benefit, abemaciclib appears to be the optimal choice for high-risk patients who have a high tumor burden or residual disease following NACT. Ribociclib, given its longer treatment window and broader eligibility criteria, may be preferred for a broader range of node-positive patients and considered in node-negative patients with high-risk biological features irrespective of chemotherapy use (47).

At our institution, we generally recommend adjuvant CDK4/6i, particularly for patients meeting the MonarchE or NATALEE criteria, based on results of the corresponding phase III trials showing improved iDFS in high-risk HR(+)/HER2(–) early-stage BC. We tend to use ribociclib in patients with high-risk, node-negative disease or

Table 8. Baseline characteristics of patients and updated efficacy outcomes of NATALEE and monarchE trials

	No of patients	Eligibility criteria	Treatment regimen	Prior chemotherapy	Treatment duration	iDFS	dRFS
NATALEE (47)	5.101	Stage II–III, incl. T2N0 + Ki-67 ≥20%, grade 3, or high genomic score (RS >26)	Ribociclib 400 mg/ day (3w on/1w off) + ET	65%	3 years	90.7% *vs.* 87.6% (3y) (Δ3.1%)	92.9% *vs.* 90.2%
monarchE (48)	5.637	≥4 positive nodes or 1–3 nodes + grade 3 or tumor size ≥5 cm	Abemaciclib 150 mg BID + ET	95%	2 years	83.6% *vs.* 76.0% (5y) (Δ7.6%)	88.4% *vs.* 82.5% (4yr)

RS: Recurrence score; ET: Encodrine treatment; BID: Twice a day; iDFS: Invasive disease-free survival; dRFS: Distant relapse-free survival

with microscopic nodal involvement. However, because of the lack of OS data, high cost, significant toxicity and limitations arising from informative censoring bias (as mentioned earlier), we discuss the available data with our patients to ensure an individualized approach and shared decision-making. We acknowledge that use of adjuvant CDK4/6i should be reserved for selected high-risk patients until final survival results from the phase III trials and translational data to guide identification of subgroups who may derive greater benefit are available.

Table 9. Gray zones in early breast cancer

Definition of intermediate-risk patients	-2–5 cm, intermediate histologic differentiation (G2) -One to three lymph nodes -Hormone receptor expression low to intermediate -Oncotype DX recurrence score of 16–25 -MammaPrint profile showing high clinical but low genomic risk -Ki-67 10–25%
Management of intermediate-risk patients	Refer Table 3
Rsk-based endocrine treatment (combined LHRH analouges with AIs)	-Node positive disease with a high-grade tumor or Ki-67 ≥20%, PR<20% -High risk of recurrence based on a genomic assay -Younger women aged ≤40 years. -Aged 40–45 years presenting with Luminal A or Luminal B, T2N0 grade 2-3 tumors or 1–3 involved lymph nodes with a Ki-67 20–25%
Duration of endocrine therapy (premenapousal)	-Stage II-III; 5 years of extended TMX or AIs following completion of an initial 5 years of endocrine therapy, regardless of prior OFS use. -Stage II-II disease Intermediate-risk patients; 6-8 years of ET depending on the changing menopausal status and toxicity profile
Duration of endocrine therapy (postmenapousal)	-5 years of upfront adjuvant AI or 2–3 years of TMX followed by an AI to complete 5 years of total ET - AI for 5 years following 2–3 years of TMX, or for 5 years following an initial 5 years of TMX (high-risk)
Extended endocrine therapy benefit	1. High clinical risk factors; a) Positive lymph nodes (especially >3) b) Larger tumor size (≥T2) c) High histologic grade (grade 2-3) d) Lymphovascular invasion e) Younger postmenopausal age (<60 years) 2. High genomic risk (if available): BCI predicts benefit from extended ET.
Adjuvant CDK4/6 inhibitor use	- High-risk patients with high tumor burden or residual disease following neoadjuvant treatment -High risk node-negative patients: should be individualized based on clinical and pathological features, genomic profiling (e.g., Oncotype DX, MammaPrint), and patient preferences Alternative in highly selected patients.
Replacing chemotherapy with ET+CDKi	- Postmenopausal women with strongly HR(+)/HER2(–), node-negative or limited node-positive disease, who have intermediate proliferation indices (Ki-67 <20%) and wish to avoid chemotherapy - Frail patients or ones with comorbidities, where chemotherapy-related toxicities pose unacceptable risks - Patients with low genomic but high clinical risk, where endocrine sensitivity is strong and risk of residual disease is modest
Adjuvant CDKi use in BRCA carriers	Sequential use of olaparib followed by CDK4/6i may be considered in select patients with a high risk of recurrence
Anthracycline use	- Less endocrine sensitive, -Luminal B, -Nod-positive stage II/III, -MP-H2 and Oncotype Dx RS ≥31 -For TNBC, tumors ≥1cm and in neoadjuvant treatment of stage II/III disease

Table 9. Continued

Omission of chemotherapy	-T1aN0 TNBC - T1N0 TNBC with histology of adenoid cystic carcinoma, secretory carcinoma, and low-grade adenosquamous carcinoma - Elderly (≥70 years) or frail patients with HER2(+) BC, especially those with small tumors or substantial comorbidities - HER2(+) tumors <3 mm
Adjuvant olaparib use	- Adjuvant treatment of *gBRCA1/2m* and high-risk TNBC - Adjuvant treatment of *BRCA* carriers with residual disease and a CPS+EG score ≥3 in HR(+) -Consideration of adjuvant olaparib in high-risk patients with germline *PALB2* mutations
Neoadjuvant endocrine therapy	Although not routinely recommended; -In the geriatric patients with locally advanced disease and significant comorbidities with ER ≥50%, PR ≥20%, Ki-67 <20%, grade 1–2, N0–N1
Adjuvant therapy in *BRCAm* TNBC patients without pCR	Concomitant use of olaparib with pembrolizumab
Management of ER low patients	Like TNBC in the preoperative setting but ET is recommended in adjuvant setting
De-escalation of adjuvant treatment in HER2(+) BC	Consider shorter durations of adjuvant trastuzumab in patients with a lower risk for recurrence, such as stage I and HR(+) disease
Treatment of elderly, frail patient with HER2(+)	Trastuzumab monotherapy may be considered

1.3.1.a. High-Risk Node-Negative Disease and Adjuvant CDK4/6i Use

Given the favorable results reported in the NATALEE trial, the use of adjuvant CDK4/6i in high-risk node-negative patients has generated increasing interest.

Unlike the monarchE trial, which almost exclusively enrolled node-positive patients, the NATALEE trial included approximately 24% node-negative patients. In a prespecified subgroup of T2N0 patients (n = 285), ribociclib plus ET led to a 4-year iDFS of 92.1% versus 87.0% with ET alone, corresponding to an absolute benefit of 5.1% (HR: 0.666; 95% CI: 0.397–1.118). Although this difference did not achieve statistical significance, it is suggestive of benefit and warrants further exploration (49). In contrast, abemaciclib has not been evaluated in node-negative patients, because the monarchE trial excluded this population by design, restricting enrollment to patients with ≥4 positive nodes or to those with 1–3 positive nodes who also had additional risk factors. Thus, there is no evidence supporting the use of abemaciclib in node-negative, high-risk disease.

When considering the clinical utility of ribociclib in this population, the modest absolute benefit must be weighed against toxicity. In the NATALEE trial, grade ≥3 neutropenia occurred in 44% of patients, and 20% discontinued treatment; this included patients in the node-negative subgroup, raising questions about the validity of the iDFS benefit, especially in a relatively low-risk patient group (49). Additionally, the treatment duration of 3 years may pose a burden for patients with an otherwise favorable prognosis.

Given these factors, a universal recommendation for CDK4/6 inhibition in all high-risk N0 patients is not currently justified. Instead, we recommend that patient selection be individualized based on clinical and pathological features, genomic profiling (e.g., Oncotype DX, MammaPrint), and patient preferences (16). Results of ongoing translational studies are awaited to identify molecular predictors of benefit in this population. According to the St. Gallen 2025 Consensus, the use of CDK4/6 inhibitors in stage II disease should follow a risk-adapted, individualized approach (50).

1.3.1.b. Can We Replace Chemotherapy With ET+CDKi?

The prospect of replacing chemotherapy with ET plus a CDK4/6i in selected HR(+)/HER2(–) early-stage BC patients has emerged as a conceptually appealing strategy, particularly in the era of biologically tailored treatment. This approach is particularly appealing for postmenopausal women with low clinical risk but high genomic risk who wish to avoid chemotherapy. Confirmatory data have been obtained from the NATALEE trial, which showed a benefit from adjuvant ribociclib in a small subgroup of node-negative patients who did not receive adjuvant chemotherapy, as discussed in the previous section. Based on encouraging data from these as well as phase I neoadjuvant proof-of-concept trials, including the neoMONARCH (abemaciclib), NeoPAL (palbociclib), and FELINE (ribociclib) showing a rapid suppression of cellular proliferation by CDK inhibitors, further clinical studies have been planned to evaluate the role of a response-guided approach that aims to identify subgroups of patients who may be spared chemotherapy (51-53). However, direct head-to-head comparisons between CDK4/6-based ET and chemotherapy in the early-stage setting remain limited. To date, no phase III trial has demonstrated non-inferiority of ET plus CDKi over chemotherapy in terms of iDFS or OS. Thus, CDKi is not a substitute for chemotherapy in patients at high clinical risk, or in those with residual disease after NAT. Nonetheless, certain patient subgroups merit individualized consideration in our daily practice;
- Postmenopausal women with strongly HR(+)/HER2(–), node-negative or limited node-positive disease, who have intermediate proliferation indices (Ki-67 <20%) and wish to avoid chemotherapy,
- Frail patients or ones with comorbidities, where chemotherapy-related toxicities pose unacceptable risks,

- Patients with low genomic but high clinical risk, where endocrine sensitivity is strong and risk of residual disease is modest. Data from ongoing studies and real-world cohorts are awaited before adopting this approach in routine clinical practice. In conclusion, while ET plus CDK4/6i cannot universally replace chemotherapy, they may serve as a valid alternative in highly selected patients. Until robust comparative efficacy data emerge, shared decision-making, incorporating clinical, genomic, and patient-preference factors, remains the cornerstone of treatment selection.

1.3.1.c. Considerations of Adjuvant CDKi Use in BRCA Carriers

Patients with HR(+)/HER2(-) early-stage BC carrying germline *BRCA1* or *BRCA2* mutations (*gBRCAm*) represent a biologically distinct subgroup. Real-world and retrospective studies have suggested that treatment outcomes with CDK4/6i may be worse in patients with pathogenic *gBRCAm* BC compared with those with *gBRCAwt* disease (54, 55). BRCA mutations are often associated with concurrent alterations in genes such as RB1 and TP53, which may contribute to resistance to both ET and CDK4/6i. In fact, confirmatory data have been reported in a recent meta-analysis of twenty-two studies, which showed significantly inferior outcomes with CDK4/6i, driven by shorter PFS in the *gBRCA2m* subgroup (56). Despite these concerns, current evidence suggests that CDK4/6i combined with ET is still more effective than ET alone for *gBRCAm* patients (53). While awaiting data from ongoing trials, sequential use of olaparib followed by CDK4/6i may be considered in selected patients at high risk of recurrence (57).

1.4. Are Adjuvant Anthracyclines Required for All Patients?

1.4.1.a. Available Evidence for Adjuvant Anthracycline Use

Although anthracyclines became standard in the 1980s–1990s, data from the mid-2000s showed that anti-HER2 and taxane-based backbones could achieve comparable efficacy with less toxicity. A patient-level EBCTCG meta-analysis across HR(+) and HR(-) disease determined that sequential use of anthracycline→taxane (AC-T) was broadly comparable to six cycles of docetaxel–cyclophosphamide (TC), with only a small overall advantage for anthracyclines, driven by concomitant anthracycline–taxane schedules that are rarely used today, regardless of hormone-receptor and nodal status (58). In the ABC trial (59), although non-inferiority of TC6 versus TaxAC was not met in the intention-to-treat population at approximately 7 years of follow-up, any clinical benefit from anthracyclines was confined to the ER-negative subset. Notably, a significant increase in leukemia risk and numerically higher cardiac deaths, together with a lack of OS benefit, do not support TC6 for most HR(+)/HER2(-) early BC. The West German Study PlanB trial (60) was a unique phase III study that evaluated the non-inferiority of TC6 versus EC-T, using either clinical or genomic risk criteria, in HER(-) early BC. Results showed that both regimens were equally effective in pN0 high-risk or pN1 with genomically intermediate-to-high-risk disease.

Data from the DBCG 07-READ trial (61), as well as other studies, are consistent with population-based case-control studies showing a higher 10-year cumulative incidence of HF with AC-T (4.1% vs 2.3%). In HER2(+) disease, BCIRG-006 trial (62) reported similar efficacy for anthracycline- and non-anthracycline trastuzumab backbones but more cardiotoxicity and leukemias with anthracyclines; while, de-escalation regimens such as 12-weekly paclitaxel–trastuzumab in the APT trial (63) and a longer non-anthracycline based chemotherapy with dual HER2 blockade in the TRAIN trial achieved excellent outcomes and high pathological complete response with lower toxicity (64).

Limited data exist specifically for patients with triple-negative BC (TNBC). Nevertheless, a recent meta-analysis of adjuvant chemotherapy in TNBC, including eight studies (n = 4292), showed non-inferiority of anthracycline-free regimens to anthracycline-based sequential regimens with respect to the risk of recurrence, but not to the risk of death (8).

1.4.1.b. Predictive Biomarkers of Anthracycline Benefit

Genomic stratification can identify subsets of HR(+)/HER2(-) early BC patients who preferentially benefit from anthracyclines. In the prospective real-world FLEX registry, MammaPrint ultra-high-risk (MP-H2) luminal B tumors had higher 3-year RFS with anthracycline-based therapy than with TC (97.7% *vs.* 86.4%); no advantage was seen for high-risk MP-H1 tumors (65). MP-H2 tumors were more frequently grade 3 and showed greater chemosensitivity, with a pathologic complete response (pCR) rate of 32% with AC-T versus 0% with TC (66). Complementary I-SPY data indicate that MP-H2 cancers share immune-related transcriptional features and clinical behavior with triple-negative disease, exhibit lower ER signaling (45% with ER 1–10% *vs.* 4% in MP-H1), and achieve higher pCR with pembrolizumab plus T-AC compared with MP-H1 (54% *vs.* 21%), consistent with anthracycline-sensitive, immunogenic biology (67). In TAILORx, among patients receiving chemotherapy, those with Oncotype DX RS≥31 experienced superior DRFI/DRFS/RFS with T-AC versus TC and showed a trend toward improved OS; benefit increased incrementally with higher RS scores when analyzed as a continuous variable, whereas no benefit was observed for patients with RS <31 (3). Approximately 58% concordance between RS≥31 and MP-H2 supports a shared aggressive phenotype in which anthracycline-containing regimens may be preferred over TC (4).

Another set of proposed predictive biomarkers to identify patients most likely to benefit from anthracyclines includes amplification or deletion (aberrations) of the *TOP2A* gene and chromosome 17 (CEP17) centromeric duplication. A pooled analysis of five trials reported improved outcomes with anthracycline-based therapy among patients harboring a *TOP2A* aberration or a CEP17 duplication (68).

1.4.1.c. Patients With HER2(+), TNBC and HR(+) Early BC Who Do Not Require Anthracycline-Based Adjuvant Chemotherapy

Contemporary evidence supports selective, rather than routine, use of anthracyclines, favoring non-anthracycline, taxane-based backbones in HR(+)/HER2(-) and many HER2(+) settings, while reserving anthracyclines for biologically or clinically high-risk subsets. In our practice, prefer anthracyclines for less endocrine-sensitive, luminal B, node-positive stage II/III, MP-H2, and Oncotype Dx RS ≥31 ER(+) BC. For TNBC, anthracyclines are essential components of adjuvant chemotherapy for tumors ≥1 cm and of neoadjuvant treatment of stage II/III disease, in combination with immunotherapy.

1.5. Which Patients Can Be Identified as Candidates for Omission of Chemotherapy?

Identifying patients in whom adjuvant chemotherapy can be safely omitted remains one of the most challenging aspects of early BC management, and is not within the scope of this paper. To optimize the risk-benefit balance for each patient, this decision requires careful integration of tumor biology, patient-specific factors, disease

characteristics, and available clinical evidence. Nevertheless, we specifically sought to examine the TNBC and HER2(+) subgroups, where the therapeutic boundaries are more clearly defined.

1.5.1. TNBC

1.5.1.a. T1a Disease

The management of very small TNBC, specifically T1a (≤0.5 cm) node-negative tumors, poses a clinical challenge, given the limited prospective data from randomized trials. Patients with T1a TNBC who did not receive adjuvant chemotherapy have consistently shown excellent outcomes in retrospective analyses, with 5-year dRFS rates ranging from 90% to 95% (69). Given the acute and long-term toxicities associated with systemic treatment, the absolute benefit of chemotherapy for this population is likely negligible. Our panel therefore concluded that patients with T1a, node-negative TNBC may safely omit adjuvant chemotherapy. However, for tumors measuring 4–5 mm, the potential for a minimal yet non-negligible benefit from adjuvant chemotherapy cannot be completely excluded. In these situations, individualized decision-making that integrates additional risk factors and includes a comprehensive discussion of the uncertain but possible advantages of systemic therapy is essential.

1.5.1.b. Low Risk TNBC Histology

The potential to omit chemotherapy also extends to certain rare histological variants of TNBC with favorable prognosis (70). Adenoid cystic carcinoma, secretory carcinoma, and low-grade adenosquamous carcinoma generally exhibit indolent behavior and excellent long-term outcomes despite their triple-negative immunophenotype. Our panel supports consideration of chemotherapy omission in patients with these special subtypes, particularly in T1N0 disease, following comprehensive multidisciplinary evaluation.

1.5.2. HER2(+) Disease

1.5.2.a. Frail Elderly Patients

The RESPECT trial (71) demonstrated that, in elderly patients (≥70 years) with HER2(+) BC, anti-HER2 therapy without chemotherapy may be considered in selected cases. This approach is particularly relevant for patients with significant comorbidities or functional limitations that preclude the safe administration of intensive chemotherapy regimens. Our panel supports the use of trastuzumab alone in elderly or frail patients with HER2(+) BC, especially those with small tumors or substantial comorbidities.

1.5.2.b. T1a Disease

Although HER2 amplification is generally associated with aggressive tumor biology, the absolute benefit of chemotherapy in very small tumors (≤5 mm) is limited. Our consensus emphasizes that chemotherapy plus trastuzumab may be omitted for selected patients with very small tumors, particularly those <3 mm. For tumors measuring 4–5 mm, however, chemotherapy plus trastuzumab should be considered, especially in HR(-) disease, which confers a higher risk of recurrence.

1.5.3. Optimal Use of Adjuvant Olaparib

The landmark OlympiA trial established olaparib as a new standard of care in the adjuvant setting for patients with *gBRCA1/2m* and high-risk early BC who had received neoadjuvant or adjuvant chemotherapy. This trial demonstrated significant improvements in both iDFS and OS (57).

1.5.3.a. TNBC

Among patients with TNBC and *gBRCA1/2m*, the evidence supporting adjuvant olaparib is strongest. Most patients with high-risk triple-negative disease, particularly those with node-positive disease or large primary tumors, undergo NAT. The management of TNBC patients with *gBRCA1/2m* who have residual disease following NAT requires careful consideration of all available options. The recently updated 6-year OlympiA analysis demonstrated a persistent benefit from adjuvant olaparib, with HRs of 0.72 for iDFS and 0.652 for OS (57). Based on these durable benefits, our panel recommends adjuvant olaparib for one year. Capecitabine administered for six months may be considered an alternative if olaparib is contraindicated or unavailable. For patients treated with neoadjuvant pembrolizumab, completion of the planned nine adjuvant cycles of pembrolizumab should remain a priority, with pembrolizumab administered in parallel with olaparib when feasible.

A subset of TNBC patients considered to have lower-risk disease proceeds directly to surgery. For BRCA carriers with either node-positive disease or a primary tumor ≥2 cm, as confirmed on the surgical specimen, our panel also supports adjuvant olaparib.

Overall, we strongly recommend adjuvant olaparib to all eligible patients with *gBRCA1/2m* and high-risk TNBC for one year following completion of definitive local and systemic therapy.

1.5.3.b. HR(+) Breast Cancer

The role of adjuvant olaparib in HR(+) disease is more limited (57). We support its use in patients with *gBRCA1/2m* who received adjuvant chemotherapy and had ≥4 positive lymph nodes.

For patients treated with NAT who did not achieve pCR, eligibility for adjuvant olaparib depends on the pretreatment clinical stage, post-treatment pathologic stage, estrogen receptor status, and tumor grade (CPS+EG score). For *BRCA* carriers with residual disease and a CPS+EG score ≥3, our consensus supports adjuvant olaparib for one year, although we acknowledge that the label excludes CPS-EG score due to concerns of undertreatment in selected cases with a lower score and higher risk of recurrence, who may be considered for adjuvant olaparib.

1.5.3.c. Role of Adjuvant Olaparib in *PALB2* PV Carriers

PALB2 mutations represent the second most common hereditary predisposition to BC after *BRCA1/2*. The *PALB2* protein interacts directly with *BRCA2* in homologous recombination repair, providing a strong biological rationale for PARP inhibitor sensitivity in *PALB2* mutation carriers (72).

The primary clinical evidence supporting the use of olaparib in *PALB2* mutation carriers derives from the TBCRC-048 trial, which reported a response rate of 82% in patients with metastatic BC harboring germline *PALB2* mutations (73). Additional support derives from the ongoing APOLLO trial, which is evaluating adjuvant olaparib in pancreatic cancer patients with *BRCA1/2* and *PALB2* mutations (74). Based on these data and the underlying biological rationale, our panel supports consideration of adjuvant olaparib for high-risk BC patients with germline *PALB2* mutations, as recommended in the St. Gallen 2025 Consensus (50). However, clinicians should carefully counsel patients regarding the off-label nature of this indication.

1.6. Neoadjuvant Treatment

1.6.1. Identification of the Patient Who Requires Neoadjuvant Treatment

Patient selection for NAT is linked to tumor biology, stage, and prognostic factors. For HER2(+) BC, NAT is strongly recommended in patients with stage II–III disease, with tumors exceeding 2 cm, or with node-positive status—particularly when accompanied by aggressive biological features. Evidence supports the combination of anthracycline/taxane-based chemotherapy with dual HER2 blockade using trastuzumab and pertuzumab (TP), which has significantly increased pCR rates in landmark studies (75-77). In TNBC, NAT should be considered for tumors ≥ T1c or those with nodal involvement, especially if tumors demonstrate high proliferation (Ki-67 ≥30%) or grade-3 histology. The integration of pembrolizumab into standard chemotherapy backbones in eligible patients is now considered standard of care (78). For HR(+)/HER2(-) disease, NAT is typically reserved for high-risk stage II–III cases. In Luminal A tumors with low proliferation, neoadjuvant ET may be considered in carefully selected older patients as a reasonable, less toxic alternative, whereas Luminal B tumors with high proliferation indices are more likely to benefit from chemotherapy (79, 80). We also consider the histopathological subtype, proliferation index, hormone receptor status, HER2 status, and nodal involvement when determining eligibility for NAT.

1.6.2. Predictive Genetic Tests to Determine Eligibility for Neoadjuvant Endocrine Therapy

Genomic assays such as Oncotype DX, MammaPrint, and EndoPredict are increasingly being evaluated for their ability to predict response to neoadjuvant ET in HR(+)/HER2(-) BC. Oncotype DX RS has been correlated with neoadjuvant ET outcomes in multiple studies, with lower RS associated with higher clinical response rates and higher rates of breast-conserving surgery (81). A meta-analysis confirmed significantly better neoadjuvant ET response rates in low-RS versus high-RS groups, and ongoing trials are investigating RS changes pre- and post-treatment as prognostic markers (82). MammaPrint, validated for adjuvant chemotherapy selection, is under evaluation for neoadjuvant ET guidance, with early data suggesting that molecular subtyping with MammaPrint/BluePrint may improve treatment prediction and the feasibility of neoadjuvant ET in low-risk cases (83). Although we rarely use this approach in our routine clinical practice — mostly in geriatric patients with locally advanced disease and significant comorbidities who would otherwise be unsuitable for chemotherapy — there is limited evidence to support its use in other settings. In such cases, integrating genomic profiling with established clinicopathological parameters (ER ≥50%, PR ≥20%, Ki-67 <20%, grade 1–2, N0–N1) may provide a more refined strategy to identify patients who are appropriate candidates for neoadjuvant ET (84).

1.6.3. Optimal Duration of Neoadjuvant Endocrine Therapy

The optimal duration for neoadjuvant ET, supported by multiple studies, is 4–6 months, allowing sufficient time for maximal tumor shrinkage (79). However, several studies have demonstrated that extending neoadjuvant ET with letrozole and exemestane for up to 24 months can further improve clinical response rates, increase BCS eligibility, and promote tumor downstaging (84, 85).

1.6.4. Role of Pembrolizumab for the Neoadjuvant Treatment of TNBC

The KEYNOTE-522 trial demonstrated that pembrolizumab combined with standard neoadjuvant chemotherapy in stage II and III TNBC significantly improved pCR rates (64.8% *vs.* 51.2%) and translated into significantly higher 3-year EFS (84.5% *vs.* 76.8%; HR: 0.63) and 5-year OS (95.1% *vs.* 94.4%; HR: 0.69), irrespective of PD-L1 expression status (78). These findings establish pembrolizumab as a backbone of NAT in high-risk early-stage TNBC, and it has been rapidly adopted in our routine clinical practice.

1.6.5. Choice of Adjuvant Therapy in *BRCAm* Breast Cancer Patients Without pCR After Pembrolizumab and Chemotherapy

Residual disease following NAT is a high-risk feature associated with recurrence, necessitating escalation of therapy. A subgroup analysis of the KEYNOTE-522 trial demonstrated that among patients with non-pCR the risk of recurrence ranged from 30% to 50%, depending on stage at presentation (86). Although adjuvant capecitabine has been established as a valid option for those with residual disease, translational analyses from the EA1131 and Geicam-Ciboma trials evaluating the role of capecitabine showed no benefit in basal subtypes, which are frequently associated with *BRCAm* tumors (87, 88). Based on the improved iDFS and OS benefits reported in the OlympiA trial (57) and the limitations of capecitabine in this subgroup, we generally recommend concomitant use of olaparib and pembrolizumab in patients with residual tumors following chemo-immunotherapy. Although the results from ongoing studies are pending, the St. Gallen Consensus, based on the available scientific evidence, also recommends capecitabine plus pembrolizumab or if the tumor is *BRCAm*, concurrent olaparib and pembrolizumab for patients with residual invasive tumor (50).

1.6.6. Optimal Use of Pembrolizumab in Patients With pCR

In patients achieving pCR after NAT, continuation of pembrolizumab to complete one year of therapy was associated with a sustained EFS benefit in the KEYNOTE-522 trial (86). At the second interim analysis, the 3-year EFS rate was 84.5% in the pembrolizumab group compared to 76.8% in the placebo group (HR: 0.63; 95% CI: 0.48–0.82; $p<0.001$) . This approach supports the concept that even in the absence of residual disease, maintaining immune checkpoint inhibition may consolidate long-term disease control. Although we acknowledge the KEYNOTE-522 data and consider continuation appropriate in our practice, treatment decisions for patients achieving pCR in the real-world setting may be guided by financial considerations.

1.6.7. Management of ER-Low Positive Breast Cancer

ER-low BC (2–5% of all BC), defined by estrogen receptor expression in 1%–10% of invasive tumor cells, represents a biologically heterogeneous subgroup with intermediate characteristics (some luminal and others basaloid) and an uncertain degree of endocrine responsiveness (89). Controversial data exist regarding management. Very recent data from the Mayo Clinic, presented at the 2024 ASCO Annual Meeting (90), demonstrated significantly worse OS in patients with ER-low tumors who received chemotherapy without adjuvant ET. However, emerging data suggest that ER-low BCs may align more

closely with TNBC in terms of their molecular profile and clinical behavior, rather than with conventional ER-positive disease (91). In our daily practice, we treat patients with ER-low BC similarly to those with TNBC in the preoperative setting, while incorporating adjuvant ET to maximize efficacy in line with available evidence.

1.7. Can Precision Approaches Refine Neoadjuvant and Adjuvant Treatment Strategies in HER2-Positive Early Breast Cancer?

1.7.1. Predictive Tests to Determine Eligibility for Neoadjuvant Treatment in HER2(+) Breast Cancer

HER2Dx is a 27-gene expression-based molecular assay designed to predict pCR and risk of recurrence in early-stage HER2(+) BC. The test evaluates four fundamental biological elements, including immune infiltration, HER2 signaling, tumor proliferation, and luminal differentiation. In the ESMO 2024 meta-analysis, patients classified as low risk by HER2Dx had a 6-year EFS of 97.2%, compared with 90.4% in the high-risk group (92). Validated by numerous prospective adjuvant and neoadjuvant trials, this diagnostic tool emerges as a promising approach for guiding individualized NAT strategies. Despite increasing support in high-resource healthcare facilities, long-term outcomes are awaited before it can be routinely used in practice.

1.7.2. Role of Dual Blockade for the Neoadjuvant Treatment of HER2(+) Early-Stage Breast Cancer

Multiple phase II trials have demonstrated that combining trastuzumab and pertuzumab with taxane-based chemotherapy provides clinical benefit through dual HER2 blockade. Earlier data from the NeoSphere and TRYPHEANA trials (75, 76) demonstrated significantly increased pCR rates, which translated into excellent long-term outcomes with taxane-backbone chemotherapy combined with HER2 blockade, including pertuzumab and trastuzumab. Confirmatory data from the phase III PEONY study, as well as meta-analyses, have established the role of dual HER2 blockade with pertuzumab as a standard approach for the neoadjuvant treatment of HER2(+) BC (93-95).

The use of a subcutaneous formulation combining TP (Phesgo®) may be considered based on results from the FeDeriCa study showing non-inferiority as compared to the intravenous formulation, offering the added benefits of reduced hospital stay and elimination of the need for an intravenous line (96).

1.7.3. Role of Non-Anthracycline-Based Regimens for the Neoadjuvant Treatment of HER2 (+) Breast Cancer

Anthracycline-free regimens reduce the risk of cardiotoxicity while maintaining comparable efficacy. The TRAIN-2 (64), a phase III trial, investigated the role of a combination of carboplatin and paclitaxel and dual HER2 blockade, compared with a standard anthracycline-based regimen. The non-anthracycline arm showed reduced cardiac dysfunction but did not differ significantly from the anthracycline-containing arm in pCR rates or EFS. Based on these and other data reviewed earlier in this manuscript, we generally prefer a non-anthracycline-based chemotherapy regimen, such as TCHP, for most patients with HER2 (+) disease who require neoadjuvant therapy, and for those who have cardiac risks or who wish to reduce long-term treatment complications.

1.7.4 Escalation of Treatment Following a Non-pCR After Neoadjuvant Treatment of HER2 (+) Breast Cancer

Residual disease following neoadjuvant HER2-targeted therapy is associated with an increased risk of recurrence. Escalation of adjuvant therapy in this setting has been validated by pivotal clinical trials.

1.7.5. Role of TDM-1

The KATHERINE trial (97) demonstrated that TDM-1 was superior to trastuzumab in the adjuvant setting, with a 50% reduction in the risk of invasive disease recurrence or death. At a median follow-up of 8.4 years, 7-year iDFS was 80.8% with TDM-1 compared with 67.1% with trastuzumab; this was accompanied by improvements in OS. Subgroup analyses showed a benefit in all subgroups, including those with residual microscopic disease. However, the 7-year iDFS rates of 69.5% and 39.6% in the ypN2 and ypN3 subgroups, respectively, highlight the need for escalation strategies in high-risk patients. We prefer TDM-1 for patients with residual HER2(+) disease following NAT.

1.7.6. Role of Neratinib

Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, demonstrated long-term efficacy in HR(+)/HER2(+) patients with early BC in the ExteNET trial (98). The final analysis of the trial showed that neratinib reduced the risk of invasive disease recurrence by 27% (HR: 0.73; 95% CI: 0.57–0.92) compared with placebo. The 8-year iDFS rates were 90.2% with neratinib and 87.7% with placebo. Twelve months of neratinib after trastuzumab-based adjuvant therapy resulted in a substantial long-term benefit, particularly in the HR(+) subgroup. Although ExteNET preceded the pertuzumab and TDM-1 era, there is a strong rationale to use neratinib as an add-on therapy in high-risk HR(+)/HER2(+) patients, especially those with residual N2 and N3 disease who may have a substantial recurrence risk, as high as 60%, as shown in a subset analysis of the KATHERINE trial (97).

1.7.7. De-Escalation Strategies in the Adjuvant Treatment of HER2(+) Early Breast Cancer

The WSG-ADAPT-HER2+/HR- trial (99) demonstrated that patients who responded well to paclitaxel and dual HER2 blockade achieved pCR rates exceeding 90% without the use of anthracyclines.

The APT trial (63), a phase II, single-arm study, investigated the role of weekly paclitaxel for 12 weeks with trastuzumab in patients with node-negative HER2(+) tumors measuring ≤3 cm. The ten-year follow-up of this combination revealed an encouraging iDFS and OS of 91.3%and 94.3%, respectively, demonstrating the effectiveness of this de-escalated regimen.

Regarding the duration of anti-HER2 blockade, numerous studies have evaluated the role of shorter trastuzumab durations, which have consistently shown outcomes similar to those of 1-year treatment. A patient-level meta-analysis of six randomized trials assessing shorter adjuvant trastuzumab durations reported similar OS, although non-inferiority could not be demonstrated (100).

In routine clinical practice, the APT regimen is the preferred adjuvant therapy for our patients with stage I HER2(+) BC. We also consider administering shorter durations of adjuvant trastuzumab in patients at

lower risk of recurrence, such as those with stage I, HR(+) disease, or those with cardiac comorbidities.

1.7.8. Treating the Elderly, Frail Patient With HER2(+) Breast Cancer

The RESPECT trial (71) investigated trastuzumab monotherapy compared with trastuzumab plus chemotherapy in patients aged ≥70 years. The 3-year DFS rates were 89.5% with trastuzumab alone and 93.8% with the combination; however, non-inferiority was not statistically confirmed. As discussed above, the results suggest that trastuzumab monotherapy provides adequate disease management with a more favorable safety profile, making it a suitable alternative for frail patients for whom chemotherapy may be harmful.

Conclusion

The recommendations presented here reflect a practice-informed, multidisciplinary approach to early BC care, supported by current evidence, yet aware of real-world variability in biology, resources, and patient preferences. We emphasize individualized risk stratification—integrating clinicopathologic features with genomic assays—alongside thoughtful use of OFS and AIs in selected premenopausal patients, selective rather than routine deployment of anthracyclines, and carefully targeted adoption of adjuvant CDK4/6 inhibitors in high-risk settings. We also outline situations where chemotherapy may reasonably be omitted (e.g., T1a TNBC and special low-risk histologies) and provide guidance for HER2-positive disease across neoadjuvant, escalation, and de-escalation pathways, including considerations for elderly or frail patients. These statements are intended to support shared decision-making at the point of care. We plan updates every two years to ensure this guidance remains a practical, patient-centered resource for clinicians navigating common—and often controversial—scenarios in everyday practice.

Footnotes

Authorship Contributions

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

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Review

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It Is Not an Obituary of Sentinel Lymph Node Biopsy or Surgery to Axilla, It's a De-Escalation of Surgery to Axilla in Early Breast Cancer: A Traditional Review

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ABSTRACT

In breast cancer (BC), surgical treatment of the axilla has undergone a paradigm shift from axillary lymph node dissection (ALND), through sentinel lymph node biopsy (SLNB), and ultimately to omission of axillary surgery. In BC, following neoadjuvant systemic therapy (NAST), there has also been a de-escalation from ALND to SLNB and targeted axillary dissection, with false-negative rates reduced to an acceptable level of less than 10%. Trials are ongoing to omit ALND when SLNB is positive in post-NAST BC cases. Additionally, ongoing trials are evaluating the omission of axillary surgery in post-NAST ycN0 patients. Based on an extensive literature search, this review highlights the sequential de-escalation of axillary surgery in patients with early breast cancer (EBC), irrespective of whether surgery was performed upfront or after NAST, with the same oncological outcomes on follow-up. cTis, 1–3 cN0 and cTis, 1–2 cN0-1 EBC patients have been included. Trials and studies involving cT0-4 and cN1-2 BC patients, and trials including both EBC and locally advanced BC patients, have been excluded to keep the study population uniform, consisting only of EBC cases. Examples of trials discussed in this review include NSABP-B04, NSABP-B 32, ACOSOG Z 11, IBCSG 23-01, AMAROS, SENOMAC, SOUND, INT 09/98, ALLIANCE A011202, AXSANA, EUBREAST-01, among others. In conclusion, de-escalation of surgical intervention to the axilla in EBC patients planned for upfront surgery or NAST requires an individualized approach based on the patient's condition and favorable tumor subtype. To date, a positive SLNB after NAST mandates ALND. Trials to nullify the same, with non-inferior oncological outcomes, are underway. There is a shift towards avoiding axillary surgery altogether in favourable BC cases.

Keywords: De-escalation of surgery to axilla; early breast cancer; post neoadjuvant systemic therapy; trials; upfront surgery

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Key Points

- Axillary surgery in early breast cancer (EBC) has shifted from axillary lymph node dissection (ALND) to the less morbid sentinel lymph node biopsy (SLNB), and initiatives are underway to address the axilla non-surgically.
- 1–2 SLNB if positive, does not mandate ALND in EBC.
- If EBC presents with a favorable subtype, SLNB may be omitted in selected patients.
- Before neoadjuvant systemic therapy (NAST), axillary ultrasound with fine need aspiration/core needle biopsy and marking of suspicious lymph nodes should be considered. False negative rate of SLNB post NAST can be decreased to <10% with removal of ≥3 SLNs, dual-agent mapping, adopting targeted axillary dissection.
- Till date, if SLNB is positive post NAST, guidelines advice ALND.

Introduction

Axillary surgery for breast cancer has evolved substantially from the 1970s to the 2000s (1). The evolution has been from axillary lymph node dissection (ALND) in all cases of breast cancer, to sentinel lymph node biopsy (SLNB) in treatment-naïve early breast cancer (EBC), to SLNB in post-neoadjuvant systemic therapy (NAST) EBC, and possibly no surgery at all in treatment-naïve or post-neoadjuvant chemotherapy (NACT) EBC (1-4).

In this article, we discuss the evolution of axillary intervention in EBC and future research directions.

Methods

An extensive literature search was conducted in PubMed on the evolution of axillary surgery in EBC. Following this, a Boolean search was also conducted using the terms "EBC" AND "no surgery to axilla". Twenty-six studies on the management of the axilla in EBC

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were thoroughly reviewed. These included trials, reviews, and original articles. Five of them were original articles, two were review articles, and the remainder were randomized controlled trials (RCTs) and ongoing trials with results pending. Only studies including patients with cTis, 1–3, cN0 EBC and cTis, 1–2, cN0-1 EBC, irrespective of upfront surgery or post-NAST surgery, were included. No age limit was applied. Among the studies identified after an extensive literature search, one trial (ACOSOG 1071) was excluded because it included patients with cT0-4 and cN1-2 stages. Another study that included cT1-4, cN1-3 BC patients and analysed axillary intervention in patients post NAST (ICARO study) was also excluded. SN-FNAC and GANEA 2 were also excluded.

Discussion

EBC Patients for Upfront Surgery

The study carried out by Magnoni et al. (1) briefly described the historical evolution of axillary surgery in breast cancer, including nearly all trials from the 1970s to the 2000s.

NSABP-B04 reported the 25-year findings of an RCT initiated in 1971 on 1079 clinically node- negative and 586 clinically node-positive patients. The node-negative patients underwent either radical mastectomy or total mastectomy without axillary dissection, the latter accompanied by postoperative irradiation [radiotherapy (RT)]. They underwent total mastectomy with ALND only if they became node-positive. The node-positive patients underwent radical mastectomy or total mastectomy without axillary dissection but with postoperative irradiation. It was found that node-negative patients had optimal outcomes even without radical mastectomy when locoregional treatment was sufficient (i.e., only mastectomy and axillary RT). Similar was the finding in node-positive patients on obtaining cumulative-incidence estimates of outcome. Adequate locoregional treatment, instead of radical mastectomy, resulted in comparable overall survival (OS) and disease-free survival (DFS) (5). Based on their inference and extrapolation of this view, axillary surgery can also be de-escalated if locoregional treatment is sufficient.

The 1990s saw the de-escalation of ALND in favor of SLNB, driven by the increased risk of lymphedema (9–15%), seroma (15–20%), shoulder dysfunction (8–10%), and pain, numbness, and paraesthesia (30–35%) following ALND (6-8). The shift was towards a less-morbid procedure with similar outcomes.

NSABP-B 32 (1999–2004) was an RCT initiated with the same objective; its primary endpoint was OS (9). This is the largest RCT on BC performed to date. A total of 5,611 patients who were cN0 and underwent lumpectomy or mastectomy and SLNB were enrolled. Stratification was based on age (≤49 y, ≥50 y), clinical tumor size (≤2.0 cm, 2.1–4.0 cm, ≥4.1 cm), and planned surgery (lumpectomy, mastectomy). One group underwent SLNB and ALND, while the other underwent SLNB followed by ALND only if the SLNB was positive. Among the 5,611 BC patients, 3,989 were SLNB-negative and were analysed. Of these, follow-up information for 3,986 SLNB-negative patients was analysed at a median of.

96.5 months (70.1–126.7 months). The OS was comparable between the two groups. The group that underwent SLNB and ALND had an OS of 97%, whereas the group that underwent SLNB only had an OS of 95%, a difference of only 2%. DFS and a forest plot summarizing the hazard ratios and 95% confidence intervals for all sites of first treatment failure showed similar results between the two groups (10).

Once it was shown that outcomes were similar in cN0 patients who underwent SLNB only and were SLNB-negative and in those who underwent ALND, the search for further de-escalation began. What if SLNB alone could suffice even if it were positive in one or two lymph nodes (LNs), or if the SLNs had micrometastases?

The ACOSOG Z0011 and the IBCSG 23-01 were trials designed to demonstrate that SLNB alone is sufficient even in patients with positive SLNB (9).

ACOSOG Z 11 (May 1999 to December 2004) (11) included BC patients who were cT1–2 and cN0, who underwent breast conservation surgery (BCS) with SLNB and had 1–2 positive nodes. A total of 891 patients were randomised to SLNB alone (n = 446) or SLNB with ALND (n = 445). In the primary analysis, 436 patients in the SLNB-only group and 420 patients in the SLNB with ALND group were included. The median total number of nodes containing metastases in both groups was 1. All patients underwent whole-breast radiation; any third-field radiation was prohibited. However, ≤50-year-old patients numbered only 160 compared to 266 patients who were >50 years of age; most patients in the study were hormone receptor positive (i.e., a favourable biological subtype); the prespecified sample size of 1,900 participants could not be achieved due to low accrual and a low event rate; and tangential breast radiation also partly irradiated the axilla. The primary outcome was OS, and the secondary outcome was DFS. The 10-year OS was 86.3% in the SLNB-only group and 83.6% in the SLNB followed by ALND group. 10y-DFS rates were 80.2% and 78.2%, respectively.

Around the same time, the IBCSG 23-01 trial (12) was conducted from 2001 to 2010. This was an RCT. In addition to patients undergoing BCS, as in the ACOSOG Z 11 trial, 9% of patients in this trial underwent mastectomy. Nine hundred and thirty-four patients with cT1-2, cN0 disease who underwent BCS or mastectomy and had SLNs with micrometastasis (SLNs were entirely sectioned at 50–200 μm intervals, and each section was examined by hematoxylin and eosin staining) were randomised to ALND and no-ALND groups. A total of 464 patients in the ALND group and 467 patients in the no-ALND group were finally analysed. The primary outcome was DFS. DFS was 87.8% in the no-ALND group and 84.4% in the ALND group.

Therefore, ACOSOG Z11 and IBCSG 23-01 demonstrated that if the SLNB burden is low, ALND can be omitted in selected patients with non-inferior oncological outcomes.

Almost simultaneously with ACOSOG Z11 and IBCSG 23-01, the AMAROS trial was conducted from Feb 19, 2001, to April 29, 2010 (9).

In the AMAROS trial (13), a randomized, multicentre, open-label, phase 3 non-inferiority trial, 1,425 of 4,823 patients with cT1-2, cN0 disease were SLNB-positive. Of these 1,425 patients, 744 were randomised to undergo ALND and 681 to undergo axillary RT. Local treatment of the breast included BCS plus whole-breast radiotherapy (WBRT), mastectomy with or without RT, and systemic therapy. Median follow-up was 6.1 years, and the primary endpoint was 5-year axillary recurrence-free survival (RFS). The 5-year axillary RFS was 0.43% after ALND versus 1.19% after axillary RT, whereas lymphedema was more frequent in the ipsilateral arm during follow-up at 1, 3, and 5 years in the ALND group.

OTOASOR Trial: After positive SLNB was a study similar to AMAROS, with tumor size ≤3 cm and 8-year follow-up data. OS in the ALND and SLNB +RT groups was comparable, at 77.9% and 84.8%, respectively (14).

Therefore, surgical intervention in the axilla for cN0 patients who have a positive SLNB could be limited to SLNB rather than proceeding to ALND, provided adequate regional and systemic treatment was given. These trials encouraged a further increase in the SLNB threshold. To date, SLNB has been considered sufficient even when positive in low-burden disease, such as 1–2 SLN-positive cases, SLNB-positive only for micro-metastasis, and EBC patients with a favorable biological subtype (10-13).

The SENOMAC trial, a prospective, randomized, non-inferiority phase 3 trial, aimed to omit ALND in cT1–3, cN0 BC patients with 1–2 positive SLNB nodes and with SLNB positive for extranodal extension (ENE). Thus, this trial was one step higher than ACOZOG Z11, IBCSG 23-01, and AMAROS. It included male patients, patients who had undergone mastectomy, and SLNB-positive patients with ENE. The primary endpoint was OS. A total of 2766 patients were enrolled from January 2015 and December 2021, across five countries, and 1335 underwent SLNB only and 1205 underwent completion ALND. Median follow-up was 46.8 months. The estimated 5-year OS was 92.9% in the SLNB-only group and 92.0% in the completion ALND group (15). However, SENOMAC had its limitations. The mean age was 61 years, and the majority of BC patients were older than 65 years. Young patients were not adequately included. T3 tumors comprised only 5.5% of the study subjects, and the mean tumor size was 2.44 cm. Only 22% were grade 3 per the Nottingham histologic grade, and 87.3% of patients were estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative. Only 68.8% required RT (BCS and T3), but 95% of the study subjects received RT, indicating RT overuse. This study focused more on lymphedema than on other side effects (16).

From the above trials, it was evident that SLNB was used only for axillary staging and did not provide any therapeutic benefit.

James et al. (2) carried out a review that claimed that omitting SLNB in select cases and introducing a non-invasive predictive model was a viable option according to currently available literature. They have mentioned several trials, such as SOUND, BOOG 213-08, INSEMA, and the Choose Wisely recommendations from CALGB trials, which indicate that SLNB is unnecessary for cN0 EBC patients. This review also reported that SLNB can be identified in 95% of cases with cN0 axilla, with a false-negative rate (FNR) of 6–10% and an overall accuracy of 96%. Furthermore, the axillary recurrence rate after negative SLNB is <1%.

Among the above-mentioned trials, the SOUND trial was a prospective non-inferiority phase 3 RCT conducted between February 6, 2012 and June 30, 2017, in Italy, Switzerland, Spain, and Chile that compared SLNB versus observation after axillary ultrasound in 1463 women with tumor size ≤2 cm and cN0 on examination and ultrasonography who were planned for BCS. The primary endpoint of the study was distant disease-free survival (DDFS) at 5 years, analysed on an intention-to-treat basis. Secondary endpoints included cumulative axillary recurrence, DFS, OS, and treatment recommendations. 708 patients were in the ALNB group and 697 in the observation group. Patients were followed for a median of 5.7 years. The DDFS was 97.7% in the SLNB group and 98% in the observation group. The 5y-DFS was 93.9% in the no-intervention group and 94.7% in the SLNB group. Thus, this trial provided evidence that the cumulative incidence of lymph-node recurrences was 0.4% at 5 years in the no-intervention group. Despite the comparable results of SLNB versus no intervention, as reported in SOUND, this trial had several drawbacks. The Majority of the patients had favourable biology (ER positive, HER2 Neu negative); 87.8% of patients were postmenopausal, and the tumors studied were T1 (4).

Further evidence from Ontario Health (Cancer Care Ontario) and ASCO suggests that SLNB is not required for patients aged ≥70 years with T1cN0 invasive breast cancer that is HR(+) and HER2-negative (17).

There is robust evidence from previous studies supporting SOUND findings. Recently, Agresti et al. (18) performed a 20-year follow-up analysis of patients recruited under INT 09/98 RCT and reported similar findings. Five hundred seventeen patients with T1N0 breast cancer, aged 18–65 years, were randomized in INT 09/98 to quadrantectomy with ALND or to quadrantectomy alone. The primary endpoint was OS, which was 93.3% and 91.5%, respectively. The current study followed these patients for 20 years and found no significant difference between the two arms. Axillary relapse with distant metastases was similar in both arms, suggesting that the adverse outcome is attributable to the aggressive biology of the tumor, which is independent of axillary intervention (18). Another RCT conducted between 1993 and 2002 compared axillary clearance versus no axillary clearance in women ≥60 years old (median: 74y) with cN0, T1-T3, of whom 80% were ER positive. Two hundred thirty-four patients underwent additional ALND, and 239 patients underwent breast surgery only. All patients received tamoxifen. The median follow-up was 6.6 years. The OS and DFS were similar: 75% vs 73% and 67% vs 66%, respectively (19). The National Comprehensive Cancer Network (NCCN) (4.2022) states that axillary staging may be considered optional for patients with favourable tumors—for whom selection of adjuvant systemic therapy and/or RT is unlikely to be affected by axillary staging—and for elderly individuals and those with serious comorbid conditions.

Therefore, in EBC patients planned to undergo upfront surgery, de-escalation of axillary surgery has resulted in omission of axillary surgical intervention. If patient selection is appropriate, de-escalation of surgical intervention can even involve omission of axillary surgery.

If that is the case with EBC, the question arises: what is the ideal treatment of the axilla in ductal carcinoma *in situ* (DCIS) and in patients with T0N1 tumors?

Patients with high-grade DCIS undergoing mastectomy should undergo SLNB because there is a 15% chance of upstaging to microinvasion or invasive carcinoma. Some suggest SLNB in DCIS patients undergoing BCS who have a palpable lump, anticipating upstaging on final histopathology. For others, an individualised approach should be adopted (20).

For T0 N1 tumors, which account for 0.8% of breast cancers, a core needle biopsy of the axillary LN to determine the tumor subtype and an MRI to locate the breast lesion are important. MRI can detect breast tumors in 85% of cases. Once the tumor subtype is known, one should proceed with the conventional treatment regimen. If the tumor is not located in the breast on imaging, only ALND leads to loco-regional recurrence (LRR). Therefore, intervention to the breast is also important, whether with mastectomy or WBRT, as both have the same LRR and OS (20, 21).

EBC Patients for NAST Followed by Surgery

With more emphasis on the tumor subtype, there are indications of giving NAST in EBC patients also.

The St Gallen Consensus (2017) established that, in patients with a clinically negative axilla who receive NAST, SLNB is appropriate and favored its being carried out after NAST (22). The German S3 guidelines state that SLNB is adequate after NAST for patients with clinically and sonographically node-negative (cN0/iN0) pre-treatment status (23).

Now that cN0 patients were subjected only to SLNB after NAST/ NACT, the initiative to de-escalate axillary surgery for patients who down-staged from cN+ to ycN0 began. A study by El-Tamer and Kovacs (24) provided the criteria for SLNB after NACT, which included N1 disease pre NACT; clinically deemed node-negative status after NACT; presence of a team well-versed in SLNB; availability of dual mapping techniques for SLNB; resection of all SLNs (or ≥3 SLNs); pathologic confirmation of complete response in axillary LNs; and evidence of treatment effect in the SLNs as the optimal conditions. On the other hand, a registry-based study on residual axillary metastases in node-positive breast cancer patients after NACT reported that no consensus exists on the optimal axillary staging method after NACT for patients who were clinically node-positive at diagnosis. This study analysed 383 cases (3).

Some ongoing trials include ALLIANCE A011202 (NCT01901094), in which SLNB-positive patients were randomized to ALND followed by nodal irradiation (undissected axilla, SCF, IMN—internal mammary node) or to no ALND and RT to the axilla, SCF, and IMN. Results will provide more refined insight into axillary management post-NAST/NACT.

Further analysis of SENTINA, which included patients who converted from N+ to N0 status showed that use of a dual tracer reduced the FNR to 8.6% and that using three SLNs reduced it to 7.3% (25). Therefore, the technique of SLNB and the number of SLNs removed post NACT governed the FNR, supporting the criteria suggested by El-Tamer and Kovacs (24). Even though ACOSOG Z1071, SN-FNAC, and GANEA 2 were excluded because they did not include only EBC patients, the findings were similar.

An acceptable FNR for SLNB after NAST is <10%, which led to the development of newer techniques. Targeted axillary dissection (TAD), using a clip or iodine seed to localize the pre-NACT positive LN, was implemented. This reduced the FNR to an acceptable 1.4%. Also, in 23% of patients, the clipped LN was not the SLN (26). A broad description of TAD is the removal of the targeted LN (pre-NACT) along with SLNs. Thus, techniques such as TAD or marking of the axillary LN with radioactive iodine (MARI) were superior to SLNB in patients with positive N who underwent NAST, achieving an excellent five-year axillary recurrence-free interval of 97% (27). In TAD, the FNR was only 2%, while in MARI it was 7%. Radioactive iodine seed localization in the axilla with the sentinel-node procedure) also demonstrated a low FNR of 3.5% (28).

An abstract from the San Antonio Breast Cancer Consortium 2023 concluded that in patients with post-NACT SLNB showing only isolated tumor cells (ITC), ALND can be omitted (26). However, this study included cT1-4, cN0-3 tumors, which is an exclusion criterion for this review. But if higher stage of tumors can have omission of ALND after SLNB with ITC post NAST/ NACT, the findings can even be applied in EBC patients.

To date, India does not have her own guidelines for the management of initial cN+ patients who have undergone NAST/NACT. European Society for Medical Oncology and NCCN recommend SLNB with additional recommendations (dual tracer/clipping/marking/minimum 3 nodes); the American Society of Breast Surgeons recommends SLNB and, if SLNB is not identified, ALND; and the German AGO guidelines suggest TAD and, if TAD is not identified, ALND as equivalent. Guidelines from Italy, Denmark, Hungary, and Russia advocate SLNB/TAD, while Swedish and Austrian guidelines still suggest ALND.

A prospective, non-interventional cohort study in 3,000 patients across 20 countries, named the AXSANA study, has been initiated to fill the knowledge gap regarding the precise treatment of the axilla for patients with cN+ who became ycN0 after systemic therapy.

Just as no axillary surgical intervention has been shown to be optimal in EBC patients undergoing upfront surgery, studies have demonstrated similar findings in patients post NAST. A pooled analysis was carried out of cN0 breast cancer patients who were HER2-positive or had triple-negative breast cancer (TNBC) and who underwent NAST. The analysis showed that the overall ypN+ rate was 2.16%. Hence, they suggested that when the risk of nodal disease is sufficiently low, axillary surgery can be safely omitted in selected patients (29).

Extrapolating these findings, investigators have initiated EUBREAST-01, a prospective non-randomized, single-arm surgical multicentre trial in patients ≥18y of age with cN0, cT1-T3 tumors who have TNBC, are HER2 Neu (+), are planned for BCS, and have achieved pathological complete response in the breast lump after systemic therapy. The study lasted 2 years and recruited 267 patients. The endpoint is axillary RFS (30). Similar to this, another European trial, ASICS, also has results pending.

Thus, even in patients who were cN+ pre-NACT/NAST and became ycN0 post-systemic therapy, studies suggest limiting axillary surgery to SLNB/TAD. However, guidelines for management of the axilla post-NAST are still awaited in treatment-naïve, non-metastatic breast cancer patients.

Conclusion

As we are de-escalating axillary surgery for EBC planned for upfront surgery and for EBC post-NAST, patient selection using an individualised approach is key. ALND is not mandated for treatment-naïve EBC patients with 1–2 positive nodes on SLNB. Before NACT, axillary ultrasound with tissue diagnosis and marking of suspicious LNs should be considered. FNR of SLNB can be reduced to <10% with the removal of ≥3 SLNs, dual-agent mapping, and adoption of TAD. To date, if SLNB is positive after systemic therapy, the long-established ALND remains the surgical treatment of choice. Results of EUBREAST-01, ASICS AND AXSANA are awaited and could herald another revolutionary change in axillary surgery for BC patients.

Footnotes

Authorship Contributions

Concept: R.M., P.R., B.K.S.; Design: R.M., P.R., B.K.S.; Data Collection or Processing: R.M., P.R., B.K.S.; Analysis or Interpretation: R.M., P.R., B.K.S.; Writing: R.M., P.R.

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Review

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Assessing Lead Exposure by Biological Matrices Analysis and Links to Breast Cancer: A Critical Review of Experimental and Epidemiological Findings

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ABSTRACT

Lead (Pb), a ubiquitous environmental contaminant, is a toxic heavy metal known to interfere with enzymatic and hormonal processes. Its classification as a probable human carcinogen by international agencies has raised concerns about its potential role in cancer, including breast cancer (BC). This review critically examines epidemiological and experimental evidence linking Pb exposure to BC, emphasizing the impact of biological matrices used for Pb measurement on the consistency of findings. A systematic review following PRISMA guidelines was conducted. Eligible studies quantified Pb in breast tissues, blood, urine, hair, or toenails and assessed its association with BC risk. Animal studies and non-English publications were excluded. Twenty-seven studies (described in 23 publications) quantified Pb in human biological matrices: breast tissue (n = 6), urine (n = 6), blood (n = 9), hair (n = 4), and toenail (n = 2). Among them, 16 reported a positive association between Pb and BC risk (breast tissues: 4; urine: 3; blood: 6; hair: 3; toenails: 0). By contrast, 11 studies found no significant correlation (breast tissues: 2; urine: 3; blood: 3; hair: 1; toenail: 2). Four studies quantified Pb in different matrices, and the same results were obtained from analyses of breast tissue, blood, and hair. Discrepancies across studies included small sample sizes, heterogeneous demographic characteristics, insufficient follow-up, and different Pb assessment methods. While the majority of studies suggest a potential link between Pb exposure and BC, significant heterogeneity in study design and population selection limits definitive conclusions. Future research should standardize Pb measurement protocols in selected populations and explore mechanistic pathways to clarify this potential association and improve prevention strategies.

Keywords: Lead exposure; breast cancer; heavy metals; endocrine disruptors; biological matrices; environmental carcinogens

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Key Points

- Lead (Pb), a ubiquitous environmental contaminant, is a toxic heavy metal known to interfere with enzymatic and hormonal processes.
- The classification of lead as a probable human carcinogen by international agencies has raised concerns about its potential role in cancer, including breast cancer (BC).
- In our review, the majority of studies suggest a link between Pb exposure and BC.
- Future research should standardize Pb measurement protocols in selected populations and explore mechanistic pathways to clarify this potential association and improve prevention strategies.

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Introduction

Lead (Pb) is a heavy metal with the symbol Pb and atomic number 82. Lead is one of the densest metals (density: 11.34 g/cm^3) and has a long history of industrial use because of its malleability and high density (1). Although it has been phased out of many applications, such as paint and gasoline, it remains a pervasive environmental pollutant. Pb can persist in soil, dust, and water, leading to chronic human exposure through inhalation or ingestion (2, 3).

Pb exerts toxic effects even at low levels. It disrupts key biological processes, including heme synthesis and neurotransmission, and contributes to anemia and neurodevelopmental impairments (4, 5). Children and pregnant women are particularly vulnerable, as Pb crosses the placenta and affects fetal development (6-8). Chronic exposure may also impair the renal and reproductive systems (4). Acute or chronic Pb poisoning, whether domestic or occupational, is a serious condition, also called lead poisoning or saturnism. Blood lead level (BLL) is the most commonly used biomarker to assess lead exposure; the intervention threshold for children is set at 50 µg/L in most countries. Lead poisoning has long been recognized as an occupational disease. Due to higher Pb absorption in women, there are sex-specific occupational exposure limits (400 µg/L for men and 300 µg/L for women), making lead the only substance with different adult exposure limits by sex (9, 10).

Over the past decades, Pb has been scrutinized for its potential carcinogenicity. The U.S. Environmental Protection Agency and the U.S. Department of Health and Human Services have classified Pb compounds as probable or reasonably anticipated human carcinogens (11, 12). The International Agency for Research on Cancer classifies inorganic Pb as probably carcinogenic to humans (group 2A), based on sufficient evidence in animals and limited evidence in humans (13). Experimental findings suggest that Pb may act as a metallo-estrogen, mimicking estrogenic activity, promoting oxidative stress, inducing DNA damage, and influencing epigenetic regulation (14).

Given that breast cancer (BC) is a hormone-sensitive malignancy (15) and the leading cause of cancer-related death in women worldwide, interest has grown in investigating whether Pb contributes to BC development. Several studies have reported elevated Pb concentrations in BC patients (16-19), yet findings remain inconsistent, possibly due to differences in Pb measurement methods, the biological matrices used (e.g., blood, urine, hair, breast tissue, and toenails), and the study populations (20-25).

This review aimed to critically evaluate current experimental and epidemiological data on the relationship between Pb exposure and BC risk. A secondary goal was to assess the reliability of different biological matrices as biomarkers of Pb exposure, to guide future research and potential public health interventions.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26).

Eligibility Criteria

We included prospective and retrospective cohort studies, case-control studies, and meta-analyses published in English before January 5, 2024. Eligible studies were required to assess the association between Pb exposure (occupational or non-occupational) and BC incidence, or to report Pb concentrations in biological matrices, including breast tissue, blood, urine, hair, and toenails. Animal studies, case reports, reviews, editorials, and studies published in languages other than English were excluded.

Search Strategy

A comprehensive literature search was performed in the PubMed, Scopus, and Web of Science databases through January 5, 2024, following PRISMA 2020 guidelines. The final search strategy combined controlled vocabulary (MeSH terms) and free-text keywords to maximize sensitivity.

PubMed search string:

((“lead”[MeSH Terms] OR “heavy metals”[MeSH Terms]) AND (“breast cancer”[MeSH Terms] OR “breast carcinoma”[All Fields] OR “mammary carcinoma”[All Fields] OR “mammary neoplasm”[All Fields])).

Scopus search string:

TITLE-ABS-KEY [(“lead” OR “Pb”) AND (“breast cancer” OR “breast carcinoma” OR “mammary carcinoma” OR “mammary neoplasm”)].

Study Selection and Data Extraction

Two reviewers (A.M. and S.E.B.) independently screened all titles, abstracts, and full texts for eligibility. Discrepancies between the two reviewers were resolved through discussion and consensus. When consensus could not be reached, a third reviewer (C.M. or M.G.) acted as an arbitrator. Full texts of eligible articles were reviewed in detail. Data extracted from each study included the first author, publication year, country of study, study design, population characteristics (sample size, age, recruitment period), biological matrix analyzed, and main findings. Only human studies were included.

Data Synthesis

Studies were categorized based on epidemiological data and/or the biological matrix used for Pb quantification. Results were synthesized narratively, and the strength of the association between Pb exposure and BC was assessed based on reported statistical significance. No meta-analysis was performed due to heterogeneity in study designs, Pb measurement methods, and outcome definitions.

All included case–control and cohort studies were evaluated using the Newcastle–Ottawa Scale, which assesses (Supplementary Table 1):

• Selection (0–4 points): representativeness of cases, selection of controls, ascertainment of exposure.

• Comparability (0–2 points): control for confounding factors (age, smoking, menopausal status).

• Exposure/Outcome (0–3 points): method of ascertainment, same method for cases and controls, non-response rate.

Results

Figure 1 presents the flowchart of the literature search and identification of relevant studies. A total of 27 studies (described in 23 publications) assessed the relationship between Pb content in biological matrices and BC risk (including one study on male BC and three studies where the gender of participants was not specified) (Figure 2).

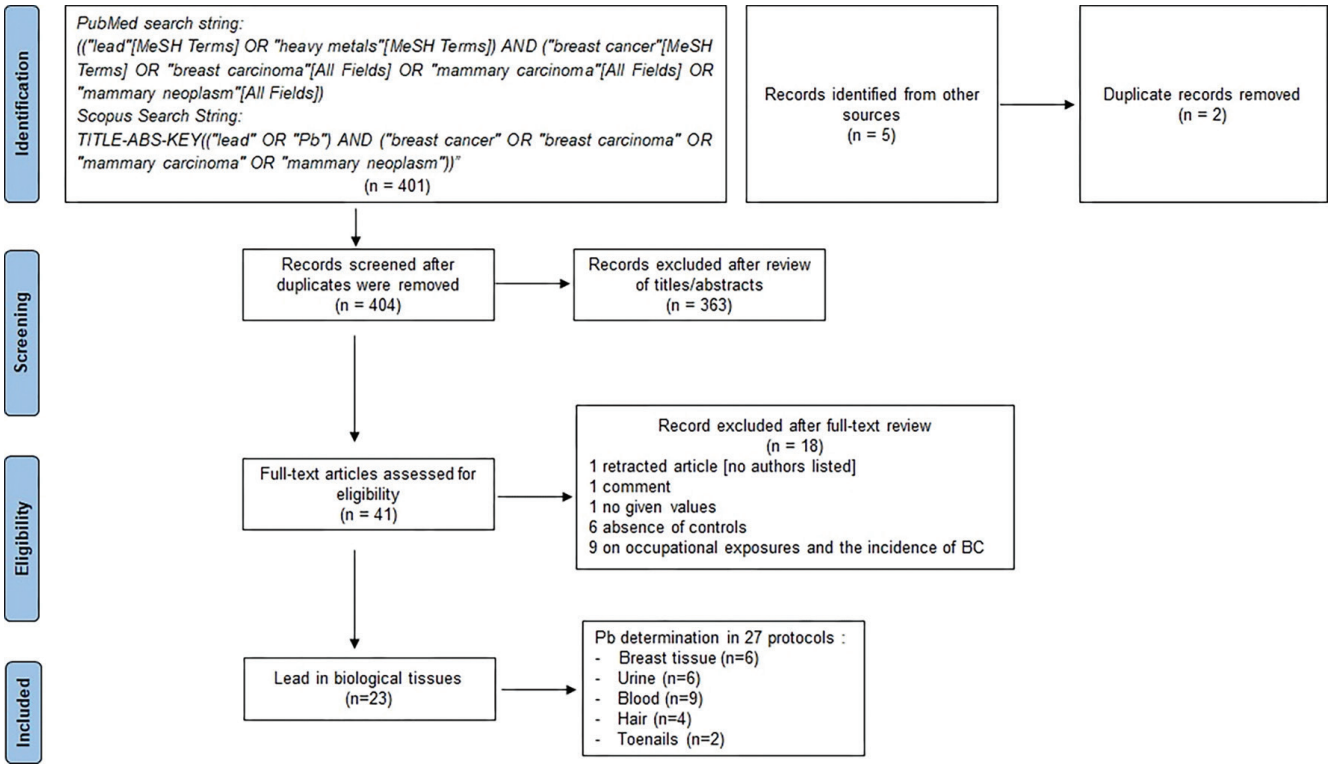

Figure 1. PRISMA flow chart of the procedure used to select the articles included in this review

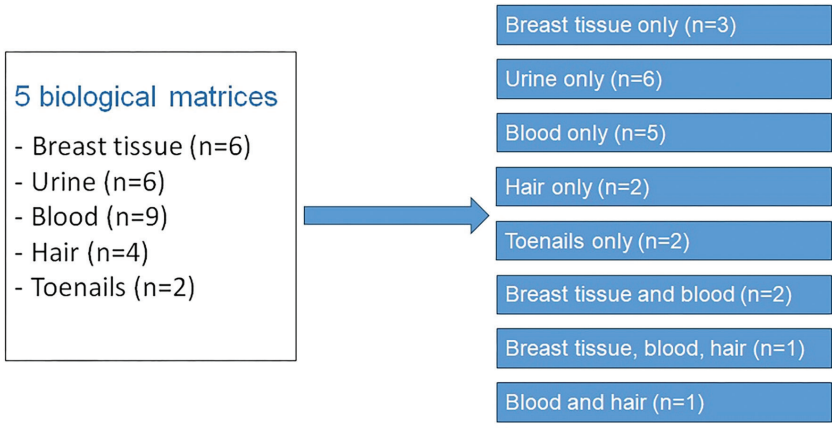

Figure 2. Pb determination in 23 publications including 27 protocols

Lead in Breast Tissues

Six studies (16-18, 20, 27, 28) analyzed Pb concentrations in breast tissue samples from BC patients and controls (Table 1a). Four of these studies reported significantly higher Pb levels in cancerous tissues (16-18, 28), suggesting a potential association with malignancy. For example, in 2006, Ionescu et al. (17) reported levels of 105 µg/kg in BC tissue versus 64 µg/kg. In 2022, Mansouri et al. (16) confirmed these findings, reporting a mean Pb concentration of 13.1 µg/kg in BC tissue versus 6.4 µg/kg in controls.

In contrast, two studies did not observe significant differences between cancerous and non-cancerous tissues. For example, Santoliquido et al. (27) found mean Pb levels of 0.60 µg/g in cancerous tissue compared to 0.68 µg/g in non-cancerous tissue, suggesting no notable variation. Recently, Anđelković et al. (20) investigated Pb levels in three types of operative specimens: benign breast lesions, malignant breast lesions, and surrounding tissue. The study included 55 women treated for BC. The control group consisted of 41 women with benign breast tumors. Pb levels were significantly higher in surrounding tissues than in tumors for both groups, but no significant differences in Pb levels were observed between the control and BC groups (Table 1a).

Two studies (19, 23), not included in our review (no control group), analyzed Pb concentration in surgical specimens obtained from BC patients treated for invasive ductal carcinoma and showed no significant differences between tumor and surrounding tissues.

Lead in Urine

Six studies evaluated urinary Pb levels in BC patients and controls (Table 1b). Three studies found significantly higher Pb concentrations in BC patients (29-31). In 2016, Burton et al. (31) reported significantly higher levels of Pb and Cu in BC patients, supporting their potential role as risk factors. Hu et al. (29), using NHANES data involving

2,795 women, reported a positive association between urinary Pb and BC in 2023, with an odds ratio of 2.22. Similarly, Bell et al. (30) (NHANES 2007–2016), published in 2023, reported significantly higher Pb levels in BC patients compared to healthy controls, with the highest Pb quartile showing a nearly threefold higher BC prevalence.

By contrast, McElroy et al. (22) found no association between urinary Pb and BC among women in Wisconsin. Interestingly, Men et al. (25) found no significant difference in Pb levels in BC patients, but they suggested a potential link between some other heavy metals and BC. Likewise, Mérida-Ortega et al. (32) reported no significant differences in Pb levels among BC patients in Northern Mexico, but identified metal combinations influencing postmenopausal BC risk.

Lead in Blood

Among nine studies assessing BLLs (Table 1c), six found a positive association with BC (18, 19, 33-36). For example, Siddiqui et al. (18) found significantly higher BLLs in malignant cases (20.33 µg/dL) than in benign cases (13.10 µg/dL) and in control subjects (6.14 µg/dL). Alatise and Schrauzer (19) found elevated BLLs that correlated with Pb content in breast tissue and hair, suggesting chronic exposure. Li et al. (35) observed significantly higher Pb levels in BC patients, along with arsenic, cadmium, and chromium, suggesting that environmental exposure to these metals might contribute to BC development. Wei and Zhu (36) also found significantly higher Pb levels in BC patients, supporting the hypothesis that Pb may contribute to BC through direct and indirect mechanisms. In 2024, Fernández-Martínez et al. (33) conducted a case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort that analyzed metal exposure in 292 BC cases and 286 controls. Even though the values reported in their manuscript are similar between BC patients and controls, they found that high levels of certain metals, including Pb, were associated with an increased risk of BC, particularly in early-stage disease. Their analysis indicated a fourfold increase in BC risk associated with a specific metal exposure profile (33). Afridi et al. (34) studied male BC (MBC) patients and found elevated Pb levels in blood and serum compared to healthy males.

In contrast, in 2019, Gaudet et al. (37) found no association between Pb levels and BC risk in three cohorts from the USA, Italy, and Sweden. Similarly, Anđelković et al. (20) in 2022 compared BLLs between BC patients and healthy women, and found no significant difference. In 2023, Caini et al. (21) published the results of a nested case-control study within the Florence EPIC cohort, measuring six heavy metals in never-smokers. No significant association was found between Pb levels and BC risk.

Table 1a. Lead levels in breast tissue

Study	Country	*n* (cases/ controls)*	Pb in breast cancer cases	Pb in controls	Association	Conclusion
Anđelković et al. (20)	Serbia	55/41	91.89 ng/g	106.32 ng/g	No	Slight difference
Mansouri et al. (16)	Iran	63/63	13.1 µg/kg	6.4 µg/kg	Yes	Higher in malignant tissue
Ionescu et al. (17)	Czech Rep Germany	20/8	105 µg/kg	64 µg/kg	Yes	Higher in malignant tissue
Siddiqui et al. (18)	India	25/25	0.54 µg/g	0.40 µg/g	Yes	Higher in malignant tissue
Rizk and Sky-Peck (28)	ND	25/25	1.55 µg/g	1.33 µg/g	Yes	Higher in malignant tissue
Alatise and Schrauzer (19)	Nigeria	12/12**	0.11 µg/g	0.10 µg/g	No	Similar levels
Santoliquido et al. (27)	ND	20/20	0.60 µg/g	0.68 µg/g	No	Similar levels

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Table 1b. Lead in urine

Study	Country	*n* (cases/ controls)*	Pb in breast cancer (BC) cases	Pb in controls	Association	Conclusion
Hu et al. (29)	USA	210/2585	0.48 µg/L	0.37µg/L	Yes	Higher in BC patients
Bell et al. (30)	USA	106/3246	0.62 µg/g-creatinine	0.42 µg/g-creatinine	Yes	Higher in BC patients
Mérida-Ortega et al. (32)	Mexico	452/439	2.71 µg/g-creatinine	2.99 µg/g-creatinine	No	Slight difference
Men et al. (25)	China	106/38	75.0 µg/L	75.0 µg/L	No	Similar levels
Burton et al. (31)	USA	52/79	0.578 µg/L	0.388 µg/L	Yes	Higher in BC patients
McElroy et al. (22)	USA	246/254	0.86 µg/L	0.64 µg/L	No	Slight difference

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Lead in Hair

Four studies analyzed Pb in hair samples. Three of them reported significantly higher levels in BC patients (19, 34, 38). In 2010, in Nigeria, Alatise and Schrauzer (19) observed elevated Pb levels in BC patients (23.6 µg/g) compared to controls (10.3 µg/g). In India in 2014, Blaurock-Busch et al. (38) reported higher Pb concentrations in BC patients (11.42 µg/g) than in controls (2.15 µg/g), suggesting that Pb is a potential factor in BC development. Afridi et al. (34) reported significantly higher Pb levels in MBC patients (8.29±0.72 µg/g) than in healthy males (4.36±0.65 µg/g). In contrast, in Türkiye in 2011, Benderli Cihan et al. (39) found lower Pb levels in BC patients (3.794 µg/g) than in controls (6.196 µg/g), contradicting previous findings (Table 1d).

Lead in Toenails

In 2019, two studies by O'Brien et al. (40, 41), conducted in the USA, measured Pb in toenail samples and found no significant association with BC (Table 1e).

Table 1c. Lead in blood

Study	Country	*n* (cases/ controls)*	Pb in breast cancer (BC) cases	Pb in controls	Association	Conclusion
Fernández-Martínez et al. (33)	Spain	292/286	0.23 ng/mL	0.22 ng/mL	No	Slight difference
Caini et al. (21)	Italy	150/150	1.70 µg/L	1.70 µg/L	No	Similar levels
Anđelković et al. (20)	Serbia	55/41	1.17 µg/dL	1.36 µg/dL	No	Slight difference
Afridi et al. (34)	Pakistan	14/37	528 µg/L	239 µg/L	Yes	Higher in BC patients
Li et al. (35)	China	105/35	24.3 µg/L	16.0 µg/L	Yes	Higher in BC patients
Wei and Zhu (36)	USA	284/8976	1.52 µg/dL	1.08 µg/dL	Yes	Higher in BC patients
Alatise and Schrauzer (19)	Nigeria	12/12**	6.1 µg/dL	5.0 µg/dL	Yes	Higher in BC patients
Siddiqui et al. (18)	India	25/25	20.33 µg/dL	6.14 µg/dL	Yes	Higher in BC patients
Gaudet et al. (37)	USA	816/816	ND	ND	No	After the authors
	Italy	294/292				
	Sweden	325/325				

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Table 1d. Lead in hair

Study	Country	*n* (cases/ controls)*	Pb in in breast cancer (BC) cases	Pb in controls	Association	Conclusion
Afridi et al. (34)	Pakistan	14/37	8.29 µg/g	4.36 µg/g	Yes	Higher in BC patients
Blaurock-Busch et al. (38)	India	15/50	11.42 µg/g	2.15 µg/g	Yes	Higher in BC patients
Alatise and Schrauzer (19)	Nigeria	12/12**	23.6 µg/g	10.3 µg/g	Yes	Higher in BC patients
Benderli Cihan et al. (39)	Türkiye	52/52	3.794 µg/g	6.196 µg/g	No	Higher in healthy patients

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Table 1e. Lead in toenails

Study	Country	*n* (cases/ controls)*	Pb in breast cancer cases	Pb in controls	Association	Conclusion
O'Brien et al. (40)	USA	1217/1217	0.144 µg/g	0.134 µg/g	No	Slight difference
O'Brien et al. (41)	USA	111/110	0.117 µg/g	0.111 µg/g	No	Slight difference

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Discussion and Conclusion

In our review investigating the potential link between Pb exposure and BC risk, 16 of 27 studies that measured Pb in biological matrices, published in 23 manuscripts (16-22, 25, 27-41), reported an association between high Pb levels and BC. Among these 16 studies, 4 of 6 studies on breast tissue (16-18, 28), 3 of 6 studies on urine (29-31), 6 of 9 studies on blood (18, 19, 33-36), 3 of 4 studies on hair (19, 34, 38) reported a link between elevated Pb levels and risk of BC. The other 11 series reported no association: breast tissue in 2 publications (20, 27); urine in 3 publications (22, 25, 32); blood in 3 publications (20, 21, 37); hair in one publication (39); and toenails in 2 publications (40, 41).

These discrepancies can be explained by different hypotheses concerning the included populations, the type of BC, and the choice of biological matrix for Pb measurement.

Populations Included in Our Review

Age and hormonal status of participants vary considerably across the included series, whereas BC mainly affects menopausal women. This discrepancy in results could also arise from the diversity of countries in which the studies were conducted (China, India, Nigeria, European countries, USA). Moreover, two studies did not specify the sex of the participants (17, 28), and a third study (38) found a link between Pb in hair and BC in a mixed cohort. The number of participants varied widely, ranging from 12 to 816, with six studies having fewer than 50 participants. Finally, some publications did not mention follow-up; only one reported a follow-up of 25 years (33).

The Type and Characteristics of the BC

Histological BC characteristics are not always reported in sufficient detail to determine whether Pb could be linked to particular types of BC. For example, the study by Alatise and Schrauzer (19) found a link between Pb in breast tissues, blood, and hair, and infiltrating ductal carcinoma. Hu et al. (29) reported an association between Pb in urine and hormone-dependent BC in a study of 210 women in the USA. Burton et al. (31) mentioned in their publication that high urinary Pb levels may be associated with advanced stages of BC in women. These distinctions are critical, as Pb may not influence all BC types equally.

Pb Measurement Protocols

Concerning Pb measurement protocols, some studies analyzed Pb alone; others analyzed different metals, including Pb. For example, Mérida-Ortega et al. (32) studied the cocktail effect and the interactions of Pb and other metals in urine and their association with BC, showing that a mixture of metals (Sn, Cr, Ni, Sb, Al, and Pb) could be linked to BC in postmenopausal women. Such interactions may be crucial to understanding Pb's role as a co-carcinogen in environmental exposure contexts.

The Choice of the Biological Matrix

Regarding biological matrices, four studies permit comparison of Pb determination across different matrices: breast tissue and blood (18, 20); breast tissue, blood, and hair (19); and blood and hair (34). The results of these studies were comparable and led to the same conclusions. Except for toenails, all biological matrices appear to be conclusive. However, considering the lifetime of Pb in the body, urine and blood could indicate recent Pb exposure (42). In contrast, hair (43) and toenails (44) provide information on Pb exposure over the past few months. The only matrix that appears to reflect both past and recent Pb exposure is breast tissue.

In our review, two studies (40, 41) examined Pb levels in toenails and did not find a significant association between Pb and BC. These dosages had not been compared with dosages in other matrices. Consequently, it is difficult to determine whether toenails are a reliable biological matrix for studying the links between BC and heavy metals, including Pb.

Studies with Link Between Elevated Pb Level and BC Risk

Considering these limitations, when we included only well-designed studies that used four biological matrices (breast tissue, urine, blood, and hair), selected appropriate participant demographics, and excluded multi-metal exposure, the majority of studies (16/25) concluded that Pb exposure is associated with an increased risk of BC.

The BC incidence for each country, corresponding to the study year when available, is presented in Supplementary Table 2. Otherwise, we included the 2022 incidence data from GLOBOCAN. We have also included in this table the acceptable limits for lead in each country mentioned in this review (BLL and acceptable levels in drinking water), and the dates on which these values came into effect (45-58). The review's data show no consistent cross-country relationship between measured Pb concentrations in BC samples and national BC incidence. High-incidence countries (the USA, Italy, and Spain) typically exhibit low Pb concentrations in biological samples. Developing countries (India, Nigeria, and Pakistan) often exhibit higher Pb levels in patient specimens, yet BC incidence is lower. These discrepancies reflect methodological, environmental, and demographic differences, rather than a true causal Pb-BC relationship. The observed variations are more likely due to differences in study design, biological matrices, laboratory techniques, and population characteristics than to a direct causal link between Pb and BC incidence.

Table 2. Summary of strength of association between Pb levels and breast cancer by biological matrix

Biological matrix	Number of studies	Association	Interpretation
Breast tissue	6	4 positive, 2 null	Consistent relationship
Urine	6	3 positive, 3 null	Inconsistent
Blood	9	5 positive, 4 null	Stronger in high-exposure regions
Hair	4	3 positive, 1 null	Tendency toward positive association
Teonails	2	2 null	No consistent relationship
Overall	27	15 positive, 12 null	No consistent global relationship

When Comparing all available numerical data, Pb concentrations measured in BC specimens are generally lower in studies conducted after 2000 than in those before 2000.

In the studies before 2000 [Santiliquido (1976), Rizk (1984), Ionescu (2006), Siddiqui (2006) and Alatise (2010)]. Although published after 2000, these early studies used specimens collected before 2000 or before local Pb regulation took effect)), the observed ranges were:

• Breast tissue: 0.6–105 µg/kg (median = 50 µg/kg)

• Blood = 20 µg/dL

• Hair = 20 µg/g

Wheras in the studies after 2000 [Mansouri (2022), Andelkovic (2022), Afridi (2021), Li (2020), Wei (2019), Hu (2023), Bell (2023), Merida-Ortega (2022) and Benderli Cihan (2011)], the observed ranges were:

• Breast tissue = 0.09–13 µg/kg (median = 10 µg/kg)

• Blood =1.5–53 µg/dL (median = 2 µg/dL excluding Pakistan outlier)

• Hair = 3.8–8 µg/g

• Urine = 0.5–3 µg/L or µg/g creatinine

This temporal decrease aligns with the timeline of international lead-exposure regulations and environmental phase-outs. Nonetheless, the decline is not universal. Countries with weaker enforcement of environmental regulations or with ongoing environmental contamination (e.g., parts of South Asia or Africa) still report relatively high Pb levels among cancer patients.

A summary of interpretations (Table 2) shows that studies in high-exposure regions (e.g., Pakistan, India, Nigeria) reported positive associations between Pb concentrations in breast tissue, urine, blood, and hair and BC, whereas studies in low-exposure or post-regulation settings (e.g., USA, Europe) mostly reported null findings. The overall evidence remains inconsistent across matrices and study designs.

We find concordance between our results and those presented in this review and by Coradduzza et al. (59), indicating a link between Pb exposure and BC, particularly in blood samples. Consistent with our review, Coradduzza et al. (59) reported higher levels of Pb in biological samples from BC patients than in healthy controls. In plasma samples, Pb levels were 1.52-fold higher in BC patients than in controls. This suggests that exposure to Pb may influence blood lipid levels and other small-molecule metabolites involved in BC development.

Contrary to our findings in urine samples, studies investigating heavy metals in the urine of BC patients have shown that environmental exposure to Pb, together with Cd and Cr, may contribute to BC development (59).

Finally, consistent with our observations in hair samples, some studies on BC patients have reported higher levels of several elements in hair; nevertheless, the specific association of Pb levels in hair with BC appears less prominent than that of other metals (59).

In these studies, Pb exposure has been implicated in BC through various mechanisms, primarily due to its role as an endocrine disruptor and its ability to cause DNA damage. Pb can mimic estrogen, a hormone that plays a significant role in BC development, by activating estrogen receptors and promoting cell proliferation. This activity is similar to that of natural estrogens and can lead to increased expression of estrogen-regulated genes, contributing to tumor growth (60, 61).

Research on the mechanism involving Pb in BC is sparse. However, the predominant findings suggest a strong correlation between Pb and the pathogenesis of BC. Pb exerts a notable influence on both the expression and functionality of ERα. It promotes the proliferation of MCF-7 cells, reduces the steady-state levels of ERα protein and mRNA, triggers the activation of two estrogen-regulated genes, the progesterone receptor and pS2, and stimulates ERα in transient transfection assays (61). Figure 3 shows the mechanistic pathway of Pb-induced ER signaling activation (62, 63).

Furthermore, Pb, a nonessential metal, can mimic or interfere with the function of essential metals, leading to toxicity associated with BC (62, 64-66).

Additional research into the relationship between lead exposure and BC is justified. This should encompass studies tailored to specific geographic regions, extensive longitudinal investigations, and mechanistic analyses, all aimed at uncovering the pathways by which Pb exposure influences estrogen receptor signaling and promotes breast carcinogenesis. Exploring the interplay between non-essential lead and essential metals in BC development is also recommended (67).

Pb can also cause direct DNA damage and generate reactive oxygen species, leading to oxidative stress and potential mutations in breast cells. This damage can contribute to carcinogenesis by altering gene expression and inhibiting DNA repair mechanisms (68). Finally, Pb exposure may result in epigenetic modifications, such as altered gene expression caused by the displacement of zinc from transcriptional regulators. This can affect the regulation of genes involved in cell growth and differentiation, further promoting cancer development (68).

While substantial evidence links Pb exposure to BC, the relationship is not entirely straightforward. Additionally, interactions between Pb with other metals and nutrients, such as selenium, can influence its carcinogenic potential. Selenium, known for its anti-carcinogenic properties, can be antagonized by Pb, potentially exacerbating cancer risk (19).

The relationship between Pb and BC is complex and influenced by various factors, including environmental exposure levels and

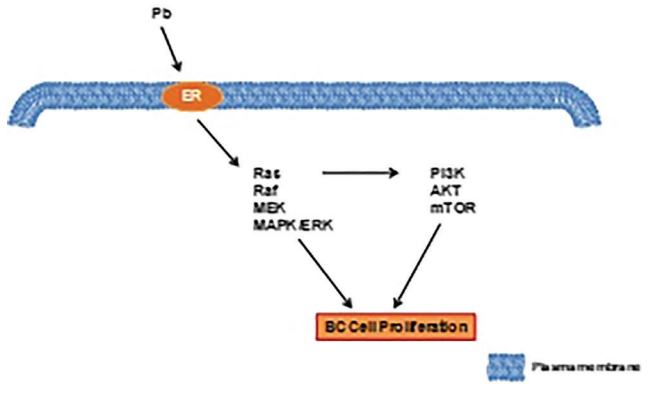

Figure 3. Signaling pathways involved in the associations between Pb and breast cancer

individual biological responses. Therefore, further research is needed to fully understand the mechanisms underlying potential Pb toxicity in BC cells.

While a majority of the reviewed studies suggest a potential association, particularly when Pb is measured in breast tissue, blood, urine, and hair, substantial variability in findings persists across different study designs. These inconsistencies underscore the importance of future studies that should prioritize larger cohorts, consider tumor heterogeneity, include both sexes and perform sex-stratified analyses, and account for cumulative exposures and metal interactions. Furthermore, prospective longitudinal studies with long-term follow-up are needed to strengthen causal inference and clarify the temporal relationship between Pb exposure and BC occurrence. Understanding the mechanisms by which Pb may influence BC development, such as endocrine disruption, oxidative stress, and epigenetic alterations, could inform more targeted public health prevention strategies.

Footnotes

Authorship Contributions

Concept: A.M., S.E.B., M.G., C.M.; Design: A.M., S.E.B., M.G., C.M.; Data Collection or Processing: A.M., S.E.B., M.G., C.M.; Analysis or Interpretation: A.M., S.E.B., M.G., C.M.; Writing: A.M., S.E.B., M.G., C.M.

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Original Article

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Comparative Evaluation of Machine Learning and Specialist Physicians in Breast Care Triaging: A Real-World Observational Study

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ABSTRACT

Objective: To evaluate the diagnostic accuracy and efficiency of a proprietary breast-specific machine learning (ML) model—built upon the open-source Open Triage platform—in comparison to specialist physicians, using standardized real-world clinical data for breast referral triaging.

Materials and Methods: A retrospective observational study was conducted using 174 standardized breast cases obtained from proprietary industry datasets, spanning 46 disease types, 23 of which were cancers. The cohort ranged from 19 to 75 years (mean: 39.4±12.0). Physicians and an ML model each generated three diagnostic predictions per case. Both modalities were compared after benchmarking their predictions against a gold-standard diagnosis established by imaging and biopsy. Performance was evaluated using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) analysis. Time efficiency was also assessed to compare diagnostic turnaround times between physician- and ML-generated predictions.

Results: The ML model demonstrated superior diagnostic accuracy (100%) compared to physicians (83.9%), with higher sensitivity (0.947 *vs.* 0.826) and PPV (0.500 *vs.* 0.442). Both groups achieved comparable specificity and NPV values. ROC analysis showed an AUC of 0.91 for the ML model's first prediction versus 0.83 for the doctor's first prediction, indicating superior predictive power of the ML model.

Conclusion: The ML model demonstrated diagnostic accuracy comparable to or better than that of physicians while significantly reducing the time required. These findings suggest that AI-powered triage tools could enhance the efficiency and standardization of breast triage.

Keywords: Artificial intelligence; clinical decision support systems; breast surgery; machine learning; predictive models; diagnostic accuracy

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Key Points

- Artificial intelligence
- Clinical decision support systems
- Predictive models

Introduction

Triage is the critical process of prioritising patients based on the urgency of their condition to ensure timely care and effective resource allocation. In breast care, this involves identifying individuals at elevated risk—such as those with suspected or confirmed cancer, genetic predispositions, or concerning symptoms—so that diagnostic evaluation and intervention can be appropriately expedited, ultimately improving patient outcomes (1-3).

In breast care, triage is typically implemented through several modes of entry, shaped by patient circumstances and the nature of the clinical encounter. Within population-based screening workflows, radiologists traditionally conduct image reviews and make recall decisions guided

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by established protocols. Artificial intelligence (AI)-enabled triage mechanisms are increasingly being explored to prioritise abnormal findings, accelerate diagnostic follow-up, and reduce radiologist workload without compromising cancer detection rates (4-8). Opportunistic triage, by contrast, occurs during unrelated healthcare encounters, such as routine clinical visits, during which clinicians take the opportunity to initiate breast assessment outside formal referral systems (9). Referral triage in breast care is predominantly symptom-driven; primary care providers submit structured referrals for patients presenting with concerning features, and these referrals are then assessed by specialist teams (3, 10).

Based on these varied clinical entry points, breast triage models have diversified to encompass manual sorting, telephonic and virtual platforms, and increasingly digital or algorithmic approaches alongside traditional pathways (11, 12). During the COVID-19 pandemic, temporary innovations such as virtual triage gained prominence; however, resource-intensive manual triage processes remain the norm today (13, 14). Research highlights that the effectiveness of triage is heavily influenced by multiple variables-most notably clinician expertise, workload fluctuations, infrastructure constraints, and the availability of supporting systems and personnel (12, 15-17). Notably, risk-averse triage may drive unnecessary investigations and overtreatment (18, 19), whereas purely rule-based digital systems may increase workload without demonstrable improvement in clinical outcomes (2, 15, 16, 20, 21). Thus far, many digital triage tools have largely digitized existing protocols without addressing broader systemic pressures such as legal anxieties and patient demand (22, 23).

Such practical constraints are reflected in referral trends: breast cancer referrals have seen a marked increase—from 432 to 1,027 per 100,000 individuals between 2009 and 2023—while conversion rates have declined from 2% to 1% (24). Evidence further suggests that consistent application of evidence-based triage protocols could raise conversion rates to 14%, highlighting the urgent need for innovation and more effective triage processes (25).

In response to these challenges, AI initiatives have gained traction across specialties-from emergency medicine and dermatology to emerging applications in radiology. Although AI adoption in breast triage remains limited, lessons from emergency medicine (26) and dermatology underscore its potential (27, 28). One major modality is multi-layered, data-driven triage, where machine learning (ML) and deep learning models analyse diverse structured inputs—such as electronic health records, imaging data, and patient histories—to deliver nuanced risk stratification and consistent decision-making (26).

A second modality is image-based triage, which leverages clinical photographs or scans, such as mammograms, to enable direct visual assessment by ML models. This pathway represents a distinct form of triage, allowing algorithms to process and prioritise visual information independently of structured datasets (29). For instance, in tele-dermatology, image-based triage enabled remote resolution of over 80% of consultations, halving the need for in-person visits (30). The third modality involves reinforcement learning (RL), where algorithms learn optimal triage policies by observing expert clinical decisions. Some evidence suggests RL models can achieve safe, consistent decision-making that mirrors expert-level reasoning, reinforcing their potential to adapt to complex, dynamic triage environments (31). Finally, natural language processing offers a flexible modality by integrating unstructured narrative data—such as free-text nursing notes—with structured clinical inputs. This fusion enables models to surpass the limitations of structured-only systems, improving triage classification accuracy and enriching contextual understanding of patient acuity (32).

This study builds upon evidence-based AI triage models used in other specialties and addresses gaps in breast care by evaluating a domain-specific clinical decision support system (CDSS) for breast triage. The CDSS augments traditional referral pathways through a structured, data-driven methodology. By integrating comprehensive patient histories, including medical records, family histories, and surgical interventions, it generates nuanced cancer risk assessments and personalised care pathway recommendations, offering alternative scenarios with associated probabilities and confidence levels. This observational study aims to assess the performance of predictive triage data models in clinical practice by benchmarking against actual diagnostic outcomes (33).

Materials and Methods

This retrospective observational study was designed to compare the diagnostic triage predictions generated by specialist physicians with those produced by an ML application, using a standardized set of performance metrics.

The study aimed to address the following research questions:

1. What level of agreement exists between the ML model's predictions and the gold standard?

2. How do the ML model's predictions compare with those of specialist physicians?

3. What is the level of agreement between physicians' predictions and the gold standard?

The study protocol, project number 342655/YD, was approved by the YouDiagnose Ethical Approval Committee under application no. 101/01022020 on February 1, 2020. All methodologies adhered to COPE guidelines and the Declaration of Helsinki. Informed consent was obtained from participants prior to study initiation. No non-anonymized human data or biological samples were used.

The study population comprised female patients aged 18 years and older who presented with breast-related symptoms. Exclusions were applied to males, individuals under 18 years, those with a history of breast cancer, and those with rare conditions such as idiopathic granulomatous mastitis or Mondor's disease. Data were sourced from proprietary industry datasets comprising 348 consecutive, anonymized breast cases. Following a three-step data standardization process, including data cleaning, completeness assessment, and independent review by senior breast consultants, 174 cases were selected for analysis.

All cases were processed using the same three-step data standardization procedure to maintain consistency and reliability, and to ensure compliance with data protection protocols. The methodology is described below, with a detailed workflow provided in Figure 1.

Data Collection: Data from 348 consecutive breast cases were collected from proprietary datasets provided by industry partners. Each case was anonymized and subjected to cleaning procedures consistent with data privacy and confidentiality requirements. A preliminary review excluded 21 cases not meeting the inclusion criteria.

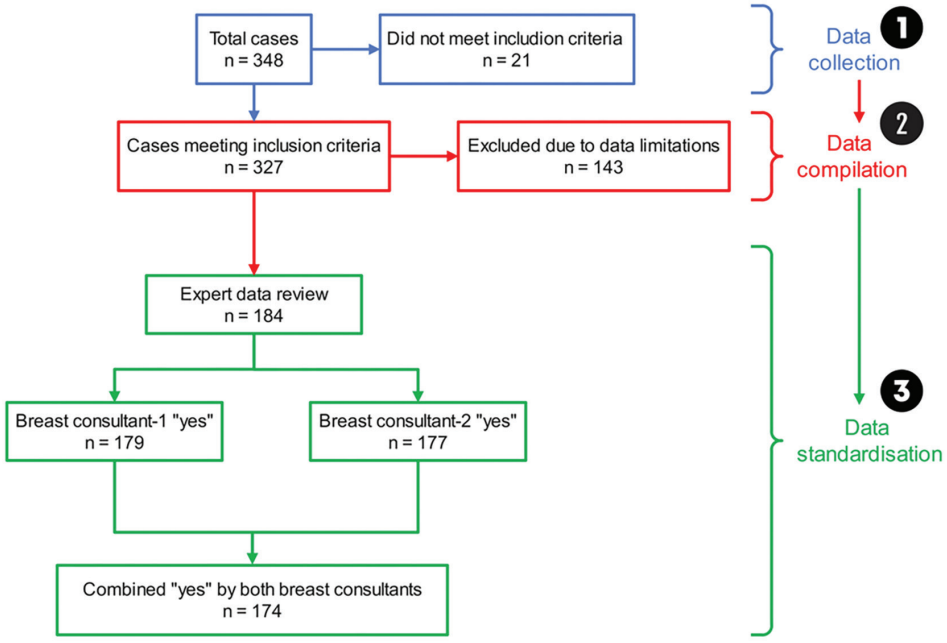

Figure 1. Various stages of data standardisation

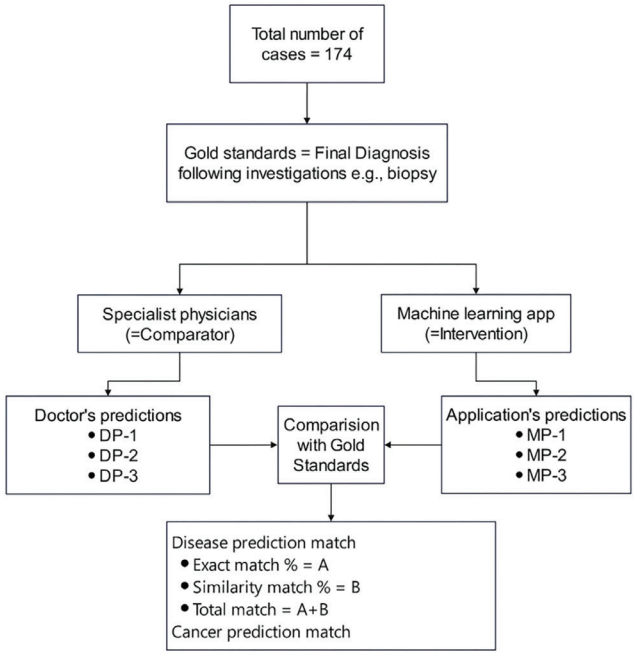

Figure 2. The study design

DP: Doctor performance; MP: Model performance

Data Compilation: Two physicians and research associates assessed the completeness of key categories, including chief complaints, medical history, diagnostic investigations, interventions, and final diagnoses. Cases with missing data in multiple categories were excluded, removing 143 from the dataset.

Data Review: Two senior breast consultants independently assessed the adequacy of the remaining cases against National Health Service (NHS) standards in the United Kingdom. After this review, 174 cases were approved for inclusion in the final dataset.

The gold standard for diagnostic benchmarking was defined as the final diagnosis established through confirmatory imaging—such as mammography, magnetic resonance imaging (MRI), and ultrasonography—and, when appropriate, biopsy-verified diagnoses.

Seventeen specialist breast surgeons from four NHS Breast Surgery Units were invited to participate, with ten agreeing after three rounds of contact. Eligible physicians had at least five years of specialist experience, were registered with the General Medical Council, and demonstrated proficiency in computer-based systems. All participants received induction training on the study's digital interface and provided differential diagnoses, cancer risk assessments, and urgency ratings for each pseudonymized case under controlled conditions.

The ML predictions were generated using a platform called Open Triage, an open-source software developed and maintained by the Uppsala Centre for Prehospital Research at Uppsala University (34). Building on this platform, we integrated a proprietary breast-specific prediction model designed to support clinical decision-making in breast health. While Open Triage is freely available as open-source software, the final deployed prediction model is a copyrighted product developed by the research team and is not commercially available.

Predictions from both physicians and the ML model were benchmarked against the gold standard, with agreement evaluated using sensitivity, specificity, positive predictive value, negative predictive value, and receiver operating characteristic (ROC) analysis. Diagnostic outcomes were classified as either perfect matches (exact correspondence with the gold standard) or similarity matches (close alignment with minor variations), providing a robust and clinically relevant measure of diagnostic performance. A detailed overview of the study design is provided in Figure 2.

Participating physicians underwent induction training on software navigation and user interface functionality. The study was conducted using laptops connected to secure internet networks under controlled conditions. Physicians accessed pseudonymized patient cases via login credentials and provided differential diagnoses alongside assessments of cancer risk and care urgency.

Predictions made by physicians and the ML model were compared with the gold-standard diagnosis and classified into three outcome types: a perfect match, in which the predicted diagnosis was identical to the gold-standard diagnosis; a similarity match, in which the predicted diagnosis had a closely related pathogenesis, clinical course, and overlapping symptoms; and a non-match, in which the predicted diagnosis did not correspond meaningfully to the gold-standard diagnosis.

For example, a similarity match includes predicting "lactation abscess" when the gold-standard diagnosis is "lactation mastitis". These conditions, while not strictly identical, involve similar underlying mechanisms (inflammation and infection within the lactating breast), present similarly, and require comparable clinical management. This approach acknowledges that certain diseases exist along a spectrum or are commonly conflated due to overlapping features. Categorizing them as similarity matches allows for a meaningful evaluation of both diagnostic accuracy and the clinician's practical reasoning.

Results

Study Population and Baseline Characteristics

A total of 174 cases were included in the final analysis after applying inclusion and exclusion criteria. The cohort's ages ranged from 19 to 75 years (mean 39.4±12.0; median 38; mode 45), indicating a moderately dispersed, approximately bell-shaped distribution that spanned young adulthood to older age brackets and was slightly skewed toward younger individuals. These cases represented 46 distinct breast disease types, including 23 cancer cases and 151 benign conditions, and the gold standard—established through final diagnoses verified by mammograms, MRIs, ultrasounds, and biopsies—served as the reference standard for evaluating diagnostic predictions.

Statistical Approach

To compare the diagnostic performance of specialist physicians and the ML model, a cumulative predictive power approach was employed. This method aggregated all diagnostic predictions—exact matches (A) and similarity matches (B)—from both groups. The combined predictions (A+B) were analysed to evaluate the overall performance of each group. For physicians, predictions were categorized as DP1, DP2, and DP3 (representing their top three differential diagnoses), while for the ML model, predictions were categorized as MP1, MP2, and MP3. Aggregated predictions for both groups were assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and ROC curve analysis. A comparative analysis of these metrics enabled a direct evaluation of performance (Table 1).

Diagnostic Accuracy

Table 2 summarizes the diagnostic accuracy of both physicians and the ML model. Among the physicians, DP1 achieved moderate performance with 66 exact matches (37.93%) and 58 similarity matches (33.33%), while DP2 and DP3 demonstrated considerably lower accuracy with only 7 and 15 exact matches, respectively, and neither had any similarity matches. In contrast, the ML model's MP1 achieved superior performance with 111 exact matches (63.79%) and 40 similarity matches (22.99%). MP2 and MP3 exhibited lower accuracy, with 23 and 11 exact matches, respectively, and no similarity matches.

When aggregated across all predictions, the ML model outperformed physicians, with an overall accuracy of 100% versus 83.9% for physicians. These findings indicate that the ML model was more effective in achieving both exact and similarity-based matches in this comparative analysis.

Table 1. Displays the years of specialist practice, and the number of cases allocated to each participating physician

Sl no	Username	No of cases	Year of specialist practice	Postgraduate qualifications
1	user291	37	20	MD, FRCS
2	user292	37	15	FRCS
3	user293	13	14	MCh, FRCS
4	user294	11	10	FRCS
5	user295	11	8	FRCS
6	user296	13	9	FRCS
7	user297	12	11	FRCS
8	user298	14	12	FRCS
9	user299	11	9	FRCS
10	user300	15	12	MD, FRCS
174		Total number of cases	Average years of specialist practice	
		12.0		

Table 2. Showing the comparative performance specialist physicians (DP1, DP2, DP3) and the machine learning model (MP1, MP2, MP3)

Variable	Exact match	Exact match accuracy	Similarity match	Similarity match accuracy	Total matches	Total matches accuracy
DP1	66	37.931%	58	33.333%	124	71.264%
DP2	7	4.022%	0	0%	7	4.022%
DP3	15	8.620%	0	0%	15	8.620%
Combined DP	88	50.574%	58	33.333%	146	83.908%
MP1	111	63.793%	40	22.988%	151	86.781%
MP2	23	13.218%	0	0%	23	13.218%
MP3	11	6.321%	0	0%	11	6.321%
Combined MP	145	83.333%	40	22.988%	174	100%

DP: Doctor performance; MP: Model performance

Performance Metrics

Table 3 presents a detailed comparison of performance metrics between the physicians (DP) and the ML model (MP). Key observations include:

- **Sensitivity:** The ML model demonstrated higher sensitivity (0.947) than physicians (0.826), indicating its superior ability to correctly identify true positives.
- **Specificity:** Both groups achieved comparable specificity, with the ML model slightly outperforming physicians (0.854 *vs.* 0.841).
- **PPV:** The ML model achieved a higher PPV (0.500) than physicians (0.442), suggesting greater reliability in predicting positive cases.
- **NPV:** Both groups exhibited high NPV, with the ML model achieving 0.992 compared with 0.969 for physicians.

ROC Analysis

The ROC curves for all predictions are illustrated in Figure 3. The dashed diagonal line represents random classification, with an area under the curve (AUC) of 0.50.

- Among physicians' predictions, DP1 achieved the highest AUC (0.83), significantly outperforming DP2 (0.50) and DP3 (0.54).
- For the ML model, MP1 demonstrated superior predictive power with an AUC of 0.91, while MP2 and MP3 performed no better than random guessing (AUC = 0.50).
- Combined predictions for both groups mirrored their highest-performing individual predictor: DP1 for physicians (AUC = 0.83) and MP1 for the ML model (AUC = 0.91).

Statistical comparison of AUCs was performed using DeLong's test for correlated ROC curves, as all predictions were made on the same dataset. The differences between top-performing and lower-performing models were statistically significant (p<0.001 for all pairwise comparisons).

Data Analysis

The Wilcoxon Signed-Rank test was employed to compare physician- and ML-generated predictions for agreement with the gold-standard diagnosis.

Table 3. Matching performance metrics: specialist physicians (DP) and the machine learning model (MP)

1. Metric	2. DP	3. MP
4. Sensitivity	5. 0.826	6. 0.947
7. Specificity	8. 0.841	9. 0.854
10. PPV	11. 0.442	12. 0.5
13. NPV	14. 0.969	15. 0.992
16. Accuracy	17. 0.839	18. 0.868

DP: Doctor performance; MP: Model performance

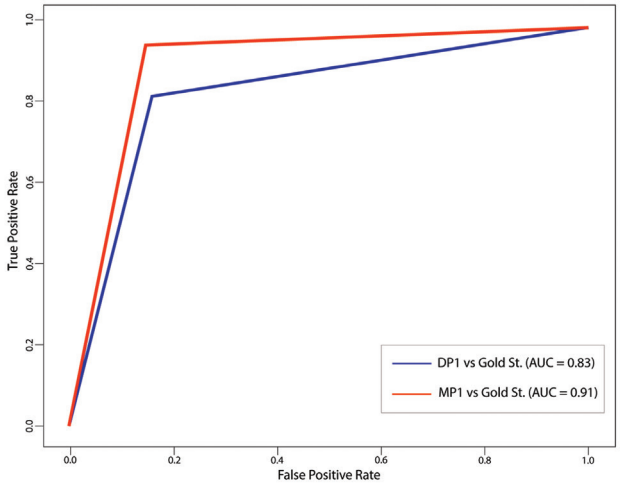

Figure 3. ROC curve all predictions

ROC: Receiver operating characteristic

- Although a test statistic of 0.0 would normally not correspond to a small p-value, the reported p-value of 1.52e-10 indicates a statistically significant difference between physician and ML predictions.
- These findings suggest that observed differences in diagnostic accuracy are unlikely to be due to random variation.

Confusion Matrix Analysis

Confusion matrices comparing diagnostic classifications by physicians and the ML model are presented in Figure 4.

• For benign cases, the ML model correctly classified 130 true negatives and produced 22 false positives, while physicians correctly identified 128 true negatives and recorded 24 false positives.

• For cancer cases, The ML model demonstrated superior sensitivity with no false negatives, correctly identifying all 22 cases as true positives. Physicians correctly identified 19 cancer cases but misclassified 3 cancer cases as false negatives.

The findings demonstrate that the ML model has superior sensitivity and precision in identifying cancer cases. However, due to the limited sample size, the difference in cancer detection performance between the ML model and specialist physicians did not reach statistical significance (p>0.05), indicating that the ML model's diagnostic capability is comparable to that of specialist physicians.

Key Observations

1. The ML model consistently and significantly outperformed physicians in diagnostic accuracy and across all performance metrics.

2. The ROC analysis confirmed that the top-performing prediction in each group dominated the overall predictive ability.

3. The ML model demonstrated superior time efficiency, processing cases almost instantaneously, compared with the several minutes per case required by physicians.

4. While both methods showed high accuracy in identifying benign cases, the ML model exhibited enhanced sensitivity in detecting cancer cases.

5. Despite these advantages, no statistically significant difference in cancer identification was observed, owing to sample size limitations (p>0.05). This suggests that in classifying cases as benign or malignant, the ML model performs comparably to industry comparators and demonstrates noninferiority relative to physicians.

Discussion and Conclusion

This study demonstrates that ML models, when applied to real-world clinical datasets in an experimental setup, exhibit diagnostic performance that is comparable to or superior to those of specialist physicians across several metrics, highlighting their effectiveness in breast triage and warranting further evaluation in live, patient-facing clinical settings. This discussion contextualizes the findings, outlines their clinical implications, and presents limitations alongside conclusions. It also highlights existing studies on AI/ML-led triage in breast surgery and identifies directions for future research.

Diagnostic Performance

Our analysis demonstrated that the ML model outperformed physicians on key diagnostic metrics, including sensitivity (94.7% *vs.* 82.6%), PPV (50.0% *vs.* 44.2%), and overall diagnostic accuracy (100.0% *vs.* 83.9%). While the ML model correctly identified all cancer cases (i.e., produced no false negatives), physicians misclassified three cancer cases as false negatives. However, statistical analysis revealed no significant difference in cancer identification performance between the ML model and physicians due to sample size limitations (p>0.05). This indicates that the ML model performs at a level comparable to industry standards and demonstrates diagnostic capability that is non-inferior to that of specialist physicians. Importantly, these findings highlight the potential of the ML model to complement physicians in early cancer triage predictions and to assist in reducing the likelihood of missed diagnostic opportunities that occur in referral pathways, a persistent challenge in breast health triage.

Both physicians and the ML model exhibited high specificity and NPV, with comparable results between the two groups (specificity: 0.854 *vs.* 0.841; NPV: 0.992 *vs.* 0.969). While both approaches demonstrated strong performance in ruling out benign cases, the ML model, as previously noted, showed a marginally higher sensitivity in detecting malignancies. However, this advantage did not reach statistical significance. These results underscore the potential for integrating ML models alongside clinical expertise to enhance diagnostic efficiency and support decision-making in breast care pathways.

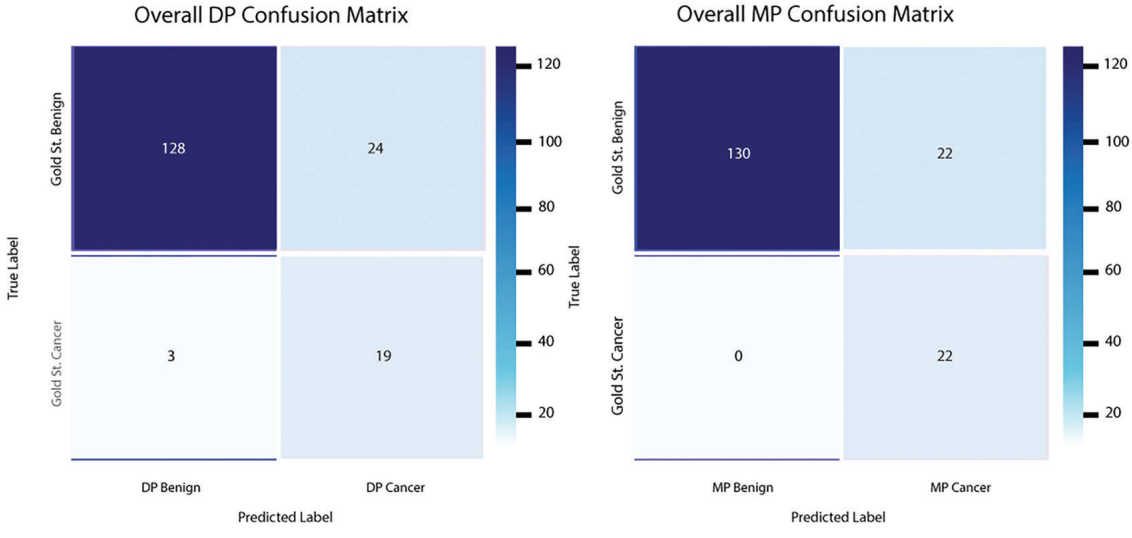

Figure 4. Confusion matrices from DP and MP

DP: Doctor performance; MP: Model performance

Efficiency and Time Savings

The time required for diagnosis differed markedly between groups. Physicians required 789 minutes to review all cases, whereas the ML model processed the entire dataset in 0.3215 seconds. Figure 5 demonstrates this efficiency gap, showing the ML model's superior speed without compromising diagnostic accuracy.

Integrating ML into triage can reduce manual workload, ease referral bottlenecks, and improve resource use, particularly in high-volume environments. Further research is needed to evaluate the practical time and cost benefits of combining ML with clinical expertise.

Implications for Clinical Practice

This study underscores the value of integrating ML analytics with physician expertise to create a hybrid triaging model that leverages the strengths of each. Physicians offer intuition, empathy, and judgment in complex cases, while ML systems contribute consistent risk assessments and pattern recognition, thereby reducing cognitive burden and standardizing decision-making.

This partnership can address inefficiencies commonly observed in manual triage by enabling timelier and more targeted patient management. ML models can assist in pre-screening referrals and identifying potentially high-risk cases, helping clinicians allocate their expertise more efficiently across all levels of care—from routine assessments to complex diagnostic decisions—while maintaining oversight and accountability at every step.

The findings confirm that ML tools can effectively support breast health triage, matching or exceeding the diagnostic accuracy of specialists, while significantly reducing time demands. When guided by patient-centred care principles, this data-driven collaboration has the potential to transform triage across healthcare systems—advancing equity, efficiency, and clinical precision.

Supporting Evidence from Contemporary Literature

The findings of this study align with substantial evidence from contemporary literature supporting the clinical utility and effectiveness of AI-assisted breast triaging systems. Mazo et al. (35) conducted a systematic review of CDSS in breast cancer care, demonstrating that such systems significantly assist healthcare staff with clinical decision-making while improving care quality and minimizing costs. This systematic review validates the conceptual framework underlying ML model implementation in breast care pathways, providing robust evidence that automated decision support systems can enhance healthcare efficiency while maintaining patient-centred care.

The DENSE trial validation studies provide particularly compelling evidence for the real-world effectiveness of AI-assisted breast triaging. These studies demonstrated that combined computer-aided triaging and computer-aided diagnosis systems dismissed 32.7% of normal examinations, while correctly identifying 46.3% of benign lesions without missing any malignant cases, yielding significantly fewer false-positive referrals (a 48.6% reduction) compared to radiological reading alone (36). Similarly, the MASAI trial showed that AI-supported screening detected 29% more cancers than traditional screening methods while reducing mammogram reading workload by 44% (37). These findings directly parallel our results, which show superior ML performance in sensitivity (0.947 *vs.* 0.826) and dramatic efficiency gains (0.3215 seconds per case *vs.* 4.5 minutes per case), reinforcing the clinical validity of AI-assisted breast triaging approaches.

Furthermore, Arıbal (38) provides a crucial perspective on the future of breast radiology, emphasizing that AI integration will transform radiologists into specialized clinicians collaborating with AI systems rather than being replaced by them, a view that aligns with our discussion of hybrid approaches that combine physician expertise with ML precision. The emphasis by Oren et al. (2020) on shifting

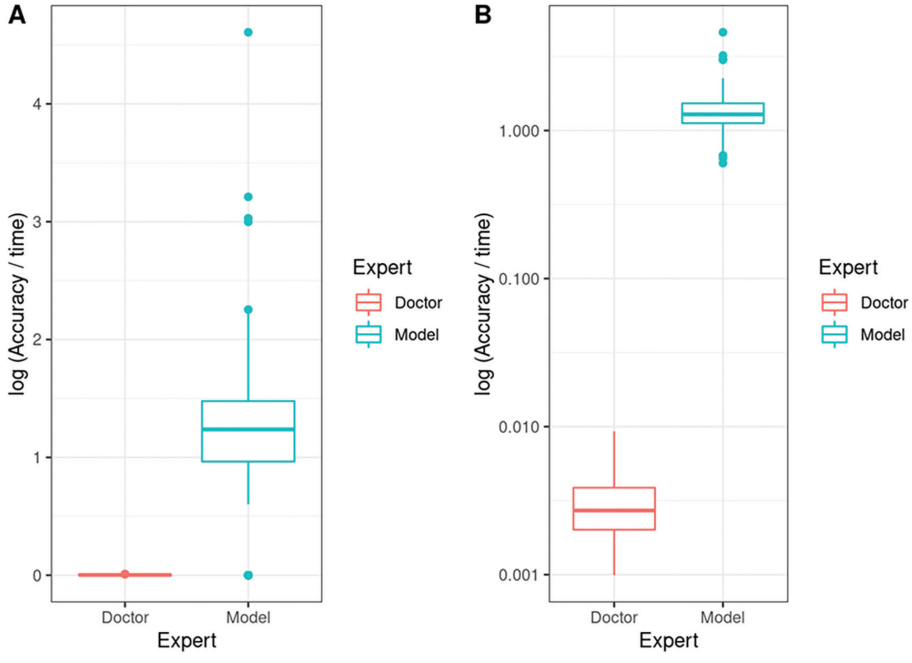

Figure 5. Comparative analysis of log accuracy between doctor and model

AI research focus from radiographic pathological data to clinically meaningful endpoints such as survival, symptoms, and treatment necessity is particularly relevant to our study's emphasis on practical clinical outcomes and diagnostic accuracy metrics that directly impact patient care decisions. These converging lines of evidence from multiple research settings strengthen the foundation for implementing ML-based triaging systems in clinical practice.

Study Limitations

This study, while yielding promising outcomes, is subject to several noteworthy limitations. The relatively small sample size of 174 cases restricts the statistical power of the findings and may hinder their generalizability to broader populations. Furthermore, the research was confined to breast health triaging and employed standardized datasets, which may not adequately represent the variability and complexity encountered in other clinical domains.

The study design also relied on a controlled environment where physicians made decisions based on pseudonymized case details. Such conditions may not fully capture the nuances of real-world clinical practice, where additional contextual and patient-specific factors are at play. Moreover, differences in physician training, experience, or familiarity with digital tools could have influenced performance outcomes. There remains a risk of bias, particularly given the potential for overinterpretation of performance metrics when comparing multiple variables.

However, validation in larger, more diverse cohorts is essential to confirm these findings and explore their generalizability. Future research should incorporate real-world clinical data across multiple specialties and evaluate the long-term impact of ML-assisted triaging on patient outcomes.

Ethics

Ethics Committee Approval: The study protocol, project number 342655/YD, was approved by the YouDiagnose Ethical Approval Committee under application no. 101/01022020 on February 1, 2020. All methodologies adhered to COPE guidelines and the Declaration of Helsinki.

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

Footnotes

Authorship Contributions

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

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

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Original Article

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Predictive Value of Dimensional and Functional MRI Parameters on Mid-Treatment MRI for Pathologic Complete Response in Breast Cancer

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ABSTRACT

Objective: To evaluate the predictive performance of dimensional and functional magnetic resonance imaging (MRI) parameters obtained from mid-treatment breast MRI for forecasting pathologic complete response (pCR) in patients with locally advanced breast cancer (LABC) undergoing neoadjuvant chemotherapy (NAC).

Materials and Methods: Sixty-five women with LABC who underwent NAC followed by surgery were retrospectively included. Quantitative MRI parameters—including % change (Δ%) in longest diameter, bidimensional size, tumor volume, apparent diffusion coefficient (ADC), and enhancement percentage (Epeak)—were calculated between pre- and mid-NAC MRI. Receiver operating characteristic (ROC) analysis and logistic regression were used to identify predictors of pCR. Logistic regression and ROC analysis (with DeLong's test) were used to assess associations with pCR and compare area under the curves (AUCs).

Results: pCR was achieved in 19 of 65 patients (29%). Compared to non-pCR cases, patients with pCR showed significantly greater reductions in tumor size and Epeak, and larger increases in ADC value (all $p<0.05$). In multiple logistic regression, Δ% longest diameter >60% [odds ratio (OR)=7.1, $p = 0.008$] and Δ% ADC value ≥32% (OR=4.7, $p = 0.016$) remained statistically significant independent predictors of pCR. Δ% tumor volume >92% had the highest univariable AUC (0.754), while Epeak ≤21% showed perfect specificity but was excluded due to wide confidence intervals. Pairwise AUC comparisons showed no significant differences among Δ% longest diameter, bidimensional size, and tumor volume (all $p>0.05$).

Conclusion: Mid-treatment MRI biomarkers, particularly Δ% longest diameter and Δ% ADC value, are effective early predictors of pCR and may support individualized treatment strategies during NAC.

Keywords: Breast cancer; neoadjuvant chemotherapy; mid-treatment; magnetic resonance imaging; pathologic complete response.

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Key Points

- Mid-treatment magnetic resonance imaging (MRI) provides valuable early information for predicting pathologic complete response (pCR) during neoadjuvant chemotherapy in breast cancer.
- Δ% longest diameter >60% and Δ% apparent diffusion coefficient (ADC) value ≥32% were identified as independent predictors of pCR in multiple logistic regression (MLR).
- Δ% tumor volume showed the highest univariable area under the curves but was not retained in the MLR model due to collinearity.
- Functional (ADC) and dimensional (size-based) MRI parameters offered comparable diagnostic performance for pCR prediction.
- These non-invasive, easily obtainable imaging biomarkers may support early risk stratification and individualized treatment planning.

Introduction

Neoadjuvant chemotherapy (NAC) has become a cornerstone in the management of locally advanced breast cancer (LABC), enabling tumor downstaging, facilitating breast-conserving surgery, and offering an *in vivo* assessment of chemosensitivity prior to surgery. One of the critical surrogate endpoints used to evaluate NAC efficacy is the achievement of a pathologic complete response (pCR), which has been shown to correlate with improved long-term outcomes, particularly in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative subtypes (1, 2).

Early prediction of pCR is critical for guiding treatment decisions, including de-escalation or intensification of therapy. Magnetic resonance imaging (MRI) has been shown to outperform conventional modalities such as mammography, digital breast tomosynthesis, and

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automated breast ultrasound, while emerging techniques like contrast-enhanced spectral mammography and positron emission tomography/MRI offer additional functional insights (3-6).

Among the various MRI time points, mid-treatment (mid-NAC) MRI, typically performed after 2 to 4 cycles of chemotherapy, provides a unique opportunity to assess early response and adapt treatment plans in real time (7, 8). This time point allows clinicians to evaluate early response and modify treatment plans accordingly, potentially avoiding unnecessary toxicity or surgical delays.

Building on this potential, several studies have evaluated the predictive value of MRI-derived quantitative parameters in predicting pCR to NAC in breast cancer patients. These parameters include not only morphologic features such as tumor diameter and volume but also functional measures like peak enhancement percentage (Epeak) and apparent diffusion coefficient (ADC) (7-10).

Tudorica et al. (8) demonstrated that early changes in functional MRI parameters after just one cycle of NAC were more effective in predicting pCR than conventional size-based criteria. Similarly, in a prospective study on inflammatory breast cancer, Le-Petross et al. (11) reported that mid-treatment median and mean ADC values were significantly associated with pCR, highlighting their potential as early imaging biomarkers. Despite these encouraging findings, the overall results remain heterogeneous, and there is still no consensus regarding the most reliable parameters or optimal cut-off values. Moreover, although mid-NAC MRI has attracted growing interest, the majority of existing research has focused on post-treatment imaging. Therefore, further validation in well-defined patient cohorts is needed to clarify the combined predictive value of morphologic and functional MRI biomarkers at the mid-NAC stage (4, 8).

Therefore, this study aims to evaluate the predictive performance of both morphologic and functional MRI biomarkers obtained at the mid-treatment stage for forecasting pCR in patients with LABC receiving NAC. By investigating multiple MRI-derived parameters, including tumor size, Epeak, and ADC, we seek to contribute to the development of reliable imaging-based predictors that can guide early treatment decisions.

Materials and Methods

Study Design and Patient Selection

This retrospective study was approved by the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (approval date: 29/11/2023; decision no: 2023/197). Patients diagnosed with breast cancer at our institution between 2019 and 2021 were evaluated for eligibility. Inclusion criteria were as follows: receipt of NAC; availability of breast MRI at three distinct time points—prior to NAC (pre-NAC), mid-treatment (after the fourth chemotherapy cycle) (mid-NAC), and post-treatment (post-NAC); and subsequent surgery performed at our institution with pathological assessment of treatment response. Of the initially screened patients, those were excluded due to incomplete or prematurely terminated NAC or non-adherence to the treatment protocol (n = 5), lack of pre-treatment pathological confirmation at our institution (n = 2), absence of appropriately timed or technically adequate MRI examinations (n = 4), history of prior malignancy or cancer treatment (n = 1), or surgery performed outside our institution without pathological response evaluation (n = 2). After applying these criteria, a total of 65 patients were included in the final analysis.

Chemotherapy Regimens

All patients completed the prescribed systemic NAC and subsequently underwent surgery. NAC regimens were categorized into three distinct groups: anthracycline-based regimens (doxorubicin or epirubicin), taxane-based regimens (docetaxel or paclitaxel), and sequential regimens combining both anthracyclines and taxanes (Table 1). No patients received neoadjuvant endocrine therapy or radiotherapy.

Table 1. Clinical and pathological characteristics of the study cohort (n = 65)

Variable	Category	n	%
Lesion laterality	Left	34	52%
	Right	31	48%
Number of lesions	Unifocal	54	83%
	Multifocal	11	17%
Lesion distribution on MRI	Multicentric	7	11%
	Multifocal	10	15%
	Solitary	48	74%
MRI enhancement pattern	Mass enhancement	53	81%
	Non-mass enhancement	12	19%
Mid-NAC MRI radiological response	Radiologic complete response	8	12%
	Non-complete response	57	88%
Post-treatment radiological response	Radiologic complete response	25	38%
	Non-complete response	40	62%
Primary tumor pCR status	pCR	19	29%
	Non-pCR	46	71%
NAC regimen	Standard AC - taxane	3	5%
	Dose-dense AC - taxane	54	83%
	EC/FEC - taxane	6	9%
	Taxane-only	2	3%
Molecular subtype	Hormone receptor-positive	36	55%
	HER2-positive	17	26%
	Triple-negative	12	19%
Clinical T stage (cT)	cT1	10	15%
	cT2	44	68%
	cT3-T4	11	17%
Clinical nodal status (cN)	cN0	2	3%
	cN1	36	55%
	cN2-N3	27	42%
Tumor grade	1	4	6%
	2	34	52%
	3	27	42%

Table 1. Continued

Variable	Category	n	%
Surgical procedure	Partial mastectomy and SLNB	22	34%
	Total mastectomy and SLNB	5	8%
	Partial mastectomy and ALND	38	58%
Estrogen receptor status	Positive	48	74%
	Negative	17	26%
Progesterone receptor status	Positive	43	66%
	Negative	22	34%
Ki-67 proliferation index	<14	12	18%
	14–20	11	17%
	>20	42	65%

pCR: Pathologic complete response; SLNB: Sentinel lymph node biopsy; ALND: Axillary Lymph node dissection; AC: Adriamycin (doxorubicin) and cyclophosphamide; EC: Epirubicin and cyclophosphamide; FEC: 5-Fluorouracil, epirubicin, and cyclophosphamide; HER2: Human epidermal growth factor receptor 2; MRI: Magnetic resonance imaging; NAC: Neoadjuvant chemotherapy

Histopathological Evaluation

Breast tumor samples obtained through tru-cut biopsy were classified into three molecular subgroups based on immunohistochemical markers: hormone receptor–positive [estrogen receptor (ER) and/or progesterone receptor (PR) positive, HER2-negative], HER2-positive (regardless of hormone receptor status), and triple-negative (ER-negative, PR-negative, and HER2-negative). A tumor was considered hormone receptor–positive if either ER or PR showed ≥1% positivity on immunohistochemistry.

Following surgery, the response to NAC was assessed using the Miller–Payne grading system (Grade 1–5) (12). Grades 1 to 4 were classified as non-pCR, while Grade 5 was defined as pCR. The presence of ductal carcinoma *in situ* was excluded from the definition of pCR. Similarly, axillary nodal status was not considered in the pCR assessment.

MRI Technique

All breast MRI examinations were performed using a 1.5 Tesla scanner (Magnetom Aera, Siemens Healthineers, Erlangen, Germany) equipped with a dedicated breast coil. Imaging was conducted at three predefined time points: pre-NAC, mid-NAC (after the fourth chemotherapy cycle), and post-NAC. Mid-NAC MRI was performed at a mean of 8.4±1.8 weeks after the initiation of chemotherapy, with a median of 8.3 weeks [interquartile range (IQR): 7.3–9.5 weeks].

The standardized protocol included the following sequences in the axial plane: T1-weighted fat-saturated (TR/TE: 476/11 ms, slice thickness: 4.0 mm), T2-weighted turbo spin-echo (TR/TE: 6240/76 ms, slice thickness: 4.0 mm), turbo inversion recovery magnitude (TR/TE: 2250/56 ms), and T1-weighted Dixon (TR/TE: 449/11 ms). Diffusion-weighted imaging (DWI) was acquired using a single-shot echo-planar imaging sequence with b-values of 50, 500, and 800 s/mm² (TR/TE: 6900/66 ms, slice thickness: 4.0 mm). Dynamic contrast-enhanced (DCE) MRI was obtained using a 3D fat-saturated T1-weighted gradient-echo sequence (TR/TE: 4.53/1.82 ms, slice thickness: 2.0 mm). A gadolinium-based contrast agent (gadobutrol, Gadovist®; Bayer, Berlin, Germany) was administered intravenously at a dose of 0.1 mmol/kg, followed by a 20 mL saline flush at a rate of 3 mL/s. Five sequential post-contrast phases were acquired, each lasting 90 seconds, with the first acquisition centering k-space at approximately 1.5 minutes after injection.

All participants were provided informed consent before undergoing imaging.

Radiologic Response Evaluation

All MRI studies were reviewed in consensus by two radiologists with 8 and 23 years of experience, using dedicated workstations (Siemens Healthineers), blinded to the pathological outcomes. Radiological response to NAC was assessed according to RECIST 1.1 criteria (13). For multifocal or multicentric breast cancer, up to two target lesions—preferably the largest—were selected for serial measurements. Non-target lesions were qualitatively assessed but not quantitatively measured.

Radiologic complete response (rCR) was defined as the complete disappearance of all measurable lesions without any residual contrast enhancement. If a residual structure was observed at the tumor site, additional evaluation with DWI was performed. Lesions lacking contrast enhancement were still classified as complete response. Patients who did not fulfill these criteria were categorized as non-rCR.

For each target lesion, the longest diameter, the second-longest diameter, and the shortest diameter were recorded. Based on these dimensions, bidimensional size and tumor volume were calculated. Bidimensional size (cm²) was defined as the product of the longest and second-longest diameters. Tumor volume (cm³) was estimated using the ellipsoid formula:

Volume = (π/6) × longest diameter × second diameter × shortest diameter

Signal intensity (SI) measurements were obtained on both pre-NAC and mid-NAC DCE-MRI scans. Two key values were recorded: The baseline SI before contrast injection (SI_pre) and the peak SI during the early post-contrast phase, approximately two minutes after injection (SI_peak) (10, 14). The early peak enhancement (Epeak) was calculated using the formula:

Epeak (%) = [(SI_peak – SI_pre) / SI_pre] × 100

In patients with rCR, SI measurements on mid-NAC MRI were obtained from the anatomical location corresponding to the original tumor site.

ADC values were measured by placing circular regions of interest (ROIs) within the most diffusion-restricted area of each lesion, identified on high b-value DWI. ROIs were placed on the corresponding hypointense region on the ADC map to accurately reflect the most cellular portion of the tumor. Each ROI had a standardized area of 0.5 cm². Necrotic or cystic areas were carefully avoided, as they could artificially elevate ADC values (Figure 1). In rCR cases, ADC values were measured from the original tumor site on mid-NAC MRI. For patients with multifocal disease, the largest lesion was selected as the primary target for quantitative analysis.

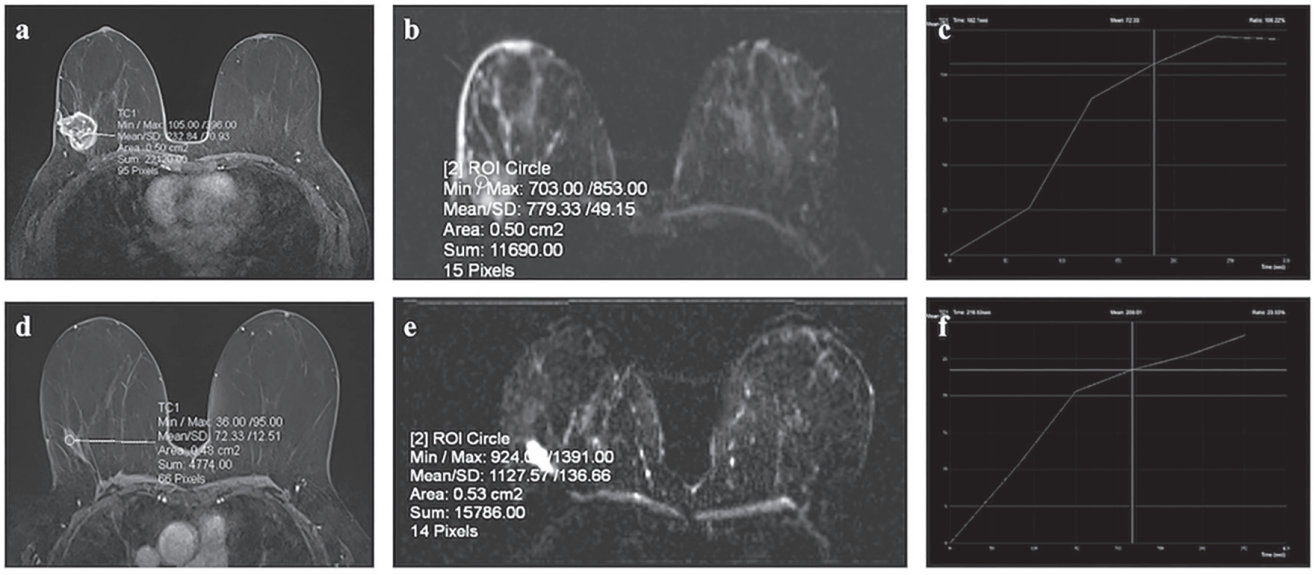

Figure 1. Pre- and mid- neoadjuvant chemotherapy (NAC) breast magnetic resonance imaging (MRI) of a 60-year-old woman with clinical stage cT2N1 triple-negative invasive ductal carcinoma who demonstrated a partial pathological response at the end of treatment, (a) axial post-contrast T1-weighted (T1W) image, (b) apparent diffusion coefficient (ADC) map, and (c) time–intensity curve (TIC) with calculated Epeak from the pre-NAC MRI, (d) axial post-contrast T1W image, (e) ADC map, and (f) TIC with Epeak from the mid-NAC MRI

All quantitative measurements were performed once per lesion without repetition.

Percentage changes (Δ%) in tumor dimensions and quantitative MRI parameters between pre-NAC and mid-NAC were calculated using the formula:

$$\Delta\% = [(Pre - Mid) / Pre] \times 100$$

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed *p*-value of <0.05 was considered statistically significant. Categorical variables, including clinical and pathological characteristics, were summarized as frequencies and percentages. Continuous variables, such as tumor dimensions and MRI-derived parameters, were presented as mean ± standard deviation, median (minimum–maximum), and IQR (25^{th}–75^{th} percentiles). The Mann-Whitney U test was used to compare non-normally distributed variables between groups. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis, and optimal cut-off values were determined using Youden's index. These thresholds were used to derive dichotomous variables for further analysis. Associations between radiologic parameters and pCR were assessed using Yates' corrected chi-square test or Fisher's exact test, depending on expected frequencies. Univariate logistic regression was used to calculate odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Variables with statistical significance in univariate analysis were included in a multiple logistic regression (MLR) model using the backward stepwise (Wald) method. Model calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test, and multicollinearity among predictors was assessed to ensure the retention of independent variables. The assumption of normality was tested using the Shapiro-Wilk test and visual inspection of Q-Q plots. Pairwise comparisons of area under the curves (AUC) values between MRI parameters were performed using DeLong's test, a non-parametric method for comparing correlated ROC curves.

Results

The study cohort included 65 female breast cancer patients, with a mean age at diagnosis of 50±9 years (IQR: 44–56). pCR of the primary tumor was achieved in 19 patients (29%), while 46 patients (71%) were classified as non-pCR (Table 1).

Quantitative MRI analysis showed a marked reduction in tumor dimensions and enhancement characteristics from pre- to mid-NAC. The mean longest diameter decreased from 3.47±1.77 cm to 2.08±1.48 cm, with a mean percent change (Δ%) of 40%. Tumor volume decreased from 17.6±36.3 cm^3 to 5.4±17.7 cm^3 (Δ%: 71%). Epeak declined from 177±101% to 100±79% (Δ%: 23%), while ADC values increased from 867±180 to 1035±148 $\times 10^{-6}$ mm^2/s (Δ%: -23%) (Table 2). Notably, due to the calculation formula [(Pre – Mid) / Pre × 100], negative Δ% ADC values indicate an actual increase in ADC.

Patients who achieved pCR exhibited significantly greater reductions in tumor size and enhancement metrics on mid-NAC MRI. The mean percent decrease (Δ%) in longest diameter, second diameter, shortest diameter, tumor volume, and bidimensional size was significantly higher in the pCR group compared to non-pCR (all $p<0.01$) (Table 3). Notably, mid-NAC ADC values were significantly higher (1107 vs. 1006 $\times 10^{-6}$ mm^2/s, $p = 0.015$), and mid-NAC Epeak values were lower (68 vs. 113%, $p = 0.007$) in patients with pCR.

ROC analysis demonstrated that several mid-NAC MRI-based parameters had good discriminatory ability for predicting pCR (Table 4, Figure 2). Δ% longest diameter >60% achieved an AUC of 0.740 (95% CI: 0.616–0.841) with high specificity (91%). Δ% second diameter >46% provided the highest sensitivity (74%) with 70% specificity (AUC=0.752; 95% CI: 0.630–0.851). Tumor volume reduction >92% also showed strong performance with an AUC of 0.754 (95% CI: 0.631–0.852) and specificity of 89%. Among functional metrics, Epeak ≤21% yielded perfect specificity (100%) with an AUC of 0.715 (95% CI: 0.590–0.820), although sensitivity

Table 2. Descriptive statistics of tumor dimensions and radiologic MRI parameters (*n* = 65)

Parameter	Mean ± SD	Median (min-max)	Percentile (25–75)
Longest diameter (cm)			
- Pre-NAC MRI	3.47±1.77	3.1 (0.94–9.7)	(2.38–4.1)
- Mid-NAC MRI	2.08±1.48	1.9 (0.0–7.5)	(1.4–2.8)
- Δ%	40±30	32 (-6–100)	(16–56)
Second diameter (cm)			
- Pre-NAC MRI	2.72±1.28	2.43 (0.93–8.7)	(2.0–3.29)
- Mid-NAC MRI	1.5±1.08	1.5 (0.0–6.3)	(0.81–2.1)
- Δ%	45±30	41 (-7–100)	(24–61)
Shortest diameter (cm)			
- Pre-NAC MRI	2.11±0.96	1.9 (0.83–6.2)	(1.5–2.46)
- Mid-NAC MRI	1.15±0.87	1.0 (0.0–5.6)	(0.6–1.5)
- Δ%	46±30	42 (-10–100)	(26–64)
Bidimensional size (cm^2)			
- Pre-NAC MRI	11.4±12.6	7.5 (0.87–84.4)	(4.5–13.9)
- Mid-NAC MRI	4.6±6.9	3.0 (0–47.3)	(1.3–5.0)
- Δ%	59±29	61 (-8–100)	(43–82)
Tumor volume (cm^3)			
- Pre-NAC MRI	17.6±36.3	7.2 (0.4–273.6)	(3.9–17.1)
- Mid-NAC MRI	5.4±17.7	1.5 (0–138.4)	(0.4–4.6)
- Δ%	71±27	79 (-18–100)	(53–92)
Pre-contrast SI			
- Pre-NAC MRI	201±61	201 (59–380)	(163–238)
- Mid-NAC MRI	196±57	208 (73–301)	(150–250)
- Δ%	-3±32	1 (-81–65)	(-18–15)
Post-contrast peak SI			
- Pre-NAC MRI	527±174	537 (156–908)	(380–648)
- Mid-NAC MRI	377±141	347 (149–750)	(269–471)
- Δ%	23±30	25 (-48–76)	(0–48)
Epeak (%)			
- Pre-NAC MRI	177±101	165 (32–441)	(86–248)
- Mid-NAC MRI	100±79	83 (0–350)	(46–126)
- Δ%	23±82	47 (-422–100)	(3–72)
ADC value (×10⁻⁶ mm^2/s)			
- Pre-NAC MRI	867±180	849 (421–1587)	(726–970)
- Mid-NAC MRI	1035±148	1025 (730–1360)	(950–1154)
- Δ%	-23±27	-20 (-125–32)	(-39 – -7)

SD: Standard deviation; NAC: Neoadjuvant chemotherapy; SI: Signal intensity; ADC: Apparent diffusion coefficient; Δ%: Percent change from pre- to mid-NAC MRI; calculated as [(Pre – Mid) / Pre] × 100, Negative Δ% ADC values represent ADC increase; MRI: Magnetic resonance imaging; min: Minimum; max: Maximum

Table 3. Comparison of pre- and mid-NAC MRI-based quantitative parameters by pCR status

Parameter	pCR (n = 19)		Non-pCR (n = 46)		
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	*p*-value
Longest diameter (cm)					
- Pre-NAC MRI	3.2±1.4	3.1 (2.4)	3.6±1.9	3.1 (1.5)	0.812
- Mid-NAC MRI	1.4±1.4	1.4 (2.5)	2.4±1.4	2.0 (1.3)	0.013*
- Δ%	60±34	55 (69)	32±25	30 (31)	0.002*
Second diameter (cm)					
- Pre-NAC MRI	2.6±1.0	2.5 (1.2)	2.8±1.4	2.4 (1.3)	0.977
- Mid-NAC MRI	1.0±0.9	0.9 (1.8)	1.7±1.1	1.6 (1.1)	0.009*
- Δ%	64±32	63 (65)	36±25	35 (40)	0.001*
Shortest diameter (cm)					
- Pre-NAC MRI	2.0±0.7	2.0 (1.0)	2.2±1.0	1.9 (1.0)	0.660
- Mid-NAC MRI	0.7±0.7	0.5 (1.5)	1.3±0.9	1.2 (0.7)	0.016*
- Δ%	66±30	63 (65)	38±26	39 (34)	0.003*
Bidimensional size (cm^2)					
- Pre-NAC MRI	9.5±6.8	7.5 (10.4)	12.1±14.3	7.3 (8.7)	0.988
- Mid-NAC MRI	2.5±3.2	1.3 (4.5)	5.4±7.7	3.2 (5.0)	0.014*
- Δ%	77±24	85 (54)	52±28	53 (43)	0.001*
Tumor volume (cm^3)					
- Pre-NAC MRI	11.6±10.7	8.3 (13.2)	20.1±42.5	7.2 (14.8)	0.806
- Mid-NAC MRI	1.9±2.9	0.3 (3.5)	6.9±20.8	2.2 (4.1)	0.013*
- Δ%	86±17	95 (29)	65±28	71 (40)	0.001*
Pre-contrast SI					
- Pre-NAC MRI	199±53	199 (87)	202±65	202 (76)	0.829
- Mid-NAC MRI	208±56	210 (100)	192±57	207 (91)	0.299
- Δ%	-10±36	-11 (47)	0±30	2 (27)	0.240
Post-contrast peak SI					
- Pre-NAC MRI	495±166	485 (280)	540±177	548 (260)	0.330
- Mid-NAC MRI	336±142	289 (221)	393±139	393 (172)	0.102
- Δ%	24±39	40 (69)	23±26	24 (41)	0.593
Epeak (%)					
- Pre-NAC MRI	159±99	117 (157)	185±102	173 (165)	0.364
- Mid-NAC MRI	68±75	60 (92)	113±77	92 (71)	0.007*
- Δ%	32±86	70 (93)	20±80	41 (55)	0.087
ADC value ($\times 10^{-6}$ mm^2/s)					
- Pre-NAC MRI	865±156	888 (251)	867±191	848 (246)	0.96
- Mid-NAC MRI	1107±128	1120 (219)	1006±147	1002 (164)	0.015*
- Δ%	-31±26	-35 (35)	-20±26	-16 (23)	0.060

SD: Standard deviation; IQR: Interquartile range (25^{th}–75^{th}); SI: Signal intensity; NAC: Neoadjuvant chemotherapy; ADC: Apparent diffusion coefficient; pCR: Pathologic complete response; Δ%: Percent change from pre- to mid-NAC MRI, calculated as [(Pre – Mid) / Pre] × 100. Negative Δ% ADC values represent ADC increase; *: $p<0.05$ indicates statistical significance; MRI: Magnetic resonance imaging

was lower (37%). Most dimensional parameters achieved AUC values >0.73 (p<0.01), supporting their predictive utility (Table 4).

Pairwise comparisons of AUC values between Δ% MRI parameters—including diameters, bidimensional size, tumor volume, and ADC—showed no significant differences (all p>0.05). Δ% dimensional metrics demonstrated highly similar performance (AUC differences <0.015), while Δ% ADC tended to yield slightly higher AUCs without reaching significance (Supplementary Table 1).

Binary analysis based on optimal cut-off values confirmed significant associations between mid-NAC MRI–derived parameters and pCR (Table 5). Patients with Δ% longest diameter >60%, second diameter >46%, shortest diameter >45%, or tumor volume reduction >92% had significantly higher rates of pCR (all p<0.01). Additionally, patients with Epeak ≤21% and Δ% ADC value ≥32% showed significantly higher pCR rates (p<0.01 for both).

In univariable analysis, multiple mid-NAC MRI–based parameters were significantly associated with pCR, including Δ% longest diameter >60% (OR=9.5; 95% CI: 2.4–37.0; p = 0.001), Δ% ADC value ≥32% (OR=6.2; 95% CI: 1.9–19.8; p = 0.003), and Δ% tumor volume >92% (OR=5.3; 95% CI: 1.6–17.2; p = 0.010) (Table 6). Epeak ≤21% demonstrated the highest univariable OR (OR=26.3; 95% CI: 2.9–234.5; p<0.001) but was excluded from the MLR model due to wide CIs indicating model instability. Δ% second diameter, shortest diameter, and bidimensional size also showed significant associations (all p<0.01) but were excluded due to collinearity.

In the final MLR model, only Δ% longest diameter >60% (OR=7.1; 95% CI: 1.3–30.1; p = 0.008) and Δ% ADC value ≥32% (OR=4.7; 95% CI: 1.3–16.5; p = 0.016) remained as independent predictors of pCR (Table 6). The model excluded redundant or unstable variables, favoring robust and non-collinear biomarkers. Overall model performance was acceptable (Nagelkerke R^2 = 0.336), with good calibration (Hosmer-Lemeshow p = 0.800).

Discussion and Conclusion

In the overall cohort, all dimensional MRI parameters showed a mean reduction from pre- to mid-NAC, while mean post-contrast SI, Epeak, decreased and mean ADC values increased, consistent with early treatment response (Table 2). Furthermore, comparison between pCR and non-pCR groups revealed significantly greater reductions in longest diameter, second and shortest diameters, bidimensional size, and tumor volume, as well as lower mid-treatment Epeak and higher ADC values in the pCR cohort (all p<0.05, Table 3). These differences underscore the utility of both morphologic and functional MRI parameters in distinguishing responders from non-responders during mid-NAC assessment, in line with prior studies that demonstrated the predictive value of early volumetric reduction and diffusion changes for pCR (7, 8, 11).

As shown in Table 3, pre-contrast SI on mid-NAC MRI exhibited a slight increase in the pCR group, whereas it remained stable or decreased in the non-pCR group; however, this difference did not reach statistical significance. This observation may be explained by treatment-induced stromal alterations such as proteinaceous or hemorrhagic content, fibrosis, and necrotic debris, which shorten T1 relaxation time and elevate SI despite fat suppression. Nevertheless, given its limited clinical relevance, this parameter should not be considered a primary predictor of therapeutic response.

Univariable ROC analysis revealed that several morphologic and functional MRI parameters demonstrated significant predictive performance for pCR. Among dimensional metrics, tumor volume reduction >92% achieved the highest AUC (0.754), followed closely by bidimensional size >69% (AUC=0.752) and longest diameter >60% (AUC=0.740). Notably, the >60% reduction in the longest diameter yielded the highest specificity (91%), suggesting its utility in identifying true responders, whereas bidimensional shrinkage provided the highest sensitivity (74%), making it more suitable for screening purposes. These findings are in agreement with prior work by Fangberget et al. (15), who demonstrated that tumor volume

Table 4. ROC analysis of radiologic features on mid-NAC MRI for predicting pCR

Parameter	AUC (95% CI)	p-value (area=0.5)	Youden's J	Cut-off value	Sensitivity (%)	Specificity (%)
Δ% Longest diameter	0.740 (0.616–0.841)	<0.001**	0.39	>60%	47	91
Δ% Second diameter	0.752 (0.630–0.851)	0.001**	0.43	>46%	74	70
Δ% Shortest diameter	0.739 (0.615–0.840)	0.001**	0.41	>45%	74	67
Δ% Bidimensional size	0.752 (0.629–0.851)	<0.001**	0.42	>69%	68	74
Δ% Tumor volume	0.754 (0.631–0.852)	<0.001**	0.42	>92%	53	89
Epeak	0.715 (0.590–0.820)	0.006**	0.37	≤21	37	100
Δ% Pre-contrast SI	0.593 (0.464–0.713)	0.267	0.27	≤-10%	58	70
Δ% Post-contrast SI	0.542 (0.414–0.667)	0.649	0.23	>45%	47	76
Δ% Epeak	0.636 (0.507–0.751)	0.138	0.34	>73%	47	87
Δ% ADC value	0.649 (0.521–0.764)	0.071	0.41	≥32%	63	78

AUC: Area under the curve; CI: Confidence interval; ADC: Apparent diffusion coefficient; SI: Signal intensity; Δ%: Percent change from pre- to mid-NAC MRI, calculated as [(Pre – Mid) / Pre] × 100; Optimal cut-off values were determined using Youden's index (J); **: p<0.01 (statistically significant); NAC: Neoadjuvant chemotherapy; pCR: Pathologic complete response; MRI: Magnetic resonance imaging

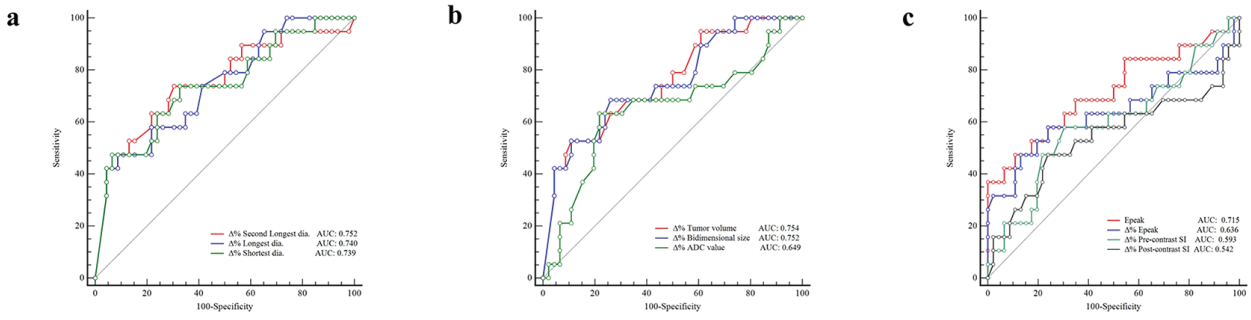

Figure 2. Receiver operating characteristic curves of mid-treatment magnetic resonance imaging parameters for predicting pathologic complete response, (a) Δ% second longest diameter [area under the curve (AUC)=0.752], Δ% longest diameter (AUC=0.740), Δ% shortest diameter (AUC=0.739), (b) Δ% tumor volume (AUC=0.754), Δ% bidimensional size (AUC=0.752), Δ% apparent diffusion coefficien value (AUC=0.649), (c) Epeak (AUC=0.715), Δ% Epeak (AUC=0.636), Δ% pre-contrast SI (AUC=0.593), Δ% post-contrast SI (AUC=0.542)

Table 5. Association between mid-NAC MRI-based radiologic parameters and pCR status (*n* = 65)

Parameter (cut-off value)	pCR (n = 19)	Non-pCR (n = 46)	*p*-value
Δ% Longest diameter			
>60%	9 (47.4%)	4 (8.7%)	0.001**
≤60%	10 (52.6%)	42 (91.3%)	
Δ% Second diameter			
>46%	14 (73.7%)	14 (30.4%)	0.003*
≤46%	5 (26.3%)	32 (69.6%)	
Δ% Shortest diameter			
>45%	14 (73.7%)	15 (32.6%)	0.006*
≤45%	5 (26.3%)	31 (67.4%)	
Δ% Bidimensional size			
>69%	13 (68.4%)	12 (26.1%)	0.004*
≤69%	6 (31.6%)	34 (73.9%)	
Δ% Tumor volume			
>92%	10 (52.6%)	8 (17.4%)	0.010*
≤92%	9 (47.4%)	38 (82.6%)	
Δ% ADC value			
≥32%	12 (63.2%)	10 (21.7%)	0.003*
<32%	7 (36.8%)	36 (78.3%)	
Epeak (%)			
≤21	7 (36.8%)	1 (2.2%)	<0.001**
>21	12 (63.2%)	45 (97.8%)	

Δ%: Percent change from pre- to mid-NAC MRI, calculated as [(Pre – Mid) / Pre] × 100; ADC: Apparent diffusion coefficient; pCR: Pathologic complete response. Group comparisons were made using chi-square or Fisher's exact test; $p<0.05$ was considered statistically significant (*); $p<0.01$ was considered highly significant (**); MRI: Magnetic resonance imaging; NAC: Neoadjuvant chemotherapy

reduction ≥83% after four cycles of NAC was the most accurate predictor of pCR, with a sensitivity of 91%, specificity of 80%, and AUC of 0.82, outperforming longest diameter reduction (AUC=0.78). This supports the notion that while unidimensional measures like longest diameter remain clinically useful, volumetric assessment better reflects the complex and often irregular patterns of tumor regression during NAC. Conversely, Minarikova et al. (16) reported that 3D diameter change outperformed volume metrics (AUC=0.933), suggesting that diameter-based measurements may offer better practicality and performance in certain clinical settings. In our cohort, however, pairwise AUC comparisons showed no statistically significant differences between Δ% longest diameter, bidirectional size, and tumor volume (all $p>0.05$), indicating comparable predictive performance across these morphologic parameters.

In the MLR analysis, Δ% longest diameter >60% (OR=7.1, $p = 0.008$) and Δ% ADC value ≥32% (OR=4.7, $p = 0.016$) emerged as the only independent predictors of pCR. These findings reinforce

Table 6. Univariable and multiple logistic regression analysis of Mid-NAC MRI-based parameters for pCR prediction

Parameter (Δ%, mid-NAC MRI)		Univariable analysis		Multivariable analysis (final model)		
		OR (95% CI)	p	OR (95% CI)	p	Model inclusion status
Δ% Longest diameter	>60%	9.5 (2.4–37.0)	0.001	7.1 (1.3–30.1)	0.008	Retained
Δ% ADC value	≥32%	6.2 (1.9–19.8)	0.003	4.7 (1.3–16.5)	0.016	Retained
Δ% Tumor volume	>92%	5.3 (1.6–17.2)	0.010	–	0.869	Dropped at Step2
Δ% Second diameter	>46%	6.4 (1.9–21.2)	0.003	–	–	Not selected
Δ% Shortest diameter	>45%	5.8 (1.8–19.1)	0.006	–	–	Not selected
Δ% Bidimensional size	>69%	6.1 (1.9–19.8)	0.004	–	–	Not selected
Epeak (%)	≤21	26.3 (2.9–234.5)	<0.001	–	–	Not selected

OR: Odds ratio; CI: Confidence interval; pCR: Pathologic complete response; ADC: Apparent diffusion coefficient; Δ%: Percent change from pre- to mid-NAC MRI, calculated as [(Pre – Mid) / Pre] × 100; the multiple logistic regression model was constructed using backward stepwise (Wald) method. Nagelkerke R^2=0.336; Hosmer-Lemeshow test p = 0.800; Constant = -1.995; MRI: Magnetic resonance imaging; NAC: Neoadjuvant chemotherapy

the complementary value of morphologic shrinkage and diffusion metrics in early treatment monitoring. While other dimensional parameters also showed strong univariable associations with pCR, they were excluded from the final model due to collinearity. Notably, Δ% tumor volume >92%—despite having the highest univariable AUC (0.754)—lost significance in MLR analysis (p = 0.869), likely reflecting overlapping predictive information with longest diameter and ADC changes. This emphasizes the importance of selecting non-collinear and stable parameters for robust modeling in clinical practice.

The increase in ADC values, reflected by Δ% ADC ≥32%, suggests reduced tumor cellularity in response to effective cytotoxic therapy. Chemotherapy-induced necrosis and decreased cell density enhance water diffusivity, which is captured by ADC elevation on DW-MRI (17, 18). In our cohort, both higher mid-NAC ADC values and greater percent increases were significantly associated with pCR, consistent with prior findings from both multicenter and single-institution studies, supporting ADC as a reliable non-invasive biomarker of treatment response (7, 11). In contrast to prior multicenter studies such as ACRIN 6698, which demonstrated moderate predictive performance for mid-treatment ΔADC without specifying an optimal cut-off (AUC=0.60), our study identified a Δ% ADC ≥32% as an independent predictor of pCR with higher specificity and multivariable significance (7). Similarly, a recent multi-institutional study on HER2-positive breast cancer also reported ΔADC as a significant early predictor of treatment response (19).

Similarly, lower mid-NAC Epeak values—particularly those ≤21%—were highly specific for pCR (100%), although their predictive utility was limited by low sensitivity (37%) and instability in MLR modeling. As a semi-quantitative indicator of early contrast enhancement kinetics, Epeak reflects tumor vascularity and perfusion. A pronounced decline in Epeak following chemotherapy may correspond to reduced angiogenic activity, vessel permeability, and microvascular density, consistent with a strong cytotoxic effect. In our cohort, both lower absolute mid-NAC Epeak values and greater percent reductions were significantly associated with pCR in univariable analysis. These findings are in line with previous studies suggesting that early changes in perfusion-related parameters may signal effective treatment response. Supporting this, one recent study demonstrated that greater reductions in early peak enhancement during NAC were associated with favorable pathological response and improved recurrence-free survival (20). Additionally, a large retrospective cohort of 168 breast cancer patients reported that both pre-NAC Epeak ≤96 and post-NAC Epeak >188 were independent predictors of pCR and survival outcomes, further underscoring the prognostic value of contrast enhancement dynamics during treatment (10).

From a clinical perspective, the integration of early mid-treatment MRI biomarkers—particularly Δ% longest diameter and Δ% ADC—offers a practical and non-invasive strategy to identify patients who are likely to achieve pCR during NAC. These parameters can be easily derived from routine clinical MRI protocols without the need for advanced post-processing or pharmacokinetic modeling, increasing their feasibility in everyday practice. The high specificity of Δ% longest diameter >60% and the independent predictive value of Δ% ADC ≥32% support their utility in guiding individualized treatment decisions. For instance, patients demonstrating suboptimal early imaging response may be candidates for treatment intensification or alternative therapeutic strategies, while early identification of good responders may inform ongoing monitoring or risk stratification efforts. Thus, the use of accessible imaging biomarkers to differentiate responders from non-responders at an early stage may support more personalized and adaptive approaches in breast cancer management.

Study Limitations

This study has several limitations. First, its retrospective design and single-center setting may limit the generalizability of the findings. Second, the sample size—though adequate for exploratory modeling—was relatively modest, particularly for MLR, which may affect the stability of certain parameters, such as Epeak. Third, manual ROI placement for ADC and enhancement measurements, although performed in consensus by experienced radiologists, may introduce variability and operator dependence. Additionally, Epeak, as a semi-quantitative measure, is susceptible to temporal resolution and sequence timing, which could limit reproducibility across different imaging protocols. Moreover, the lack of inter-reader reproducibility testing further limits generalizability.

Mid-treatment MRI biomarkers—including Δ% longest diameter and Δ% ADC—demonstrated significant predictive value for pCR in patients undergoing NAC for LABC. These easily obtainable and non-

invasive parameters may serve as reliable early indicators of treatment response, potentially enabling more personalized therapeutic strategies in clinical practice.

Ethics

Ethics Committee Approval: This retrospective study was approved by the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (approval date: 29/11/2023; decision no: 2023/197).

Informed Consent: All participants were provided informed consent before undergoing imaging.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.B., L.A.; Concept: A.B., H.E.G.; Design: L.A., H.E.G.; Data Collection or Processing: A.B., H.E.G.; Analysis or Interpretation: L.A.; Literature Search: A.B., L.A.; Writing: A.B.

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

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Original Article

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Turkish Translation, Cross-Cultural Adaptation and Psychometric Evaluation of the Tool of Myofascial Adhesions in Patients After Breast Cancer

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ABSTRACT

Objective: Myofascial adhesions are an important cause of upper extremity dysfunction among breast cancer surgery (BCS) patients. Myofascial-adhesions-in-patients-after-breast-cancer (MAP-BC) is a quantitative method developed to assess scar tissue and adhesions. This study aims to create a Turkish version of the MAP-BC tool and to test its validity and reliability.

Materials and Methods: This cross-cultural adaptation and validation study included 81 female BCS patients aged 18–80 years. For convergent validity, patients were assessed using MAP-BC and the Patient and Observer Scar Assessment Scale observer subscale. For test-retest reliability, the patients were assessed on days 0 and 14. Thirty-two patients were evaluated by a second researcher to assess interrater reliability.

Results: Validity was fair to good (rho = 0.631). For test-retest reliability, intraclass correlation (ICC) values for the subgroups ranged from 0.798 to 0.954, with an ICC = 0.948 for the total score, indicating good-to-excellent test–retest reliability. Interrater ICC values ranged from 0.417 to 0.949, with ICC = 0.938 for the total score, suggesting good to excellent interrater agreement, except for the "frontal chest wall" section.

Conclusion: The Turkish MAP-BC tool is valid and reliable for evaluating myofascial adhesions and scars after BCS and adjuvant treatments. Clinicians are encouraged to use MAP-BC to detect myofascial adhesions and evaluate treatment efficacy, as this is the first tool available in Turkish for this purpose.

Keywords: Breast cancer; myofascial adhesion; myofascial dysfunction; scar tissue

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Key Points

- Myofascial adhesions are an important yet often overlooked cause of upper extremity dysfunction in breast cancer survivors.
- Myofascial Adhesions in Patients after Breast Cancer (MAP-BC) is a valid and reliable evaluation method for detecting myofascial adhesions and assessing scar tissue after BCS and adjuvant treatments.
- The availability of a reliable and valid tool enables the detection and early treatment of myofascial adhesions in breast cancer survivors, contributing to improved rehabilitation outcomes and quantitative monitoring of tissue recovery.
- The Turkish form of the MAP-BC tool is found to be valid and reliable, and clinicians are encouraged to use MAP-BC to detect myofascial adhesions and evaluate treatment efficacy.

Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy worldwide, accounting for 11.7% of all cases (1). With current screening methods, early diagnosis is achievable, and advances in treatment approaches have led to steadily increasing survival rates. Therefore, understanding and managing the long-term effects of cancer treatments has become increasingly important as the population of BC survivors grows (2).

The International Consortium for Health Outcomes Measurement defines upper extremity function as one of the most important health outcomes for women with BC (3). As a result of axillary and breast surgery, radiotherapy, hormone therapy, and chemotherapy, patients may develop upper extremity dysfunction (UED) and pain, leading to limitations in daily activities and reduced quality of life (4-7). The primary factors affecting upper extremity function in patients with BC include lymphedema, severe pain, limited shoulder range of motion,

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diminished muscle strength, axillary web syndrome, myofascial trigger points, and myofascial adhesions (8).

Mastectomy, breast-conserving surgery, axillary lymph node dissection, sentinel lymph node biopsy, and radiotherapy have notable effects on the skin, muscle, and fascial tissues of the chest wall and upper extremity, leading to myofascial dysfunction (9). Myofascial dysfunction is characterized by trigger points, adhesions, and restricted mobility and impaired gliding of myofascial tissues over one another (10, 11). Manipulation of the muscles during surgery, scar tissue formation, soft tissue adhesions, development of an adaptive posture following surgery, and radiation-induced fibrosis can lead to myofascial adhesions (10, 12). Myofascial release techniques may be used in the treatment (10, 13, 14).

Commonly used criteria exist for the diagnosis of myofascial trigger points (15). However, there are gaps in both the literature and daily clinical practice regarding the assessment of scar tissue and adhesions. Fourie (13) evaluated the presence of myofascial adhesions by palpating restrictions in tissue gliding; however, they did not develop a quantitative assessment method. A diagnostic tool named myofascial adhesions in patients (MAP) after BC was developed by De Groef et al. (9) to evaluate myofascial adhesions and was shown to be a reliable and valid assessment method.

The identification, quantitative measurement, and scoring of myofascial adhesions in BC patients with UED are of great importance for both planning targeted interventions and evaluating the effectiveness of treatments, such as myofascial and physical therapy modalities. In the long term, this would not only enhance physical functioning but also improve quality of life among BC survivors. According to the literature review, no Turkish translation, cultural adaptation, or study of the validity and reliability of the MAP-BC assessment tool has been conducted in the Turkish population. The aim of this study is to develop the Turkish version of the MAP-BC and to assess its validity and reliability in women who have undergone BC treatment.

Materials and Methods

Study Design

This is a cross-cultural adaptation, validation, and reliability study of the MAP-BC Turkish version. The study was approved by the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 23/337, date: 26.05.2023) and was registered in the ClinicalTrials.gov database (ID: NCT05923164, registration date: 16/08/2023). Written and oral consent was obtained from all participants, and the research was conducted in accordance with the Declaration of Helsinki.

Development of the Turkish Version of the MAP-BC: Translation and Cross-Cultural Adaptation

The translation and cross-cultural adaptation were carried out in accordance with the international guidelines (16, 17). One of the researchers contacted the developer of the MAP-BC tool (Lore Dams) and obtained consent to translate and use the assessment tool.

First, the original version of MAP-BC was translated into Turkish, and two separate forms were created by two translators who were native Turkish speakers and fluent in English. These two researchers collaborated to resolve discrepancies, producing a single Turkish version. This initial Turkish version of the tool was then back-translated into English by a translator who was a native English speaker, fluent in Turkish, and unfamiliar with the original form. Finally, a committee consisting of two translators and four expert physiatrists compared the original and translated versions of the MAP-BC in terms of semantic and conceptual equivalence and finalized the Turkish version. Two researchers assessed pilot testing involving 15 patients and addressed the results, challenges, and experiences (18).

Assessment of Convergent Validity, Test-Retest and Interrater Reliability

A total of 81 female patients, aged between 18 and 80 years, who had undergone BC surgery, who had applied to the Physical Medicine and Rehabilitation oncology rehabilitation subspecialty outpatient clinic, and who had given oral and written consent were included in the study. Patients who did not give consent, who were illiterate, or who had active skin disease or infection that may prevent palpation-based examination were excluded from the study.

Power Analysis: For patient allocation, the sample size was determined using the commonly applied rule of thumb in psychometric evaluation studies, which recommends at least 10 participants per item (19). A sample size of ten participants was calculated for each of the eight parameters of the MAP-BC tool. To account for a 10% potential dropout rate, it was deemed appropriate to include 88 patients.

Convergent Validity: The convergent validity of the Turkish version of MAP-BC was assessed by analyzing correlations with the observer subscale of the Turkish version of the patient and observer scar assessment scale (POSAS) (20, 21).

Test-Retest Reliability: All participants were evaluated twice by the same researcher, 14 days apart, and the assessments were recorded as T0 and T1. No interventions or treatments were given during this period.

Interrater Reliability: Thirty-two patients were independently evaluated by two researchers using the MAP-BC form; the researchers were unaware of one another's results.

POSAS: This assessment tool consists of two separate scales, one evaluated by the observer and one by the patient, and its validity and reliability for detecting scar tissue in patients who have undergone BC surgery have been established (20, 21). The observer subscale rates five variables—vascularity, pigmentation, thickness, surface pliability, and elasticity—on a scale from 1 to 10 (with 1 indicating normal skin), with the total score ranging from 5 to 50. The validated Turkish version of the observer subscale of the POSAS was used to assess convergent validity in this study (22).

MAP-BC: This assessment method was developed to evaluate scar tissue and to quantitatively measure myofascial adhesions following BC treatment (9, 23). The degree of adhesion is scored using a 4-point scale (0: no adhesion – 3: very severe adhesion) at three tissue-depth levels (skin, superficial, deep) in each of seven areas: axillary scar, breast/mastectomy scar, pectoral region, anterior pectoral wall, lateral pectoral wall, axilla, and inframammary fold. The total score is calculated by summing the scores from all three levels in each region, with a maximum possible score of 63. The interrater reliability of palpation-based assessment of myofascial adhesions in BC patients has been reported to be good to excellent (9).

Statistical Analysis

Statistical analyses were conducted using SPSS v22 (IBM Corp., Armonk, NY, USA). Normality of the data distribution was assessed using the Shapiro-Wilk test. For validity assessment, Spearman correlation coefficients were interpreted as very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), and very strong (0.80–1.00). To calculate the test-retest and interrater reliability, the intraclass correlation (ICC) for single measurements [ICC (2.1)], based on a two-way random-effects analysis of variance (ANOVA) model, was applied to the total score for each area and its subscores (skin, superficial, and deep). The ICC values for test-retest and interrater measurements were interpreted as indicating poor (<0.50), moderate (0.50–0.74), good (0.75–0.89), or excellent (≥0.90) reliability. For all analyses, statistical significance was set at $p<0.05$ (corresponding to a 95% confidence level).

Results

During the translation and cross-cultural adaptation process, several changes were made to increase clarity. The word "therapist" was replaced with "examiner" to represent both physiotherapists and clinicians that are expected to use the tool. The word "gliding" was replaced with "mobility" to maintain the semantic integrity of the instructions in Turkish. The pilot testing of the final version concluded with no disagreements regarding semantics, understandability, or methodological challenges. The final Turkish version of the form is provided in the Supplementary Figure 1.

A total of 88 patients were included in the study. Two patients were excluded due to breast implant surgery. One patient was excluded due to a localized, active fungal infection in the inframammary fold. Four patients discontinued participation before the second (T1) evaluation. The study included 81 patients whose results were analyzed. The flowchart of the study is shown in Figure 1. The sociodemographic characteristics of the patients are provided in Table 1.

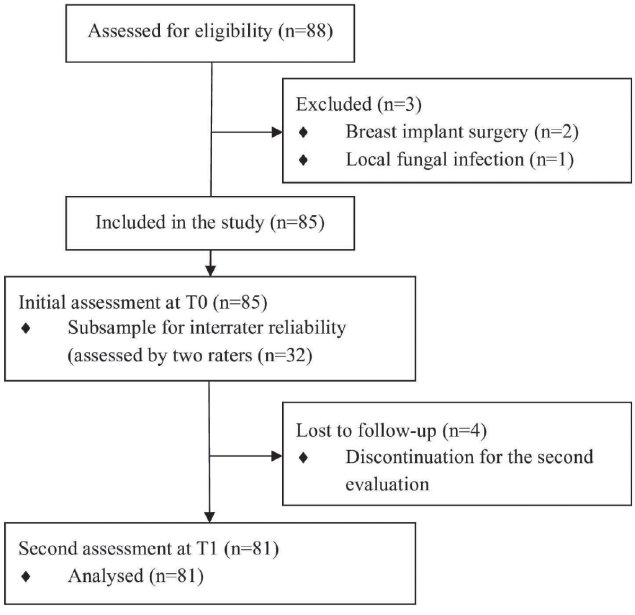

Figure 1. The flowchart of the study

Convergent Validity

The validity of the MAP-BC tool, calculated by comparing the total scores of MAP-BC and POSAS, was found to be moderate-to-strong (rho = 0.631, $p<0.001$).

Test-Retest Reliability

ICC values for subgroups and the total score, calculated for test-retest reliability ranged from 0.798 to 0.954. The ICC for the total score was 0.947 [95% confidence interval (CI), 0.919–0.966], indicating good to excellent test-retest reliability of the questionnaire (Table 2). The test-retest reliability for each region and examination level (skin, superficial, and deep) is presented in the Appendix (Supplementary Table 1).

Interrater Reliability

Interrater ICC values ranged from 0.405 to 0.948; the total-score interrater ICC was 0.937 (95% CI: 0.874–0.969). This suggests good to excellent interrater agreement, except for the "frontal chest wall" subsection (Table 3). The interrater agreement scores for each depth level of the regions are given in the Appendix (Supplementary Table 2).

Discussion and Conclusion

Myofascial adhesions are recognized as significant factors that can affect quality of life and contribute to UED in patients with BC (10, 11). Myofascial release techniques and manual therapy may be used in the treatment of these adhesions; however, there is a need for quantitative assessment tools to support diagnosis and monitor treatment outcomes (13, 14). The MAP-BC was developed as an evaluation instrument for this purpose. The test is equipment-free, requires approximately 15 minutes to complete, and evaluators found the Turkish version easy to apply. This study revealed moderate to strong validity, good to excellent test-retest reliability, and good to excellent interrater agreement for the Turkish version of the MAP-BC tool.

This study found moderate-to-strong validity of the MAP-BC compared with the POSAS tool. The developers of the tool reported moderate validity (23). However, it is noteworthy that in that study the comparative tool was a cutometer, which evaluated only the mastectomy scar. In the Spanish validity study, correlations between MAP-BC and POSAS were found to be moderate at T1, consistent with the results of this study (18). To date, no gold-standard method exists for evaluating myofascial adhesions. POSAS evaluates scar tissue across multiple components, in addition to elasticity, including surface area, pigmentation, vascularity, and thickness, which may account for its relatively limited validity.

The test-retest reliability was good to excellent in all areas. Since test–retest reliability has not been assessed by the original developers or in any prior translation and cultural adaptation studies, it is not possible to interpret the findings within this context.

This study found good to excellent interrater agreement regarding the total scores. Although the overall interrater reliability was not mentioned in the developers' article, they found good interrater agreement for axillary scars (0.82) and excellent agreement for breast (0.99) and mastectomy (0.96) scars (9). Similarly, this study revealed good to excellent interrater agreement for scar tissue: 0.829 for axillary scar, 0.907 for breast scar, and 0.948 for mastectomy scar. It is a well-established fact that the frequency of breast implant surgeries has been increasing over time. Although patients with breast implants were

Table 1. The sociodemographic data of the patients

Age mean (SD) (min-max)		56.85 (11.19) (33–80)
BMI mean (SD)		28.73 (4.76)
median (Q1; Q3)		28 (25.43; 32.22)
Occupation n (%)	Homemaker	54 (66.7%)
	Civil servant	11 (13.6%)
	Retired	11 (13.6%)
	Self-employed	5 (6.2%)
Educational status n (%)	Primary	37 (45.7%)
	Elementary	10 (12.3%)
	Highschool	24 (29.6%)
	University	10 (12.3%)
Smoking n (%)	Yes	12 (14.8%)
	No	69 (85.2%)
Physical activity n (%)	Sedentary	1 (1.2%)
	Walks for pleasure	42 (51.9%)
	Regular activity	26 (32.1%)
	Sportive activity	12 (14.8)
Alcohol intake n (%)	Yes	12 (14.8%)
	No	69 (85.2%)
Pack years of smoking mean (SD) (min-max)		4.56 (11.64) (0–5)
Breast cancer diagnosis yrs. mean (SD) (min-max)		6.01 (5.51) (0.50–22)
Surgery n (%)	Breast conservative surgery	42 (51.9%)
	Mastectomy	39 (48.1%)
Lymph node dissection n (%)	Yes	45 (55.6%)
	No	36 (44.4%)
Metastasis n (%)	Yes	21 (25.9%)
	No	60 (74.1%)
Radiotherapy n (%)	Yes	66 (81.5%)
	No	15 (18.5%)
Hormonetherapy n (%)	Yes	63 (77.8%)
	No	18 (22.2 %)
Lymphedema duration mean (SD) (min-max)		1.65 (2.42) (0–10)
Lymphedema stage n (%)	Stage 0/No clinical lymphedema*	41 (50.6%)
	Stage 1	23 (28.4%)
	Stage 2	14 (17.3%)
	Stage 3	3 (3.7 %)

n: number of patients; SD: Standard deviation; min: Minimum; Max: Maximum

*It is well established that microscopic changes occur in the lymphatic system of patients who have undergone breast cancer treatment, conferring a lifelong risk of clinical lymphedema. To emphasize this, patients with no clinical symptoms were graded as stage 0/no clinical lymphedema.

Table 2. Test-retest reliability analysis

Location	First evaluation Median (Q1; Q3)	Second evaluation Median (Q1; Q3)	ICC (95% CI)
Axillary scar (*n* = 69)	3.0 (2.0; 5.0)	4.0 (2.0; 5.0)	0.839 (0.752–0.897)
Breast scar (*n* = 40)	5.5 (3.0; 6.0)	5.0 (4.0; 6.0)	0.929 (0.871–0.962)
Mastectomy scar (*n* = 41)	6.0 (4.0; 7.0)	6.0 (3.0; 6.0)	0.954 (0.915–0.975)
Mm pectorales region (*n* = 81)	0.0 (0.0; 1.0)	0.0 (0.0; 2.0)	0.883 (0.824–0.923)
Frontal chest wall (*n* = 81)	0.0 (0.0; 1.0)	0.0 (0.0; 1.0)	0.798 (0.702-0.865)
Lateral chest wall (*n* = 81)	0.0 (0.0; 1.0)	0.0 (0.0; 1.0)	0.847 (0.771–0.899)
Axilla (*n* = 81)	2.0 (0.0; 3.0)	2.0 (0.0; 3.0)	0.888 (0.831–0.926)
Inframammary fold (*n* = 81)	1.0 (0.0; 3.0)	0.0 (0.0; 2.0)	0.890 (0.833–0.928)

The intraclass correlation coefficient was used in the analysis. CI: Confidence interval; ICC: Intraclass correlation coefficient; n: Number of patients, $p<0.05$ for all

Table 3. Interrater reliability analysis

Location	Rater 1 Median (Q1; Q3)	Rater 2 Median (Q1; Q3)	ICC (95% CI)
Axillary scar (*n* = 28)	4.0 (2.0; 5.25)	4.0 (3.0; 5.25)	0.829 (0.664–0.917)
Breast scar (*n* = 16)	6.0 (3.75; 6.0)	5.5 (3.75; 6.0)	0.907 (0.755–0.966)
Mastectomy scar (*n* = 15)	6.0 (3.5; 6.0)	6.0 (3.0; 6.5)	0.948 (0.854–0.982)
Mm pectorales region (*n* = 32)	0.0 (0.0; 0.25)	0.0 (0.0; 1.0)	0.870 (0.750–0.934)
Frontal chest wall (*n* = 31)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.405 (0.065–0.661)
Lateral chest wall (*n* = 31)	0.0 (0.0; 2.0)	0.0 (0.0; 1.0)	0.621 (0.346–0.797)
Axilla (*n* = 31)	2.0 (0.5; 3.0)	2.0 (0.0; 3.0)	0.919 (0.838–0.960)
Inframammary fold (*n* = 32)	0.0 (0.0; 2.0)	0.5 (0.0; 2.0)	0.702 (0.471–0.842)

The intraclass correlation coefficient was used in the analysis. CI: Confidence interval; ICC: Intraclass correlation coefficient; n: Number of patients, $p<0.05$ for all

excluded from the present study, they may be considered a separate category in future studies.

Conversely, this study demonstrated lower interrater reliability in non-scar areas, except for the axillary and Mm pectorales regions, which showed good-to-excellent and good agreement, respectively. In the axillary area, the deep myofascial tissue level showed moderate reliability, as postsurgical alterations and radiation-induced fibrosis may complicate palpation and differentiation of tissue depth (9). The results for the pectoral region align with the previous study, although the deep tissue level was moderate in the current study (9). This can be attributed to postsurgical in the area, such as direct damage; development of myofascial trigger points resulting from pain, adaptive posture, and muscle shortening; and radiation fibrosis (24).

The frontal chest wall had poor-to-moderate reliability, whereas the lateral chest wall had moderate reliability, and the inframammary fold showed moderate-to-good reliability in this study. The developers found good agreement in all areas except for the inframammary fold, where agreement was moderate (9). Discriminating between the superficial and deep tissue levels in this region posed a challenge. This can be attributed to the absence of muscle in the frontal chest wall. As proposed by the developers, this site can be evaluated in two layers, skin and tissue, to increase reliability (9). Myofascial adhesions can develop in the lateral chest wall from drains placed at both the breast and axillary sites. Similar to the previous study, the lower reliability may be explained by the possible presence of two different drain scars (9). Adhesions in the inframammary fold may develop due to a drain or to the suture site, especially in the case of breast-conserving surgery. It may be difficult to differentiate depth levels or to distinguish normal tissue from adhesions, because the area may be naturally firm with reduced flexibility. The developers recommend that this area be evaluated at two levels, as with the frontal chest wall, which could increase interrater agreement in these regions (9). Overall, it is recommended to use total scores for the areas in clinical settings (9).

Study Limitations

This study has several limitations. First, a more precise method for measuring elasticity and tissue gliding, such as a Cutometer, may have been used to assess the validity of the tool. Second, there was no intervention during the study, so responsiveness could not be evaluated. Responsiveness may also be assessed in future studies through interventions such as physical therapy. In light of the increasing number of patients with breast implants, developing alternative evaluation methods or including an additional region in MAP-BC is recommended.

Several strengths can be highlighted in this study. First, a quantitative assessment method developed for evaluating scars and adhesions was translated into Turkish and culturally adapted to make it accessible to the target population. An additional strength of the study lies in its comprehensive evaluation of both validity and reliability, including inter-rater and test-retest analyses.

The Turkish form of MAP-BC is a valid and reliable tool for evaluating myofascial adhesions and scars after BC surgery and adjuvant treatments. Myofascial adhesions are an often-overlooked musculoskeletal problem in patients with BC and may result in additional pain, upper-extremity-related disability, and decreased quality of life if left untreated. Using such a rapid assessment tool may contribute to the diagnosis, early treatment, and quantitative evaluation of this condition during treatment follow-up. Clinicians are encouraged to use this tool for detecting myofascial adhesions and evaluating treatment efficacy, as this is the first tool in the Turkish language to evaluate myofascial adhesions after BC treatment.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 23/337, date: 26.05.2023)

Informed Consent: Written and oral consent was obtained from all participants, and the research was conducted in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Y., F.N.Y., Ö.T.; Concept: G.Y., Y.B.Ö., E.A.; Design: G.Y., F.N.Y., Y.B.Ö.; Data Collection or Processing: Ö.T.; Analysis or Interpretation: G.Y., F.N.Y., Ö.T., C.Ş.; Literature Search: G.Y., Y.B.Ö., E.A.; Writing: G.Y., F.N.Y., Ö.T., Y.B.Ö., C.Ş., E.A.

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Original Article

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Sentinel Lymph Node Biopsy for Breast Cancer in North Africa: A Retrospective Analysis of Feasibility, Safety, and Morbidity Reduction in a Real-World Setting

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ABSTRACT

Objective: Conventional axillary lymph node dissection (ALND) carries significant morbidity in breast cancer surgery. Sentinel lymph node biopsy (SLNB) offers a less invasive alternative but lacks validation in resource-constrained environments. To compare postoperative morbidity between SLNB and ALND in breast cancer and assess SLNB feasibility.

Materials and Methods: A retrospective study was conducted at the Mother-Child Department of Bizerte, Tunisia (January 2022-August 2024). Patients with early-stage breast cancer undergoing SLNB or ALND were included. Primary outcomes were: lymphedema, lymphocele, pain [visual analog scale (VAS)], hemoglobin drop, and length of hospital stay. Statistical analyses were performed using SPSS v26.0. The Student's t-test was used for normally distributed quantitative variables, the Mann-Whitney U test for non-normally distributed variables, and Fisher's exact test for categorical variables with small sample sizes. Normality was assessed using the Shapiro-Wilk test.

Results: Among the 64 included patients, SLNB (n = 26) significantly reduced lymphedema (3.8% *vs.* 23%, p = 0.039), early postoperative pain (mean VAS: 3.92 *vs.* 4.7, p = 0.025), and length of hospital stay (5.69 *vs.* 7.71 days, p = 0.001) compared with ALND (n = 38). Lymphocele incidence was lower but not statistically significant (4% *vs.* 11; p = 0.640). The SLNB detection rate was 89%.

Conclusion: SLNB significantly reduces postoperative morbidity compared with ALND and is feasible in this resource-limited North African setting. Our findings support its integration into routine breast cancer surgery as a safe and effective alternative to axillary dissection.

Keywords: Sentinel lymph node biopsy; lymphedema; postoperative morbidity; breast cancer; axillary lymphadenectomy; feasibility

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Key Points

- Sentinel lymph node (SLN) biopsy is feasible and safe in a resource-limited North African setting when performed using a dual-tracer technique (technetium-99m and methylene blue).
- Compared with axillary dissection, SLN biopsy significantly reduces postoperative morbidity while preserving arm mobility.
- This study provides a real-world model for implementing SLN biopsy in low- and middle-income countries, contributing to the modernization of breast cancer surgical care.

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide, with over 2.3 million new cases reported in 2022, accounting for approximately one in four female cancers (1). Despite advances in systemic therapies, surgery remains a cornerstone of treatment, particularly for axillary staging. Traditionally, axillary lymph node dissection (ALND) has been used to assess nodal involvement, but it is associated with significant morbidity, including lymphedema, shoulder dysfunction, and postoperative pain (2, 3).

Sentinel lymph node (SLN) biopsy has emerged as a less invasive alternative that enables accurate nodal staging while minimizing complications (4). The SLN is defined as the first LN to receive drainage from a tumor, and its pathological status reflects the likelihood of metastasis to the remaining axillary basin (5). In many low- and

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middle-income countries, the adoption of SLN biopsy has been limited by the availability of nuclear medicine services and necessary surgical equipment. Nevertheless, several centers have demonstrated that with adequate team training and basic infrastructure, SLN biopsy can be implemented even in constrained environments.

This study aimed to evaluate the implementation and clinical outcomes of SLN biopsy for early-stage breast cancer at the Maternity Center of Bizerte, Tunisia. Specifically, we compared SLN biopsy with ALND for detection rate, feasibility, and postoperative morbidity, including lymphedema, hemoglobin loss, hospital stay lengh, pain, and arm mobility.

Methods

Study Design and Setting

We conducted a retrospective, single-center, descriptive study in the Department of Gynecology and Obstetrics at the Bizerte University Hospital, Tunisia. SLN biopsy was introduced in our unit in January 2022. Data were collected from January 1, 2022, to August 31, 2024. During the study period, 80 patients with breast cancer were screened for eligibility; 64 met the inclusion criteria and were retained for the final analysis, while 16 were excluded (Figure 1).

This study was approved by the Ethics Committee of Bougatfa Hospital (approval no: 13/2022, date: 20.12.2022). Information regarding the committee name and approval number has been provided as required. In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for additional analyses or to support the reproducibility of this study at other centers, if requested.

Population

We included patients with histologically confirmed early-stage breast cancer (T1-T3, N0-N1, M0) who underwent either SLN biopsy or ALND.

Inclusion criteria included patients undergoing mastectomy, lumpectomy, or wide local excision, and patients receiving neoadjuvant chemotherapy (NAC) for tumor downstaging or for triple-negative or human epidermal growth factor receptor 2 (HER2)-positive disease.

Exclusion criteria included patients with bilateral cancer; patients with advanced (T4d or metastatic) tumors; patients operated at other institutions; patients who did not undergo surgery or who were receiving palliative care; pregnant or breastfeeding patients; and those whose medical records were incomplete or missing.

SLN Procedure

SLN biopsy was performed using a dual-tracer approach combining technetium-99m radiolabeled human albumin nanocolloid (99mTc-HANC; Nanocoll®) and methylene blue.

• Radiotracer Injection

99mTc-HANC was injected according to the standard two-day protocol (preoperative day 1: tracer injection and imaging; day 2: surgery with or without imaging) at the Nuclear Medicine Department of the Salah Azaïez Institute in Tunis. The nuclear medicine physician administred 4 periareolar intradermal injections each delivering 9–13.7 MBq (0.1–0.3 mL) per site (total activity of 37–55 MBq). Local massage was used to enhance lymphatic drainage. Initial lymphoscintigraphy (LS) was performed, using a gamma camera, 30 minutes to 2 hours post-injection. If no lymphatic drainage was observed during this phase, delayed imaging was acquired for up to 18 h.

• Intraoperative Detection

On the day of surgery, 15 minutes before the skin incision, methylene blue dye was injected in the periareolar region at the same sites as those used for 99mTc-HANC. Detection was achieved via both visual identification of stained nodes and radio-guided localization using a single-photon gamma probe.

SLNs were sent for frozen section (extemporaneous) analysis. In the case of positive results or failed detection, ALND was performed.

Data Collection and Primary Outcomes

Data were collected from patient records, histopathology reports, surgical logs, and follow-up consultations. Supplemental information was obtained through telephone interviews when required. A single surgical team managed all patients and performed all procedures to ensure procedural consistency.

The primary outcomes were: SLN detection rate, hemoglobin loss (pre- and postoperative delta), postoperative lymphedema, lymphocele incidence, pain presence and intensity (using EVA scale) at postoperative day 1, 6 months, and 1 year), length of hospital stay, arm mobility limitation

Statistical Analysis

Data analysis was performed using SPSS v26.0. Quantitative variables were expressed as means, medians, and standard deviations. Qualitative variables were presented as frequencies and percentages. Normally distributed quantitative variables were compared using Student's t-test; non-normally distributed variables were analyzed using the Mann-Whitney U test. Comparisons between the SLNB and ALND groups

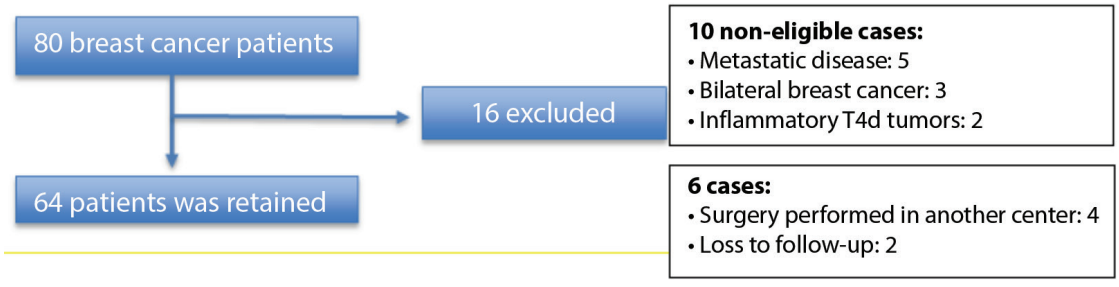

Figure 1. Flowchart of patient selection for the study

for categorical variables were assessed using Pearson's chi-square test or Fisher's exact test, as applicable based on sample sizes. Normality was verified using the Shapiro-Wilk test. A p-value <0.05 was considered statistically significant.

Results

During the study period, a total of 80 breast cancer patients were screened for eligibility; 64 met the inclusion criteria and were retained for the final analysis, while 16 were excluded. Among the 64 retained patients, 27 underwent mastectomy, 25 underwent lumpectomy, and 12 underwent wide local excision. NAC was administered to 14 patients: 6 for tumor downstaging, 5 with triple-negative disease, and 3 with HER2-positive tumors.

SLN biopsy was successfully performed in 89% of the cohort. The 11% failure rate was attributed to intraoperative non-visualization of the LN (n = 4) or weak preoperative radiotracer uptake on LS (n = 2), which necessitated immediate conversion to ALND. Intraoperative frozen-section analysis of the SLN revealed no metastatic involvement in 79% of patients, whereas a positive SLN in 18% of patients led to immediate ALND during the same surgical session. Postoperative outcomes demonstrated a clear benefit of SLNB over ALND in terms of morbidity. The mean hospital stay was significantly shorter in the SLNB group than in the ALND group (5.7 *vs.* 7.7 days, p = 0.001), and perioperative blood loss, as reflected by the mean hemoglobin drop, was markedly reduced (0.71 g/dL *vs.* 1.57 g/dL, p = 0.02). Lymphedema occurred in 3.8% of SLNB patients compared with 23% of ALND patients (p = 0.039). Although lymphocele rates were less frequent in the SLNB group (4% *vs.* 11%), this difference was not statistically significant (p = 0.64). Pain assessment using VAS showed significantly lower scores in SLNB group both on postoperative day 1 (3.92 *vs.* 4.7, p = 0.025) and at 6 months (1.27 *vs.* 2.08, p = 0.002), whereas the difference was not statistically significant at 1 year (p = 0.079). Functional outcomes were also superior in the SLNB group: all patients retained full arm mobility, whereas 43% (n = 16) of patients in the ALND group reported persistent movement restriction (p = 0.001) (Table 1).

Discussion and Conclusion

Our study reinforces the clinical relevance and practicality of SLN biopsy in breast cancer surgery within a resource-limited North African healthcare system. Despite restricted access to advanced nuclear imaging modalities and hybrid tracers, we successfully implemented SLN biopsy at our institution, demonstrating significant advantages in terms of postoperative outcomes and patient quality of life. These results are in line with the growing international consensus supporting SLN biopsy as the standard of care for axillary staging in early-stage breast cancer.

Compared with axillary dissection, SLN biopsy was associated with substantially lower postoperative morbidity. We observed shorter hospital stays, a smaller hemoglobin drop, and less postoperative pain, with statistically significant differences maintained at both early and intermediate follow-up assessments. Importantly, all patients in the SLN group preserved full arm mobility, whereas nearly half of those who underwent axillary dissection developed functional limitations.

A better understanding of tumor biology and the availability of new systemic therapies have reshaped breast cancer management, shifting the surgical approach toward less invasive procedures. Within this evolving paradigm, our findings highlight that SLN biopsy represents not only a safe and effective alternative to axillary dissection but also a cornerstone of modern, patient-centered surgical strategies (6).

The incidence of lymphedema was also markedly reduced, from 23% to 3.8%, a finding consistent with international meta-analyses (2, 3, 7). These benefits underscore the value of SLN biopsy not only for accurate staging but also for safeguarding postoperative quality of life. Given the chronic and disabling impact of axillary morbidity, particularly lymphedema and reduced mobility, SLN biopsy represents a major advance for breast cancer patients, especially those treated conservatively. Moreover, it reduces demand for rehabilitation services and long-term follow-up clinics, which are often overburdened in public health systems (2, 3, 7-10).

The introduction of SLN biopsy in our hospital was achieved by adapting international protocols to local realities. While high-income centers commonly employ radiotracer–fluorescent dye combinations

Table 1. Summary of clinical outcomes

Primary outcomes	**SLNB (n = 26)**	**ALND (n =38)**	**Statistic test**	***p*-value**
Lymphedema (%)	1 (3.8%)	9 (23%)	Chi²/Fischer exact test	0.039
Arm mobility impairment	0 (0%)	16 (43%)	Chi²/Fischer exact test	0.001
Lymphocele (%)	1 (4%)	4 (11%)	Chi²/Fischer exact test	0.64
	SLNB (n = 26)	ALND (n = 38)	Statistic test	*p*-value
Postoperative day 1: mean visual analog scale	3.92%	4.7%	Student's t-test	0.025
	SLNB (n = 26)	ALND (n = 38)	Statistic test	*p*-value
Hospital stay lengh (days)	5.69 Standard deviation: 1.61	7.71 Standard deviation: 2.27	Student's t-test	0.001
	SLNB (n = 26)	ALND (n = 38)	Statistic test	*p*-value
Hemoglobin drop (g/dL)	0.71 Standard deviation: 0.71	1.57 Standard deviation: 1.57	Student's t-test	0.02

SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection

and intraoperative gamma probes with real-time imaging, we used to technetium-99m-label human albumin nanocolloids in combination with methylene blue, an approach that remains accessible and cost-effective (11, 12). Our detection rate reached 89%, which is comparable to published reports during the early phases of SLN program implementation. Most identification failures were related to limited tracer migration or technical difficulties during intraoperative localization. Nevertheless, the dual technique we used was adequate for reliably mapping axillary drainage and enabled the safe avoidance of unnecessary axillary dissection in N0 patients. This demonstrates that SLN biopsy can be successfully integrated into practice even without near-infrared cameras or intraoperative single photon emission computerized tomography-computed tomography, provided that minimal nuclear medicine infrastructure and adequate surgical training are available (7, 13).

A particularly promising innovation in SLN mapping is the use of indocyanine green (ICG), a near-infrared fluorescent tracer that provides real-time visualization of lymphatic drainage with high sensitivity. Several studies have shown that ICG achieves detection rates equal to or exceeding those of radiotracers, including patients with altered lymphatic anatomy or prior surgery (14, 15). In our setting, ICG holds great potential, as it eliminates the need for radiotracers and allows SLN mapping entirely within the operating theater. However, its adoption remains constrained by two main challenges:

1. The high cost and limited availability of near-infrared imaging systems,

2. The absence of structured training and accreditation pathways in fluorescence-guided surgery.

To overcome these barriers, phased implementation strategies could be considered, starting with pilot programs in high-volume centers, supported by national initiatives or international collaborations. Regional training workshops and knowledge-sharing with centers already experienced in ICG use would further facilitate dissemination.

It is also important to address the role of SLN biopsy following NAC, which remains the subject of ongoing debate (16). Evidence from multiple studies indicates acceptable false-negative rates (<10%) in carefully selected T1-T2 patients. Systematic reviews and meta-analyses have supported the overall feasibility and accuracy of SLNB post-NAC. Tan et al. (17) and Kelly et al. (18) both concluded that SLNB after NAC can be performed reliably, particularly when combined with adjuncts such as immunohistochemistry or dual tracer mapping. These conclusions were further validated by Kuehn et al. (19) in the SENTINA trial, a large prospective multicenter study, which standardized the timing and technical approach to SLNB in this context. Our protocol followed these evolving guidelines, but long-term oncological outcomes require ongoing monitoring.

Study Limitations

This study does, however, present certain limitations. It is retrospective and has a modest sample size, which restricts generalizability. In addition, long-term oncological outcomes, such as recurrence and disease-free survival, were not assessed, as the focus was limited to perioperative parameters. Finally, the unavailability of ICG or hybrid tracers may limit detection sensitivity in anatomically complex cases.

Nonetheless, our findings provide strong real-world evidence that SLN biopsy can be safely and effectively implemented in public hospitals operating under resource constraints. This model could be replicated in other low- and middle-income countries aiming to modernize breast cancer surgical management without imposing unsustainable costs.

Our experience demonstrates that SLNB is a feasible, safe, and effective approach to axillary staging in early-stage breast cancer, even in a resource-limited setting. The technique significantly reduces postoperative morbidity—particularly lymphedema, pain, and impaired arm mobility—while maintaining acceptable detection rates and oncologic validity. With proper protocol adaptation, interdepartmental collaboration, and apprenticeship-based training, SLNB can and should be integrated into routine breast cancer surgery across low- and middle-income countries.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Bougatfa Hospital (approval no: 13/2022, date: 20.12.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.B.S.; Concept: A.B., N.K.; Design: Y.C., M.Mab.; Data Collection or Processing: L.Z., A.M.; Analysis or Interpretation: W.J., M.Mo.; Literature Search: M.M., Writing: M.B.

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

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Original Article

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Ultra-Hypofractionated Radiotherapy Plus Boost for T1-2 Breast Cancer Patients: Early Results of a Prospective Study Based on the Fast-Forward Scheme

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ABSTRACT

Objective: Hypofractionated radiotherapy (RT) is the standard adjuvant treatment for breast cancer patients after surgery. The recent results of the FAST-FORWARD trial on ultra-hypofractionated RT, delivered over one week, support a viable alternative regimen for early-stage breast cancer. Whether the addition of a tumor bed boost could further improve patient outcomes is still under investigation.

Materials and Methods: We report the results of a single-center prospective study involving 26 early-stage (T1, 2N0) breast cancer patients treated with whole-breast RT consisting of five daily fractions of 5.2 Gy (FAST-FORWARD regimen) followed by a tumor-bed boost of three daily fractions of 3 Gy.

Results: Grade 1 early breast toxicity (skin changes and altered breast consistency) was documented in 20% of patients within the first 3 months after treatment completion. No events of acute pneumonitis were reported. Whole-breast and tumor-bed boost volumes did not affect the occurrence of breast toxicity. Minimal radiation-induced lung injury (grade 1) was noted in 95.8% of patients, while one patient (4.2%) developed grade 2 lung toxicity, which was later downgraded to grade 1 at the 12-month post-RT time point. With a median follow-up of 72 months, none of the patients presented with locoregional recurrence or distant metastases.

Conclusion: The present study highlights the safety of a hypofractionated RT boost to the tumor bed after ultra-hypofractionated whole-breast RT. No clear evidence exists to date regarding the superiority of delivering a tumor bed boost after ultra-hypofractionated RT or the specific patient subgroups to which a boost should be prescribed.

Keywords: Breast cancer; radiotherapy; ultra-hypofractionation; toxicity; prospective trial; boost

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Key Points

- Ultra-hypofractionated radiotherapy (ultra-hypo-RT) for early-stage breast cancer has shown promising results.
- A hypo-RT boost to the tumor bed after whole-breast ultra-hypo-RT appears to be safe and effective.
- Radiobiological analysis of the radiotherapy dose delivered to the whole breast and to the booster field area further supports the excellent cosmetic results.

Introduction

Breast cancer is the most commonly diagnosed malignancy, accounting for approximately 315.000 new cases per year in the United States of America. It is also the fourth leading cause of cancer deaths (1). Breast conserving surgery (BCS) and mastectomy are central components of breast cancer treatment, while neoadjuvant and/or adjuvant systemic therapy and adjuvant radiotherapy (RT) are routinely applied according to tumor and patient characteristics and the surgical procedure utilized. Regarding RT, irradiation of the breast and regional lymph nodes (in cases of nodal involvement) is prescribed after BCS, whereas RT to the chest wall and nodal areas is reserved for patients with large tumors, nodal metastases, or positive surgical margins on pathological evaluation (2). The Early Breast Cancer Trialists' Collaborative Group meta-analysis cemented the importance of adjuvant RT post-BCS, reporting reductions of 16% and 4% in the 10-year risk of locoregional and distant recurrence and the Fifteen-year risk of breast cancer death, respectively (3).

Standard RT to the breast and lymph nodes originally consisted of 25 daily fractions of 2 Gy each, delivered over 5 weeks, with or without a tumor bed boost (4, 5). However, during the past 20 years, an improved

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understanding of tumor and normal tissue radiobiology has paved the way for randomized trials assessing the efficacy of hypofractionated RT (hypo-RT) schedules, which comprise daily RT doses >2 Gy and aim to achieve a significant reduction in overall treatment time, providing greater convenience for patients and busy RT departments. In 2008, the START B randomized trial demonstrated that adjuvant RT delivered as 15 daily fractions of 2.66 Gy conferred 5-year locoregional relapse rates of 2.2% in women with early-stage breast cancer, similar to the rate with standard fractionation (3.3%). In addition, late adverse RT events reported by patients were fewer in the hypofractionated arm (6). Similar to the START B trial, Whelan et al. (7) [Ontario Clinical Oncology Group (OCOG)] reported no difference in the 10-year local recurrence rates of women with node-negative, early-stage breast cancer who underwent hypo-RT (42.5 Gy/2.65 Gy/f in 22 days) versus standard RT (6.7% *vs.* 6.2%) (77. Further hypofractionation in the range of 5–6 Gy per fraction was originally tested in the UK FAST trial, which compared standard daily RT with once-weekly RT of 5.7 or 6 Gy for five weeks in early-stage (N0) breast cancer, and showed that once-weekly schedules (including 28.5 Gy delivered in five weekly fractions) produced local control and toxicity outcomes similar to those of standard fractionation (8, 9).

In 2020, the results of the FAST-FORWARD phase III trial, comprising 4,096 breast cancer patients (pT1–3, pN0–1) previously treated with BCS or mastectomy, were published (10). Patients were randomly assigned to adjuvant RT directed to the breast and/or nodal areas: 40 Gy in 15 daily fractions over 3 weeks (START B fractionation), 27 Gy in 5 daily fractions of 5.4 Gy, or 26 Gy in 5 daily fractions of 5.2 Gy (overall treatment time of 1 week for the ultra-hypo-RT arms). It was shown that RT of 26 Gy delivered over 1 week conferred outcomes comparable to those with 40 Gy irradiation (0.7% difference in 5-year local relapse rates; 2-year moderate-to-marked arm and hand swelling rates were 10% with 40 Gy versus 7% with 26 Gy) (11). A tumor-bed RT boost (10 or 16 Gy, delivered in 2-Gy fractions) was optional and was not part of the randomization protocol; approximately 75% did not receive an RT boost. This was also the case for patients enrolled in the START B trial, whereas a tumor-bed boost was omitted in the FAST and OCOG studies. The authors of the FAST-FORWARD trial suggested that a study focusing on a sequential or synchronous RT boost alongside hypo-RT should be conducted.

In this prospective study, we investigated the safety of a sequential RT tumor-bed boost in breast cancer patients undergoing adjuvant RT (FAST-FORWARD).

Materials and Methods

In this single-center prospective study conducted in the Department of Clinical Radiation Oncology at ATTIKON University Hospital, 26 patients with early-stage breast cancer were treated with adjuvant hypofractionated, accelerated RT (hypo-ART) according to the FAST-FORWARD RT scheme after BCS between 2018 and 2019. The study continues to recruit patients. Since assessing late radiation effects in hypofractionated regimens is crucial, we decided to submit this interim report, which includes patients with more than five years' follow-up. Patient and disease characteristics are displayed in Table 1. The study was approved by the local Ethics and Research Committee (approval number: A1.4.17-4-2018, date: 24.05.2018). Inclusion criteria were patients older than 18 years who had a pathological diagnosis of epithelial breast cancer, with pathological stage pT1-2/pN0 without distant metastasis, and who were treated with BCS as primary treatment. Patients with locally advanced disease, nodal involvement on pathological evaluation, a synchronous diagnosis of another malignancy, a history of autoimmune disease, known genetic susceptibility to increased radiation sensitivity, or pregnancy were excluded. All patients gave written informed consent to participate in the study and to allow their laboratory and clinical data to be used anonymously for research purposes. One patient was lost to follow-up immediately after RT completion, and another patient was lost after three months of follow-up. Thus, 25 and 24 patients were available to assess acute and late toxicity, respectively.

Radiotherapy

The prescribed RT schedule incorporated 5 daily fractions of 5.2 Gy delivered over 1 week via a linear accelerator (VitalBeam, Varian). 6 MV was the standard energy applied, although higher-energy 10 MV fields were also required to achieve better dose homogeneity in patients with large breasts. A sequential tumor-bed boost was delivered in three fractions of 3 Gy each. The clinical target volume (CTV) consisted of breast tissue, as defined by the area between the pectoralis major muscle and 3 mm below the skin surface. A margin of 10 mm beyond the CTV was applied to define the planning target volume (PTV), accounting for patient setup errors and respiratory motion. A 3D-conformal RT (3D-CRT) technique with tangential fields was used. The CTV of the tumor bed boost was defined as the area encompassed by surgical clips placed during lumpectomy; a 1 cm margin was applied for PTV delineation. A 3D-CRT technique – with anterior/oblique fields – was also used for the sequential boost. Daily cone-beam computed tomography (CT) was performed on all patients.

Regarding PTV coverage goals, the lower dose limit was set so that 95% of the PTV volume receives at least 95% of the administered dose. Regarding the upper dose limit, less than 5% and less than 2% of the PTV should receive ≥105% and ≥107% of the administered dose, respectively, with a maximum dose <110%. Dose constraints for the heart and ipsilateral lung were V_EQD2 (25 Gy) <10% for the cumulative RT plan.

Radiobiological Considerations

To clearly portray the biological effects of this ultra-hypofractionated, accelerated regimen, we calculated the equivalent dose delivered in 2-Gy fractions (EQD2) using the linear-quadratic model. We used the α/β values of 3, 4, and 10 Gy for late normal tissue effects, breast cancer, and early normal tissue toxicity, respectively. Treatment acceleration was also taken into account: λ values of 0.2 Gy/day and 0.6 Gy/day (daily dose required to compensate for cell repopulation) were considered for slow-proliferating normal tissues and for breast cancer and rapidly-proliferating normal tissues, respectively. Treatment acceleration ($\Delta\tau$) was defined as the number of days needed to deliver the EQD2 dose minus the 5 or 10 days required for the FAST-FORWARD and the FAST-FORWARD plus boost regimens, respectively (12-15). The mathematical formulas applied are as follows:

$$EQD2 = \text{Total dose} \times ([\alpha/\beta + \text{dose per fraction}]/[\alpha/\beta + 2])$$

$$EQD2\text{-}T = EQD2 + (\lambda \times \Delta T)$$

Toxicity Evaluation

Acute breast toxicity was evaluated at completion of breast RT, at one week, and at three months, or at any time patients reported signs or symptoms involving the skin, breast, or arm. Late breast toxicity was assessed clinically 1 year after treatment completion, acute and late lung

Table 1. Patient, disease and treatment characteristics

No pts	26
Age	
Median	57
Range	39–76
Menopausal status	
Pre	7
Post	19
PS	
0	26
Location	
Left breast	10
Right breast	16
Histology	
NOS (*)	26
Lymphovascular invasion	
Yes	3
No	23
T-stage	
T1	21
T2	5
Node involvement	
N0	26
Grade	
1	11
2	12
3	3
ER status	
Negative	2
Positive	24
Positivity range (%)	50–100
PgR status	
Negative	4
Positive	22
Positivity range (%)	3–100
HER-2 status	
Negative	22
Positive	4
Ki-67	
<14%	12
≥14%	14
Molecular status	
Luminal A	10
Luminal B	14
HER2-enriched	2
Triple negative	0
Surgery (invasive tumors)	
Conservative	26
SLNB (**)	25
Axillary dissection	1
Resection margins (mm)	
Range	2–10
Median	2.5
Chemotherapy	
None	21
Postoperative	5
Hormone therapy	
Yes	24
No	2
During radiotherapy	13

(*)NOS: Non-otherwise specified; (**)SLNB: Sentinel lymph node biopsy; HER2: Human epidermal growth factor receptor 2; ER: Estrogen receptor

toxicities were assessed with high-resolution CTs at 3- and 12-months post-irradiation, respectively. Late toxicity was evaluated annually. Acute toxicity grading of dermatitis, breast edema, and pneumonitis was conducted using the Common Terminology Criteria for Adverse Events version 5.0 (16). Late RT adverse events were graded using the Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer Late Radiation Morbidity scale (17). In addition, radiation-induced lung toxicity was assessed using a grading scale previously proposed by our group (Supplemental Table 1) (18).

Follow-up

Patients were assessed for ipsilateral breast tumor recurrence or regional recurrence every 6 months during the first 2 years and annually thereafter. Physical examination and mammography or ultrasound were performed at each visit, while CT of the chest and abdomen was required to evaluate potential nodal and distant metastases.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software Inc., La Jolla, CA, USA). The Mann-Whitney non-parametric test was used for intergroup analysis.

Results

The majority of patients (73%) were postmenopausal, and 62% of tumors were located in the right breast. Histologically, all tumors were ductal adenocarcinomas (no special type), had no nodal involvement, and were locally staged as T1 (81%) and T2 (19%). Ninety-two percent of tumors (92%) were estrogen receptors (ER)-positive, while human epidermal growth factor receptor 2 expression was noted in 15% of cases. BCS was performed with negative resection margins in all patients. Adjuvant chemotherapy was administered to 19% of patients, and all ER-positive patients received hormonal therapy. Fifty-four percent of them received hormonal therapy during RT. The Median follow-up was 72 months (range, 61–86 months).

Dosimetric Data

Regarding whole-breast irradiation, the average conformity and homogeneity indices were 1.3 and 0.26, respectively. The breast volumes receiving 105% and 107% of the prescribed dose were 32.39 cc and 2.65 cc, respectively. The average dose to 95% of the breast volume (D95%) was 25.42 Gy.

Breast/Arm Toxicity

Early grade 1 breast toxicity (skin and breast consistency) was noted in 5 of 25 patients (20%) during the first 3 months of follow-up. Figure 1 presents a typical image of a patient's breast before and one week after treatment completion. No patients (0%) experienced late breast or arm toxicity of any grade (edema, breast fibrosis, lymphedema). Figure 2a illustrates the progression of breast toxicity during the first year after RT. With a median follow-up of 72 months, no further deterioration in late toxicity was observed.

Breast Volume and Toxicity

Breast toxicity was further analyzed by breast volume (CTV-breast) and by the volume of the breast included in the boost field (PTV-boost). Overall, the breast CTV ranged from 200.8 to 1,510 cc (median 663.8 cc; mean 661.8 cc). Among the five patients who developed grade 1 toxicity, the median CTV-breast was 733.8 cc, compared with 643.3 cc in the remaining patients; this difference was not statistically significant (p = 0.65). The PTV-boost volume ranged from 37.9 to 246.5 cc (median 100.3 cc, mean 112.2 cc). The median PTV-boost volumes were 125.3 cc and 89 cc in patients with grade 1 and 0 toxicity, respectively (p = 0.34).

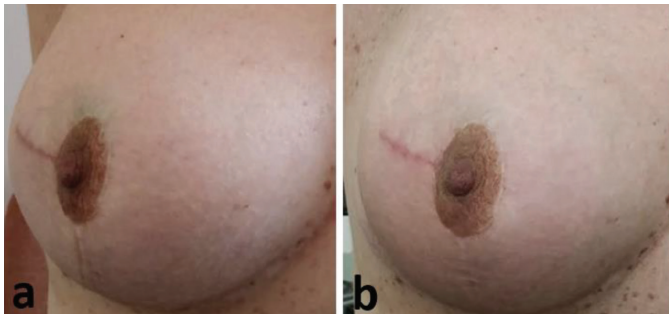

Figure 1. Typical images of a patient's breast before and one week after treatment completion, showing lack of any toxicity

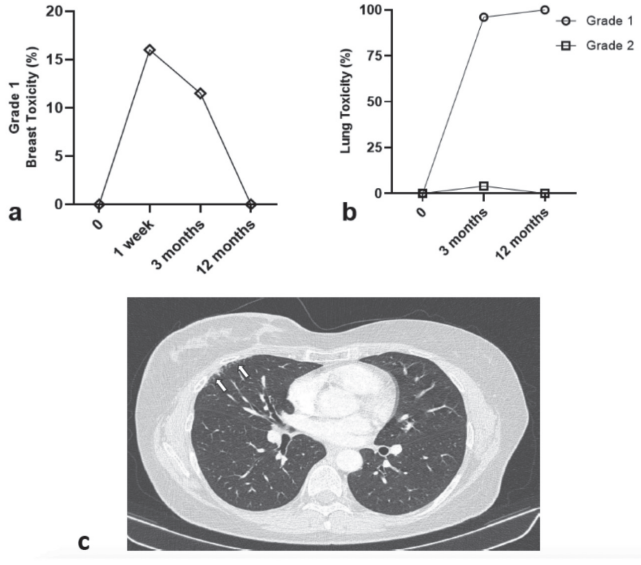

Figure 2. Toxicity in time: (a) Percentage of patients developing grade 1 breast toxicity (skin and breast consistency) during the first year after radiotherapy, (b) Percentage of patients developing lung grade 1 and 2 toxicity during the first year after radiotherapy (time zero corresponds to the start of treatment), (c) Typical computed tomography image of a grade 1 lung toxicity 12 months after radiotherapy (white arrows)

Lung Toxicity

None of the patients developed acute pneumonitis. Grade 1 lung toxicity (ground-glass opacities without obscuration of the subjacent pulmonary vessels within the tangential fields) was noted in 23 of 24 patients (95.8%) on CT scans performed 3 months after RT. One additional patient (4.2%) developed grade 2 lung toxicity (limited consolidations), which had regressed by the 12-month follow-up. All patients were asymptomatic. Figure 2b shows the time course of lung toxicity during the first year after RT. During a median follow-up of 72 months, no additional cases of lung fibrosis were recorded. Figure 2c presents a representative CT image showing grade 1 lung toxicity 12 months after RT.

Radiobiological Analysis

Table 2 shows the EQD2 for the FAST-FORWARD RT regimen and for the regimen used in our study (FAST-FORWARD plus boost), compared with a conventionally fractionated RT scheme across the previously mentioned α/β and λ values (with and without time correction). Appendix I presents an example of detailed calculations.

Local, Regional and Distant Control

Over a median follow-up of 72 months, none of the patients developed local, regional, or distant metastases.

Discussion and Conclusion

Standard fractionation of RT is a well-established and effective approach for patients with cancer. However, it became evident early on that multiple visits to RT departments can reduce compliance—especially among patients with low performance status and those who must commute long distances to the hospital—or even lead to refusal to undergo RT (19, 20). In addition, accelerated RT schedules facilitate the treatment of more patients per year in busy RT departments. The FAST-FORWARD trial established the efficacy and safety of ultra-hypofractionated and accelerated RT in early-stage breast cancer patients after BCS or mastectomy. In this prospective study, we evaluated the safety and efficacy of 26 Gy of adjuvant RT delivered in 5 daily fractions followed by a tumor bed boost of 9 Gy (3 Gy/fraction) in 26 patients with early-stage breast cancer.

The role of an RT tumor-bed boost after whole-breast irradiation has been debated since RT established its role in the adjuvant treatment of patients with breast cancer. A strong indication for prescribing higher radiation doses to the surgical cavity is the presence of positive surgical margins on pathological evaluation, a finding that suggests an increased probability of tumor recurrence and distant metastases (21, 22). Nevertheless, Bartelink et al. (23) assessed the efficacy and safety of a 16 Gy boost given to 2,658 breast cancer patients after whole-breast RT. Although a survival benefit was not observed, there was a statistically significant decrease in local recurrence rates in the RT-boost arm of the study, with 20-year ipsilateral breast tumor recurrence rates of 16.4% versus 12% in the no-boost and boost groups, respectively. However, a significant increase in the 20-year incidence of breast fibrosis was observed in the group receiving the boost (5.2% *vs.* 1.8%).

A subgroup analysis by patient age revealed that patients younger than 40 experienced the greatest reduction in local recurrence compared

Table 2. Equivalent dose delivered in 2 Gy fractions, with and without time correction (EQD2 and EQD2-T), for conventional radiotherapy (RT) and the FAST-FORWARD and FAST-FORWARD plus boost regimens

α/β (Gy)	Radiotherapy regimens				
	Conventional RT	FAST-FORWARD		FAST-FORWARD plus boost*	
	EQD2 and EQD2-T (Gy) + boost	EQD2 (Gy)	EQD2 – T (Gy)	EQD2 (Gy)	EQD2-T (Gy)
3	50+10 (60)	42.64	47.44	42.64+10.8 (53.44)	47.44+11.4 (58.84)
4	50+10 (60)	39.87	52.47	39.87+10.5 (50.37)	52.47+11.7 (64.17)
10	50+10 (60)	32.93	43.13	32.93+9.75 (42.68)	43.13+10.95 (54.08)

*: Breast tissue within the booster dose area

with other age groups, leading the authors to suggest that the tumor-bed boost could be safely omitted in breast cancer patients older than 60 years. In addition, patients with high-grade, hormone-receptor-negative disease have been shown to benefit from an additional radiation dose (24), which should also be considered across all age groups. In the import high trial, patients were randomized to receive a sequential boost (16 Gy in 8 fractions after 40 Gy hypo-RT) or a concomitant boost (48 or 53 Gy in 15 fractions to the surgical cavity) (25). Boost sequencing had no effect on treatment outcome; however, a higher boost dose was associated with a 4%–5% higher incidence of moderate-to-marked breast induration compared with the other trial arms. A phase III randomized trial (HI-RISE) is ongoing, comparing hypo-RT (40 Gy in 15 fractions) with a simultaneous integrated boost (SIB) to the tumor bed and standard fractionated RT with a sequential boost of 10 Gy in 5 fractions (26).

Approximately 25% of patients in the FAST-FORWARD trial received an RT boost of 10-16 Gy, delivered in 2-Gy fractions (10). To date, no publications have focused on this patient subgroup. Zanoguera et al. (27) reported on 126 breast cancer patients (<60 years old, with high-grade disease, or with lymphovascular or perineural invasion) who were treated with adjuvant RT (FAST-FORWARD) and a SIB of 3 Gy (29 Gy/5.8 Gy per fraction to the tumor bed). During a median follow-up of 6.25 months, no significant adverse events were documented. Acute skin toxicity post-RT was minimal: only nine patients presented with grade 1-2 dermatitis. Similarly, Montero et al. (28) assessed the efficacy and safety of an SIB in breast cancer patients: 29 Gy (5.8 Gy/fraction) to the tumor bed in 272 patients, or 30–31 Gy (6–6.2 Gy/fraction) in 111 patients with close/positive margins. No patients developed locoregional recurrence or distant metastasis during the median follow-up of 18 months. Grade 1 and grade 2 dermatitis were noted in 48% and 4% of patients, respectively; minimal late RT sequelae (grade 1 or 2) were also reported in less than 5% of patients. Breast and boost volumes were associated with increased skin toxicity.

In the current study, we demonstrated that a sequential boost of 3 fractions of 3 Gy after ultra-hypo-RT was well tolerated, as no increase in toxicity was documented in our patient cohort. Moreover, the volume of the whole breast and the volume of the breast included in the boost area did not affect the occurrence of breast toxicity. This has also been confirmed by radiobiological analysis. According to the EQD2-T values to the whole breast, the FAST-FORWARD regimen appears to be associated with far less early toxicity compared to conventionally fractionated RT, in accordance with a subanalysis of the FAST-FORWARD trial (29). Our analysis further suggests that this improved toxicity profile also applies to breast tissue within the boost field. Moreover, predicted late toxicity from EQD2-T analysis indicates a slightly lower burden with the FAST-FORWARD plus boost regimen. Regarding the efficacy of the RT scheme applied in this study, the EQD2-T values predict a higher biological anti-tumor dose to the breast tissue within the boost area.

The aforementioned data indicate the safety of a hypo-RT boost to the tumor bed following ultra-hypofractionated whole-breast RT. No clear evidence exists as of yet about the superiority of delivering a tumor bed boost after ultra-hypo-RT, or the specific patient subgroups to which a boost should be prescribed. Certain limitations exist in our study. A larger patient cohort would permit drawing more reliable conclusions, while the inclusion of a control arm could further shed light on the necessity of an RT boost. The prospective nature and novelty of this report, however, could form the basis for future trials.

Ethics

Ethics Committee Approval: The study was approved by the local Ethics and Research Committee (approval number: A1.4.17-4-2018, date: 24.05.2018).

Informed Consent: All patients gave written informed consent to participate in the study and to allow their laboratory and clinical data to be used anonymously for research purposes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., I.M.K., K.P., G.P., N.K., E.E., N.K., A.Z., V.K.; Concept: E.E., N.K., A.Z., V.K.; Design: E.E., N.K., A.Z., V.K.; Data Collection or Processing: E.K., I.M.K.; Analysis or Interpretation: E.K., I.M.K., K.P., G.P., N.K., E.E., N.K., A.Z., V.K.; Literature Search: E.K., I.M.K.; Writing: E.K., I.M.K., K.P., G.P., N.K., E.E., N.K., A.Z., V.K.

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

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Original Article

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Detection of the Superior Perforator with Doppler Ultrasonography in Superomedial Pedicle Reduction Mammaplasty: A Retrospective Evaluation of Vascular Safety

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ABSTRACT

Objective: The superomedial pedicle technique combines aesthetic advantages with reliable vascularity in reduction mammaplasty. This study evaluated the safety and clinical outcomes of Doppler ultrasonography–guided identification of the superior perforator in the superomedial pedicle design.

Materials and Methods: This retrospective study included 22 female patients who underwent bilateral superomedial pedicle reduction mammaplasty between April 2023 and April 2025. In all patients, the superior perforator was detected preoperatively using a portable handheld Doppler ultrasonography device and was incorporated into the pedicle design. All patients underwent surgery via an inverted-T pattern with the superomedial pedicle. The mean follow-up period was 1.2 years.

Results: The superior perforator was identified in all patients (mean time: 3.0±0.4 minutes). No partial or total necrosis of the nipple-areola complex was observed in any patient. Wound dehiscence occurred at the T-incision site in four patients, transient areolar hypoesthesia was observed in three patients, and hypertrophic scarring developed in one patient. Aesthetic outcomes were evaluated in all patients by physical examination and standardized photography.

Conclusion: Detection of the superior perforator with Doppler ultrasonography enables individualized planning of the superomedial pedicle and enhances vascular safety. This approach provides a feasible, individualized, and reliable surgical technique for reduction mammaplasty, thereby reducing complication rates.

Keywords: Doppler ultrasonography; mammaplasty; perforator flap; surgical flaps; treatment outcome

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Key Points

- Preoperative Doppler ultrasonography enables identification of the superior perforator and individualized planning of the superomedial pedicle.
- Incorporating the superior perforator increases vascular safety and minimizes the risk of nipple–areola complex necrosis.
- The superomedial pedicle technique provides reliable outcomes, low complication rates, and satisfactory aesthetic outcomes in reduction mammaplasty.

Introduction

Reduction mammaplasty is one of the fundamental procedures in plastic surgery, performed to alleviate physical complaints and improve aesthetic appearance (1-3). One of the most critical factors determining surgical success in these operations is the safe transposition of the nipple-areola complex (NAC) to its new anatomical location while preserving adequate vascularity. Therefore, the choice of pedicle in surgery plays a crucial role in maintaining circulation and achieving aesthetic outcomes.

Several pedicle techniques have been described in the literature, including inferior, superior, medial, lateral, central, and superomedial approaches (3, 4). The superomedial pedicle provides dual perfusion by incorporating both superior and medial perforators. This dual perfusion offers an anatomical advantage, particularly in large and ptotic breasts in which the rotational distance of the NAC is increased (5). However, despite its anatomical reliability, variability in the location and dominance of perforators may still pose a risk for ischemic complications.

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Doppler ultrasonography is increasingly used in pedicle planning due to its noninvasive nature, practicality, and ability to localize perforators in real time (6). In particular, since the superior perforators run approximately 1 cm beneath the skin, these vessels can be identified by Doppler ultrasonography (3).

The aim of this study was to retrospectively evaluate the effects on vascular safety and complication rates of including superior perforators, identified by handheld Doppler ultrasonography, in the medial pedicle during reduction mammaplasties performed with the superomedial pedicle technique. We hypothesized that preoperative Doppler identification of the superior perforator would enhance vascular safety and reduce complication rates in superomedial pedicle reduction mammaplasty.

Materials and Methods

Study Design

This retrospective study included 22 female patients who presented to the Yeditepe University Kozyatağı Hospital from April 2023 to April 2025 with complaints of breast hypertrophy (macromastia) and underwent bilateral superomedial-pedicle reduction mammaplasty. All surgeries were performed by the same plastic surgeon (M.E.). This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Yeditepe University Non-Interventional Clinical Research Institutional Review Board on September 9, 2025. The approval was documented under the application number 2025-08-Y0918. Informed consent was obtained from all participating patients. This study received no external funding. The primary outcome of the study was the incidence of NAC necrosis. Secondary outcomes included other postoperative complications, such as hematoma, seroma, and surgical site infection, and minor complications, including wound dehiscence, hypertrophic scarring, and areolar hypoesthesia. In addition, aesthetic satisfaction was assessed based on standardized clinical examination and photographic evaluation.

Patient Selection

Female patients aged 18–59 years, classified as American Society of Anesthesiologists (ASA) I or II by the ASA, were included in the study. Breast ultrasonography was requested for all patients under 40, and mammography for those aged 40 or older. Patients with BIRADS 1 or 2 results were included, while those with BIRADS 3 findings were referred to the general surgery department for further evaluation by specialists before inclusion in the study. Patients scheduled for revision surgery, those with a history of breast or axillary surgery, those diagnosed with breast cancer or other prior breast disease, those with coagulopathy or severe systemic disease, and those unable to provide informed consent were excluded from the study.

Ultrasonographic Mapping

A portable high-frequency ultrasound device (Clarius L20, Clarius Mobile Health, Canada) was used to detect the superior perforator. During ultrasonography, power Doppler mode was activated to evaluate flow direction and intensity in the vessels. The procedure was performed directly by the primary surgeon (M.E.). The ultrasonographic image of the superior perforator is shown in Figure 1.

Imaging was performed with the patient supine during preoperative markings to ensure consistency with the surgical position. The superior perforator was typically sought and identified along the medial border of the pectoralis major muscle at the level of the second intercostal space. The Power Doppler mode, using a high-frequency linear probe, clearly visualized arterial flow approximately 1 cm beneath the skin surface.

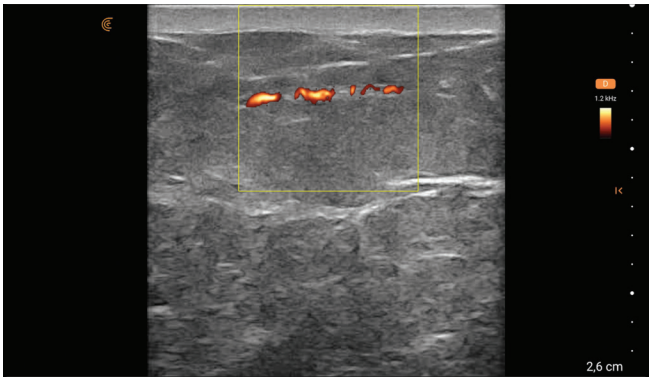

Figure 1. Visualization of the superior perforator using a high-frequency ultrasound device (Clarius L20, Clarius Mobile Health, Canada)

The identified perforator was marked on the skin and included in the surgical plan. Once the patient was positioned on the operating table, the same region was re-evaluated intraoperatively, and the location of the perforator was confirmed. This allowed the preoperative mapping and intraoperative vascular localization to be harmonized and the pedicle boundaries to be determined to include this vascular structure.

Using this method, the superior perforator was incorporated into the pedicle, creating a superomedial pedicle supplied by both superior and medial sources and enhancing vascular safety.

Surgical Technique

All patients were placed under general endotracheal anesthesia. After appropriate positioning, skin antisepsis was performed, and sterile draping was applied. The surgical plan, previously drawn to include the superior perforator identified by Doppler ultrasonography, was followed for bilateral superomedial pedicle-based breast reduction.

The pedicle was de-epithelialized within the planned borders. Adequate amounts of breast parenchyma were excised from the inferior and lateral quadrants via surgical incisions. The superior perforator was identified during excision, and its vascular integrity was preserved. After achieving hemostasis, the pedicle was transposed to its new position.

Flap fixation was achieved with 2/0 polydioxanone sutures in combination with 2/0 and 3/0 poliglecaprone sutures. Subcutaneous tissue was closed continuously with 4/0 poliglecaprone, and the areolar circumference with 5/0 poliglecaprone. Size-10 active silicone drains (Jackson-Pratt; Ethicon, Johnson & Johnson, USA) were placed in each breast. Steri-Strip (3M, USA) was applied along the incision lines. The procedure was completed with the application of appropriate dressings and a medical-grade breast support garment.

Postoperative Evaluation

Patients were evaluated postoperatively at 1, 3, 6, and 12 hours and on postoperative day 1 for NAC circulation and possible complications. Discharge was planned when drainage volumes fell below 25 mL (typically postoperative day 1 or 2), and patients were prescribed antibiotics and anti-inflammatory medications.

At the first-week follow-up, wound sites were re-evaluated, Steri-Strips were reapplied, and wound care instructions were provided. Patients were instructed to continue wearing the medical breast support bra until postoperative week 4.

At postoperative week 1 and at months 1, 3, 6, and 12, standardized photographs were taken using a digital camera (Canon EOS 5D Mark II, Canon Inc., Tokyo, Japan).

Statistical Analysis

The data obtained in this study were analyzed using descriptive statistics. For continuous variables, the mean, standard deviation, minimum, and maximum were reported; for categorical variables, frequencies and percentages (%) were presented. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). In addition, an a priori power analysis was performed using PASS software (NCSS, Power Analysis and Sample Size, Version 11.0, Utah, USA), based on the complication rates reported in the literature, to determine the required sample size (2). To assess a reduction in complication rates from 15% ($P_0 = 0.15$) to 5% ($P_1 = 0.05$), a two-sided binomial test at the 0.05 significance level ($\alpha = 0.05$) was used. The required sample size was calculated to be 75 breasts (corresponding to 38 patients) to achieve 83% statistical power. However, due to the retrospective design and strict inclusion criteria, the final sample consisted of 22 patients (44 breasts), which limited the study to descriptive analysis. There were no missing data, and no patients were lost to follow-up during the study period.

Results

As the sample size was limited, only descriptive statistics were presented; no comparative or inferential analyses were performed. The mean age of the 22 female patients included in the study was 39 years (range: 24–56 years), and the mean body mass index was 30.8 kg/m² (range: 23.4–36.2). Two patients (9.1%) had type 2 diabetes, and three (13.6%) were active smokers. The mean follow-up period was 1.2 years, with the shortest follow-up being 6 months and the longest being 24 months.

In all cases, the superior perforator was successfully identified preoperatively using handheld Doppler ultrasonography. The superior perforator was identified in all patients within 3.0±0.4 minutes. The perforators were typically located at the level of the second intercostal space and approximately 1 cm below the skin surface. Video 1 and Video 2 show sagittal and transverse sectional views and power Doppler imaging of the superior perforator. In all patients, the superomedial pedicle was shaped to include this perforator. Surgical excisions were performed using the inverted-T resection pattern in all cases.

The mean weight of excised tissue was 512 g for the right breast (range: 312–1220 g) and 503 g for the left breast (range: 323–1118 g). The mean operative time was 138±16 minutes. Pedicle rotation was performed while preserving vascular integrity in all cases.

No partial or total NAC necrosis was observed in any patient (Figure 2). Major complications such as hematoma, seroma, or infection were not observed. Minor complications included dehiscence at the junction of the T-incision in four patients (18.1%), hypertrophic scarring in one patient (4.5%), and transient areolar hypoesthesia resolving within three months in three patients (13.6%).

In follow-up evaluations conducted through physical examination and standardized photography, all patients reported high levels of satisfaction both aesthetically and functionally (Figure 3). Demographic, surgical, and postoperative data are presented in Table 1.

Discussion and Conclusion

In this series of 22 patients, Doppler-guided identification of the superior perforator enabled consistent inclusion of a reliable vascular source, with no cases of NAC necrosis and a low overall complication rate. Reduction mammaplasty is an effective surgical intervention that addresses not only aesthetic concerns but also functional problems such as neck and shoulder pain, intertrigo, physical limitations, and social discomfort (7). The primary determinant of surgical success is the ability to safely transfer the NAC to its new anatomical position while preserving circulatory integrity. In this context, the type of pedicle selected plays a critical role in both vascular safety and aesthetic outcomes.

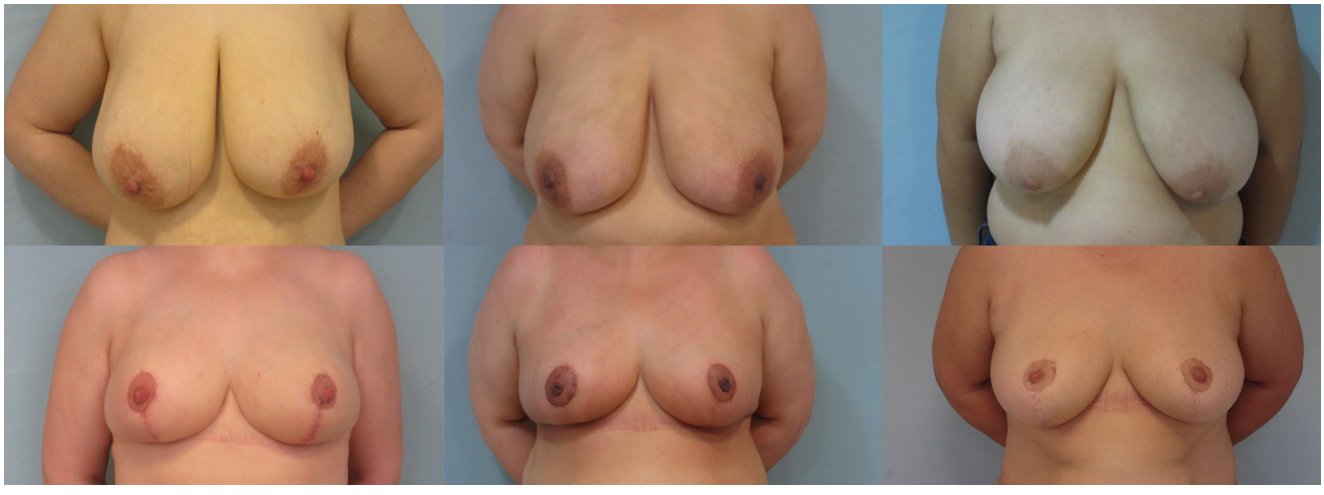

Figure 2. Preoperative and postoperative images (1st month, 6th month, and 1st year from left to right) of three different patients. Neither partial nor total nipple-areola complex necrosis was observed in any patient

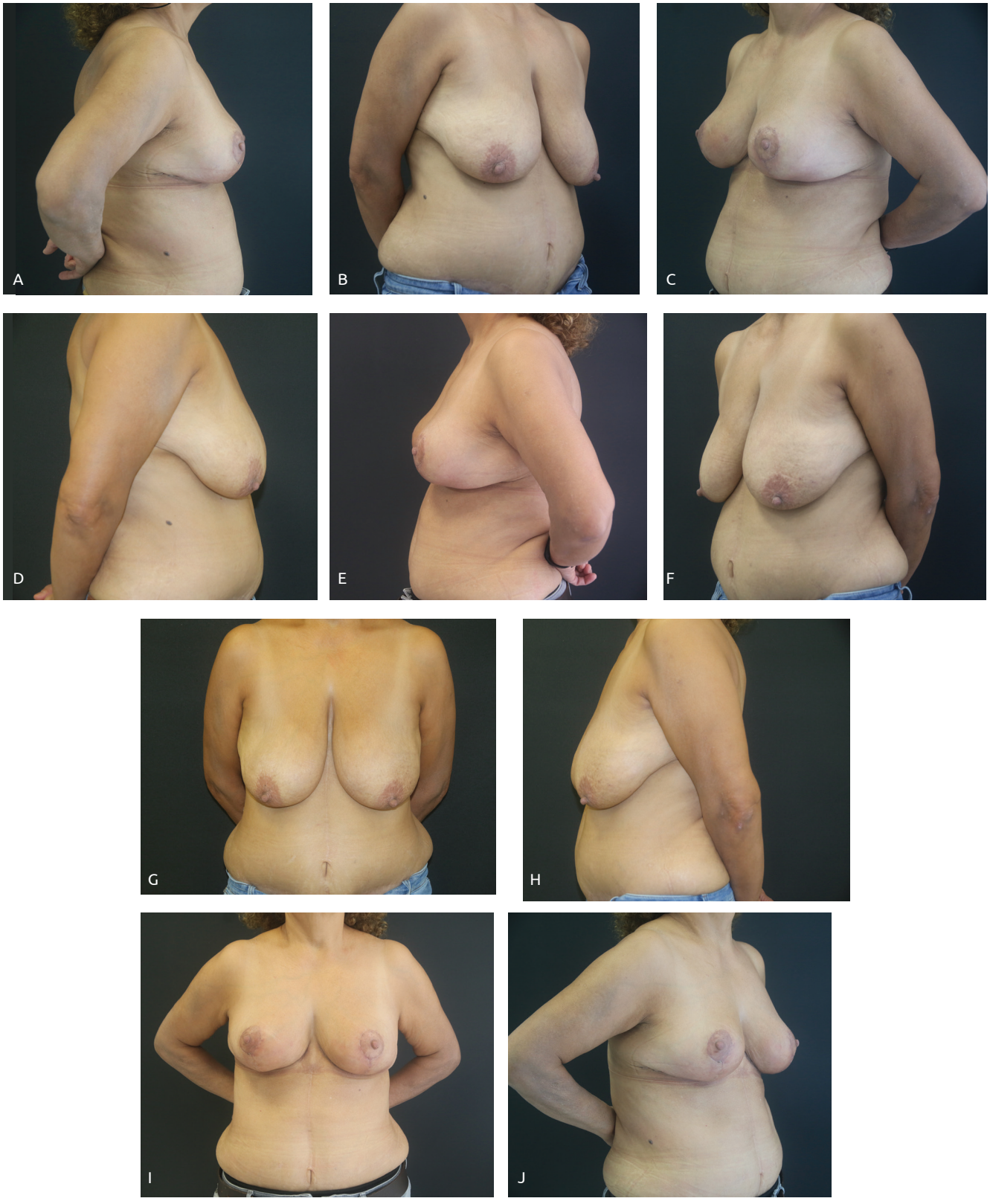

Figure 3. Preoperative and postoperative 1st month views of a 43-year-old patient presenting with macromastia, who underwent superomedial pedicle inverted-T scar reduction mammaplasty after localization of the superior perforator by ultrasound. No major complications, including partial or total nipple-areola complex necrosis, hematoma, seroma, or infection, were observed, A: Preoperative frontal view, B: Preoperative right oblique view, C: Preoperative right lateral view, D: Preoperative left oblique view, E: Preoperative left lateral view, F: Postoperative 1st month frontal view, G: Postoperative 1st month right oblique view, H: Postoperative 1st month right lateral view, I: Postoperative 1st month left oblique view, J: Postoperative 1st month left lateral view

Table 1. Demographic, surgical and postoperative data

Variable	Mean ± standard deviation or n (%)
Age (years)	39±17
Body mass index (kg/m²)	30.8±7.4
Patients with type 2 diabetes	2 (9.1%)
Active smokers	3 (13.6%)
Follow-up period (months)	6–24
Superior perforator detection time (minutes)	3.0±0.4
Excised tissue (right breast, g)	512±205
Excised tissue (left breast, g)	503±198
Operative time (minutes)	138±16
Nipple-areola complex necrosis	0
Hematoma, seroma, infection	0
Minor complications	Dehiscence: 4 (18.1%), hypertrophic scar: 1 (4.5%), areolar hypoesthesia: 3 (13.6%)

The main pedicle techniques described in the literature include the inferior, superior, medial, central, lateral, and superomedial pedicles (3, 4). Each technique is vascularized by different arterial sources and varies in surgical applicability, rotational flexibility, aesthetic projection, and risk of complications. The inferior pedicle is supplied by anterior perforating branches of the internal thoracic artery and superficial branches of the lateral thoracic artery. It is technically straightforward but has been associated with long-term disadvantages such as "bottoming-out" deformity (8). The central pedicle directly supplies the NAC through internal thoracic perforators within the breast parenchyma (9). However, because of the intraparenchymal location of the perforators, it carries certain risks during breast reduction surgery (10).

The superior pedicle is nourished by internal thoracic artery perforators emerging at the level of the second intercostal space. Because of its more superficial course, it can be easily identified using Doppler ultrasonography and safely used in small- to moderately sized breasts owing to its short rotation distance (3). The medial pedicle is usually supplied by branches of the internal thoracic artery arising at the level of the third intercostal space. Advantages of this pedicle include preservation of the breast ducts, preservation of breast sensation, and the potential to provide aesthetically pleasing medial breast fullness (3).

However, when planned alone, the medial pedicle may limit vascular safety, particularly in large reductions or when long rotational distances are required. Insufficient perfusion at the distal tip of the pedicle may lead to venous congestion or necrosis of the NAC.

The superomedial pedicle offers a significant advantage in overcoming the limitations of the medial pedicle. The combined use of medial and superior perforators expands the vascular base of the pedicle. This dual perfusion plays a critical role, particularly in large-volume breasts and cases of advanced ptosis. Moreover, support from the superior perforator to the upper pole helps maintain breast projection and enhances its aesthetic fullness over time (11). When ultrasonographic planning is added to the surgery, preoperative mapping of the superior perforator further increases the safety of this modification of the medial pedicle. Moreover, by allowing full-thickness rotation without thinning, the superomedial pedicle preserves dermoglandular integrity and supports both arterial inflow and venous drainage via internal thoracic perforators and the dermal plexus, thereby reducing the risk of NAC necrosis and potentially shortening operative time compared to other pedicle techniques (12).

The clinical utility of Doppler ultrasonography becomes particularly evident in cases where perfusion may be uncertain. In such scenarios, relying solely on anatomical landmarks may not account for patient-specific variations. Preoperative Doppler mapping enables the surgeon to identify the dominant perforator, allowing for more confident pedicle planning and potentially reducing intraoperative uncertainty. This approach may be especially helpful in large reductions where the nipple–areola complex must be transposed over longer distances.

In this study, an individualized superomedial pedicle was created by incorporating the superior perforator into the medial pedicle using Doppler ultrasonography. The reduction in complication rates through Doppler-guided planning has been emphasized in many studies. For instance, Elmelegy et al. (4) reported no NAC necrosis among 105 cases in which dominant perforators were identified by Doppler ultrasonography. Similarly, Başaran et al. (13) utilized Doppler-guided pedicle planning in 16 patients with gigantomastia and successfully maintained low complication rates despite high excision volumes.

The relatively constant, superficial anatomical position of the superior perforators enables rapid mapping with power Doppler. In this study, the superior perforators were successfully identified in an average time of 3.0±0.4 minutes. The identified perforators were included in the surgical planning for all cases. This approach enabled harmonization between the preoperative and intraoperative vascular mapping, thereby providing a safe zone for pedicle selection and rotation planning (5, 6, 12).

The use of preoperative Doppler in this study enabled more precise identification of dominant perforators and minimized intraoperative uncertainty regarding vascular supply. Individualizing pedicle selection based on confirmed perforator anatomy yielded a reproducible, patient-centered surgical approach that enhances vascular safety. The clinical outcomes of this approach were also highly favorable. In our study, no major complications such as NAC necrosis, seroma, hematoma,

or infection were observed in any patient. Only a limited number of patients experienced transient areolar hypoesthesia, T-incision dehiscence, and hypertrophic scarring. Notably, three of the four cases of T-incision dehiscence occurred in active smokers. This once again demonstrates the adverse effects of smoking on wound healing (14). In the series of 938 cases reported by Bauermeister et al. (2), a 16% complication rate associated with the superomedial pedicle was noted; however, the vast majority of complications were minor, and no NAC necrosis was observed. When evaluated alongside these findings, the low complication rates observed in our study further support the reliability of Doppler-guided pedicle planning.

Study Limitation

However, certain limitations of the study should be acknowledged. Although a priori power analysis was conducted to determine the appropriate sample size, the final number of participants remained below the target due to the retrospective design. As a result, statistical analysis was limited to descriptive measures. Aesthetic outcomes were evaluated only through physical examination and standardized photography; validated patient-reported outcome instruments, such as the BREAST-Q, were not used. Therefore, the absence of objective patient-reported data represents a notable limitation. Additionally, the lack of a comparison group precluded direct comparison with other pedicle techniques. Although a notable association was observed between active smoking and T-incision dehiscence, no statistical analysis could be performed due to the small sample size. Likewise, potential associations between diabetes and minor complications were not assessed. To address these limitations, prospective studies with larger cohorts should incorporate comparison groups, validated patient-reported outcome measures, and objective perfusion imaging techniques such as indocyanine green angiography.

The integration of the superior perforator, identified preoperatively with Doppler ultrasonography, enables a vascularly reliable and technically feasible superomedial pedicle design for reduction mammaplasty. Although descriptive, this study provides preliminary evidence that preoperative Doppler identification of the superior perforator allows for individualized pedicle planning and may improve vascular safety. Larger prospective comparative studies are warranted to validate these findings and to clarify their potential impact on complication rates.

Video 1. Sagittal and transverse localization of the superior perforator with power Doppler imaging

Video 2. Oblique course of the superior perforator and power Doppler imaging

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Yeditepe University Non-Interventional Clinical Research Institutional Review Board on September 9, 2025. The approval was documented under the application number 2025-08-Y0918.

Informed Consent: Informed consent was obtained from all participating patients.

Footnotes

Authorship Contributions

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

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

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Original Article

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Impact of Socioeconomic Factors on Surgical Approach and Outcomes in Young Women with Breast Cancer

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ABSTRACT

Objective: Breast cancer treatment disparities persist and include surgical approach. This study evaluated the association of race, ethnicity, employment, and insurance status with the selected surgical approach and the effect on recurrence-free survival (RFS) and overall survival (OS) in young women with breast cancer.

Materials and Methods: A retrospective review of a prospectively maintained institutional database (Sandra Levine Young Women's Breast Cancer Program) identified women aged ≤40 years diagnosed with non-metastatic breast cancer from 2010–2019 who underwent surgery. Multivariable logistic regression models and Cox proportional-hazards models were fitted.

Results: Of the 700 women, 4% were Asian, 26% Black, and 69% White. Reported ethnicity was: 67% non-Hispanic, 5% Hispanic, and 27% unknown or unreported. Clinical stage distribution was 86% early stage (0–II) and 11% stage III. Among patients with invasive cancer (n = 624), 51% were hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative, 21% were HR-negative/HER2-negative, 20% were HR-positive/HER2-positive, and 8% were HR-negative/HER2-positive. Local, regional, or distant recurrence occurred in 13.1% of patients who underwent lumpectomy and in 16.4% of those who underwent mastectomy (p = 0.22). Death occurred in 6.5% of patients after lumpectomy and in 10.7% of patients after mastectomy (p = 0.07). Black women were more likely to undergo lumpectomy than White women [odds ratio = 2.26; 95% confidence interval (CI), 1.49–3.43; p<0.001; adjusted for ethnicity]. Private insurance was associated with improved OS (hazard ratio = 2.47; 95% CI, 1.26–4.84; p = 0.003) and RFS (hazard ratio = 2.02; 95% CI, 1.28–3.20; p = 0.010) compared with Medicaid. No association was noted between employment status and surgical approach, OS, or RFS.

Conclusion: Young Black women were more likely than White women to elect the less-invasive surgery (lumpectomy). Private insurance was associated with better OS and RFS.

Keywords: Breast cancer; disparities; lumpectomy; mastectomy; surgical approach; young women

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Key Points

- Young Black women with breast cancer were more likely to elect less invasive surgery, lumpectomy, compared to young White women.
- Surgical approach did not impact overall survival or recurrence rates.
- Private insurance was associated with increased overall and recurrence-free survival.

Introduction

Social determinants of health are increasingly being studied to understand their impact on breast cancer outcomes. However, most studies have included postmenopausal women. It is unclear whether racial and socioeconomic disparities in breast cancer diagnosis, stage at presentation, and outcomes persist among women aged 40 years and younger. Social determinants of health include race, ethnicity, education, employment status, income, access to transportation, and insurance status. There are known racial and socioeconomic disparities in diagnosis, stage at presentation, and outcomes among patients with breast cancer (1). Specifically, existing literature indicates that Black and Hispanic patients are more likely than White patients to present with late-stage disease, in part because of limited access to

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healthcare, inadequate insurance coverage for screening tests, and delays in diagnosis (2, 3). Black patients with breast cancer also have higher mortality, which has recently been confirmed in two large national database studies (4, 5). Additional studies indicate that having Medicaid or being uninsured, and residing in a rural location, are associated with increased mortality, independent of race (6-8). However, studies evaluating the impact of socioeconomic factors on breast cancer outcomes have primarily included postmenopausal women.

The data on choice of surgical approach by race have been mixed. Some data suggest that mastectomy rates are higher among Black women, while other data suggest that Black women are more likely to undergo breast-conserving therapy. This variability has been suggested to be related to socioeconomic status, while others report it to be independent (9-12). Specifically, in North Carolina, home to our institution, the rate of mastectomy usage has been declining, a trend that continues even among Black women and women of all races residing in rural areas (13).

We aimed to evaluate the relationships of race and ethnicity, employment status, and insurance status with surgical approach among young women with breast cancer. The secondary analysis aimed to determine recurrence-free survival (RFS) and overall survival (OS) by race, stratified by surgical approach.

Materials and Methods

Data Source

Following institutional review board approval from the Wake Forest School of Medicine, we retrospectively reviewed the Sandra Levine Young Women's Breast Cancer Program's prospectively maintained database at Atrium Health Levine Cancer. Women aged ≤40 years who were diagnosed with ductal carcinoma *in situ* (DCIS) or invasive breast cancer between 2010 and 2019 and who underwent lumpectomy or mastectomy were included. Patients with metastatic disease, those with a concurrent cancer diagnosis, and those with missing treatment and/or follow-up data were excluded. Data pertaining to patient demographics, clinical characteristics, surgical approach, and oncologic outcomes were collected. Insurance status was categorized as private, Medicaid, Medicare, or self-pay/uninsured. Employment was categorized as employed (part-time or full-time), unemployed, or unknown. Receptor status groups were categorized as hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-positive (HR+/HER2+), HR-positive and HER2-negative (HR+/HER2-), HR-negative and HER2-positive (HR-/HER2+), and HR-negative and HER2-negative (HR-/HER2-; triple-negative). OS was calculated as the time from diagnosis to death from any cause, or was censored at last follow-up. RFS was calculated as the time from diagnosis to recurrence or death, or was censored at the last assessment date.

Statistical Analysis

Patients' demographic and clinical characteristics were compared between lumpectomy and mastectomy cohorts using descriptive statistics. For continuous variables, means and standard deviations were reported, while categorical variables were reported as frequencies and percentages. Corresponding *p*-values were calculated using the chi-square or Fisher's exact test for categorical variables and the two-sample t-test for continuous variables. Univariate and multivariable logistic regression analyses were performed to evaluate whether race, ethnicity, insurance type, and employment status were associated with the surgical approach. The Kaplan-Meier method was used to estimate OS and RFS across groups. Differences among primary groups of interest, including race, insurance type, and employment status, were assessed using log-rank tests. Cox proportional hazards models were used to analyze the associations between outcomes (OS and RFS) and the primary factors of interest: race, insurance type, and employment status. Additional risk factors for these outcomes were evaluated using stepwise model selection procedures in which all covariates were first included in univariate analyses, and those with $p<0.10$ were entered into the multivariable model. Covariates with a *p*-value <0.1 were retained in the base model. Race, insurance status, and employment status were then added to this base model to develop the final model. All statistical tests were two-sided, and a *p*-value <0.05 was considered statistically significant.

Results

Demographics and Clinical Characteristics

A total of 1,084 female patients diagnosed with DCIS or invasive breast cancer were identified in our Sandra Levine Young Women's Program breast cancer database. After excluding patients older than 40 years or with missing date of diagnosis, metastatic disease at presentation, a history of other cancer, or missing treatment data, 700 patients were included in the analyses (Figure 1). Of these women, 69% (*n* = 480) were White, 26% (*n* = 184) were Black, 4% (*n* = 28) were Asian, 1% (*n* = 7) were American Indian or Alaska Native, and 0.1% (*n* = 1) were Native Hawaiian or Pacific Islander (Table 1). Reported ethnicity was 67% (*n* = 472) non-Hispanic, 5% (*n* = 37) Hispanic, and 27% (*n* = 191) unknown or unreported. Disease stage at presentation was: stage II, 44% (*n* = 311); stage I, 28% (*n* = 198); stage 0, 14% (*n* = 96); stage III, 11% (*n* = 76); and unknown, 3% (*n* = 19). Of patients with invasive cancer (*n* = 624), 51% (*n* = 317) were HR+/HER2-, 21% (*n* = 133) HR-/HER2-, 20% (*n* = 126) HR+/HER2+, and 8% (*n* = 48) HR-/HER2+.

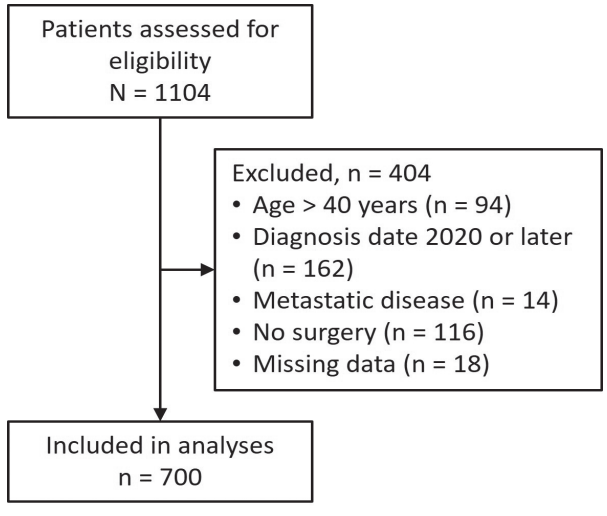

Figure 1. Study diagram

Table 1. Patient demographics and clinical characteristics by surgical approach

Characteristic	Total (*n* = 700)	Lumpectomy (*n* = 260)	Mastectomy (*n* = 440)	*p*-value
Age, years (mean ± SD)	36±3.8	36±4.0	36±3.7	0.10
Race, n (%)				<0.001
American Indian or Alaska Native	7 (1.0)	3 (1.2)	4 (0.9)	
Asian	28 (4.0)	7 (2.7)	21 (4.8)	
Black or African American	184 (26.3)	93 (35.8)	91 (20.7)	
Native Hawaiian or Pacific Islander	1 (0.1)	1 (0.4)	0 (0)	
White or Caucasian	480 (68.6)	156 (60)	324 (73.6)	
Ethnicity, n (%)				0.58
Hispanic or Latino	37 (5.3)	15 (5.8)	22 (5.0)	
Non-Hispanic or non-Latino	472 (67.4)	170 (65.4)	302 (68.6)	
Unknown or not reported	191 (27.3)	75 (28.8)	116 (26.4)	
Insurance status, n (%)				0.47
Private	544 (77.7)	197 (75.8)	347 (78.9)	
Medicare	11 (1.6)	4 (1.5)	7 (1.6)	
Medicaid	93 (13.3)	35 (13.5)	58 (13.2)	
Self-pay or uninsured	46 (6.6)	22 (8.5)	24 (5.5)	
Unknown	6 (0.86)	2 (0.77)	4 (0.91)	
Employment status, n (%)				0.82
Unemployed	140 (20.0)	49 (18.8)	91 (20.7)	
Employed†	543 (77.6)	205 (78.8)	338 (76.8)	
Unknown	17 (2.4)	6 (2.3)	11 (2.5)	
Clinical TNM stage, n (%)				<0.001
Stage 0	96 (13.7)	40 (15.4)	56 (12.7)	
Stage I	198 (28.3)	78 (30.0)	120 (27.2)	
Stage II	311 (44.4)	120 (46.2)	191 (43.4)	
Stage III	76 (10.9)	12 (4.6)	64 (14.5)	
Unknown	19 (2.7)	10 (3.8)	9 (2.0)	
Invasive status, n (%)				0.66
Non-invasive (DCIS)	76 (10.9)	30 (11.5)	46 (10.5)	
Invasive	624 (89.1)	230 (88.5)	394 (89.5)	
Receptor status*, n (%)				0.68
HR+/HER2+	126 (20.2)	43 (18.7)	83 (21.1)	
HR+/HER2-	317(50.8)	114 (49.6)	203 (51.5)	
HR-/HER2+	48 (7.7)	20 (8.7)	28 (7.1)	
HR-/HER2-	133 (21.3)	53 (23.0)	80 (20.3)	
Recurrence status, n (%)				0.22
Yes	106 (15.1)	34 (13.1)	72 (16.4)	
No	580 (82.9)	222 (85.4)	358 (81.4)	
Unknown or not reported	14 (2.00)	4 (1.5)	10 (2.3)	
Survival status, n (%)				0.07
Alive	636 (90.9)	243 (93.5)	393 (89.3)	
Dead	64 (9.14)	17 (6.5)	47 (10.7)	

†: Part-time and full-time employment

*: Receptor status reported for those with invasive disease (*n* = 624)

DCIS: Ductal carcinoma *in situ*; HR: Hormone receptor; SD: Standard deviation; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor

Regarding insurance status, 78% (n = 544) had private insurance, 2% (n = 11) had Medicare, 13% (n = 93) had Medicaid, and 7% (n = 46) were uninsured. The majority of both Black (66%, 121 of 184) and White (82%, 392 of 480) women had private insurance, while 23% (42 of 184) of Black women and 10% (48 of 480) of White women had Medicaid (Table 2). When employment status was examined, 78% (n = 543) were employed, 20% (n = 140) were not employed, and 2% (n = 17) had an unknown employment status. A majority of both Black and White women were employed: 82% (151 of 184) and 77% (368 of 480), respectively.

Surgical Approach

Of the 700 young women, 37% (n = 260) underwent lumpectomy while 63% (n = 440) underwent mastectomy. There was no significant difference in recurrence rates between the surgical approach groups [13% (n = 34) for lumpectomy vs 16% (n = 72) for mastectomy; p = 0.22]. Among the 106 participants who experienced a recurrence, 25% (n = 27) were local, 10% (n = 11) were regional, 58% (n = 61) were distant, and 7% (n = 7) were unspecified. No significant difference in recurrence location was observed by surgical approach (p = 0.21). There was no significant difference in death rates between the surgical approach groups [6.5% (n = 17) for lumpectomy *vs.* 10.7% (n = 47) for mastectomy; p = 0.07].

In multivariable logistic regression analysis, young Black women were significantly more likely to undergo lumpectomy than young White women [odds ratio (OR) = 2.26; 95% confidence interval (CI), 1.49–3.43; p<0.001; Figure 2], a finding that was consistent across all receptor subtypes. There was no statistically significant association between surgical approach and ethnicity (OR = 1.49; 95% CI, 0.74–2.99; p = 0.262).

Table 2. Insurance type and employment status by race

Characteristic	Race			*p*-value
	Black (n = 183)	White (n = 476)	Other (n = 35)	
Insurance type, n (%)				<0.001
Private	121 (66.1)	392 (82.4)	31 (88.6)	
Medicare	6 (3.3)	5 (1.1)	0 (0.0)	
Medicaid	42 (23.0)	48 (10.1)	3 (8.6)	
Self-pay/uninsured	14 (7.7)	31 (6.5)	1 (2.9)	
Employment status, n (%)				0.10
Unemployed	27 (14.7)	102 (21.3)	11 (30.6)	
Employed	151 (82.1)	368 (76.7)	24 (66.7)	
Unknown	6 (3.3)	10 (2.1)	1 (2.8)	

Rounded percentages may not sum to 100

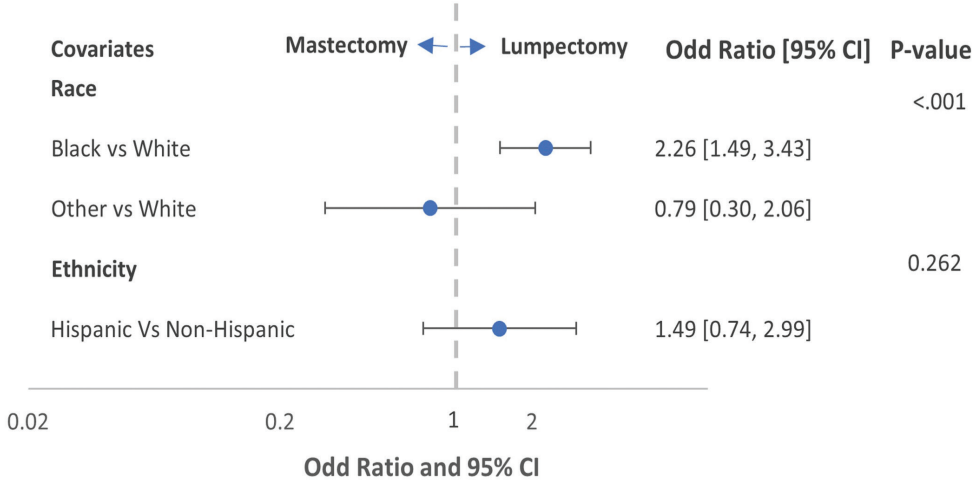

Figure 2. Forest plot depicts odd ratios, along with corresponding 95% confidence intervals (CIs) and p-values, categorized by racial and ethnic subgroups

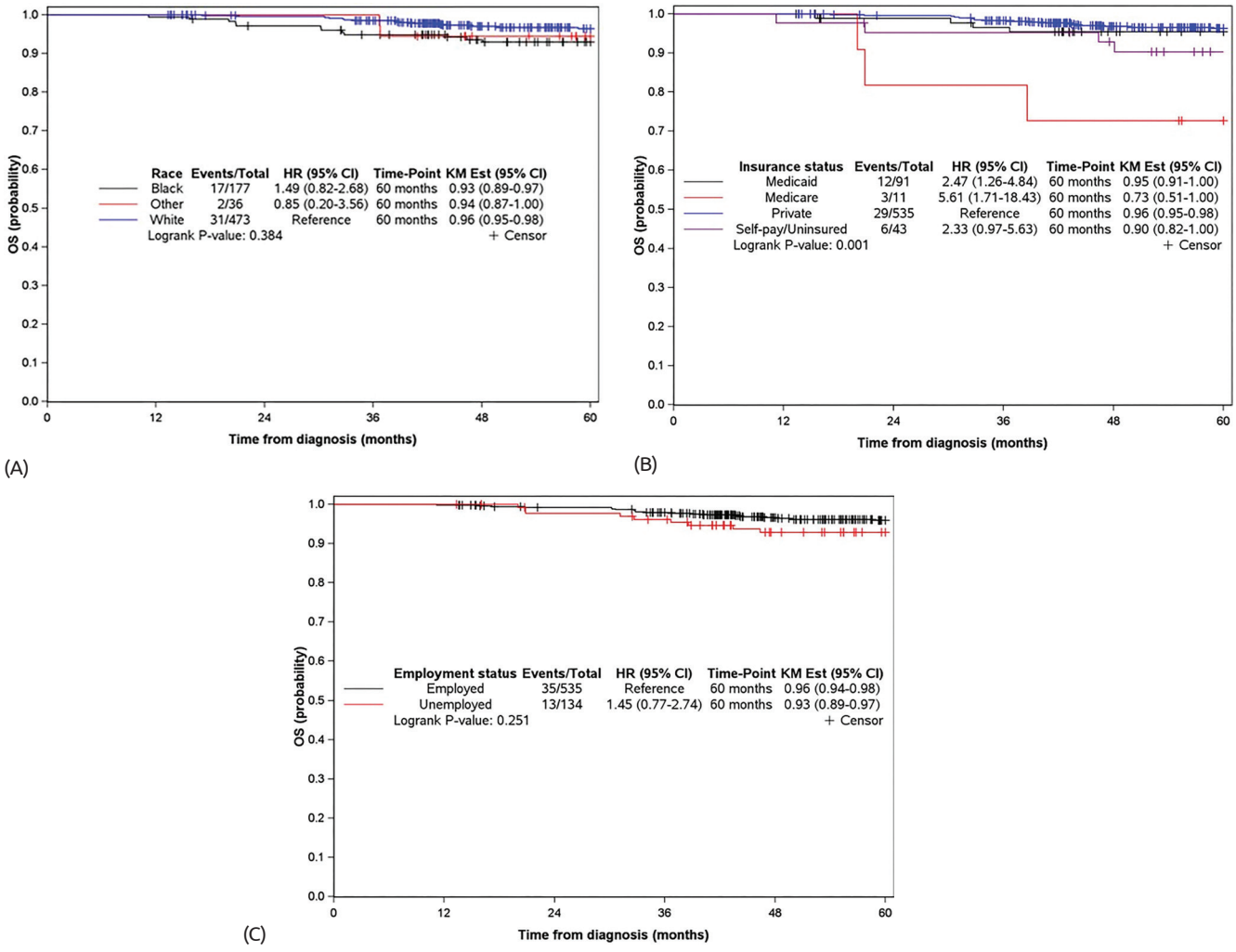

Figure 3. Kaplan-Meier curves of overall survival by race (A), insurance status (B), and employment status (C)

The effect of health insurance status on surgical approach was not significant in univariate analysis (p = 0.49) or in multivariable interaction analysis (p = 0.73); these analyses were performed to control for previously reported significant effects of race on surgery type. Similarly, there was no significant effect of insurance status or ethnicity on surgical choice (p = 0.57). There was no difference in surgical approach between employed and not employed (OR = 0.89; 95% CI, 0.60–1.31; p = 0.55). This was true across all races (p = 0.50) and ethnicities (p = 0.14).

Overall Survival

Kaplan-Meier curves demonstrate no difference in OS by race (Figure 3A). OS was significantly worse in patients with Medicaid or Medicare than in patients with private insurance (Figure 3B). There was no difference in survival by employment status (Figure 3C).

On univariate analysis, there was no significant effect of race on OS (p = 0.39). There were statistically significant differences in OS between Medicaid and private insurance (hazard ratio = 2.47; 95% CI: 1.26–4.84) and between Medicare and private insurance (hazard ratio = 5.61; 95% CI: 1.71–18.4) (overall p = 0.003). There was no significant difference in OS (p = 0.25) based on employment status. Younger women had an increased risk of death [HR per 1-yr increase = 0.92 (95% CI, 0.86–0.98); p = 0.008]; however, there was no significant effect of age decade on OS (p = 0.61). Those with HR-/HER2- receptor status had an increased risk of death compared to those with HR+/Her2- receptor status (hazard ratio = 2.39; 95% CI, 1.24–4.60; p = 0.03). OS differed significantly between clinical stage 0 and clinical stage III (hazard ratio = 0.05; 95% CI, 0.01–0.36; p = 0.001), between clinical stage I and clinical stage III (hazard ratio = 0.21; 95% CI, 0.09–0.48; p = 0.001), and between clinical stage II and clinical stage III (hazard ratio = 0.37; 95% CI, 0.19–0.71; p = 0.001). The final multivariable model included race, insurance status, employment status, age, clinical stage, and receptor status. In multivariable analysis, young women with Medicaid or Medicare had an increased risk of death compared with young women with private insurance (overall p = 0.03) (Figure 4).

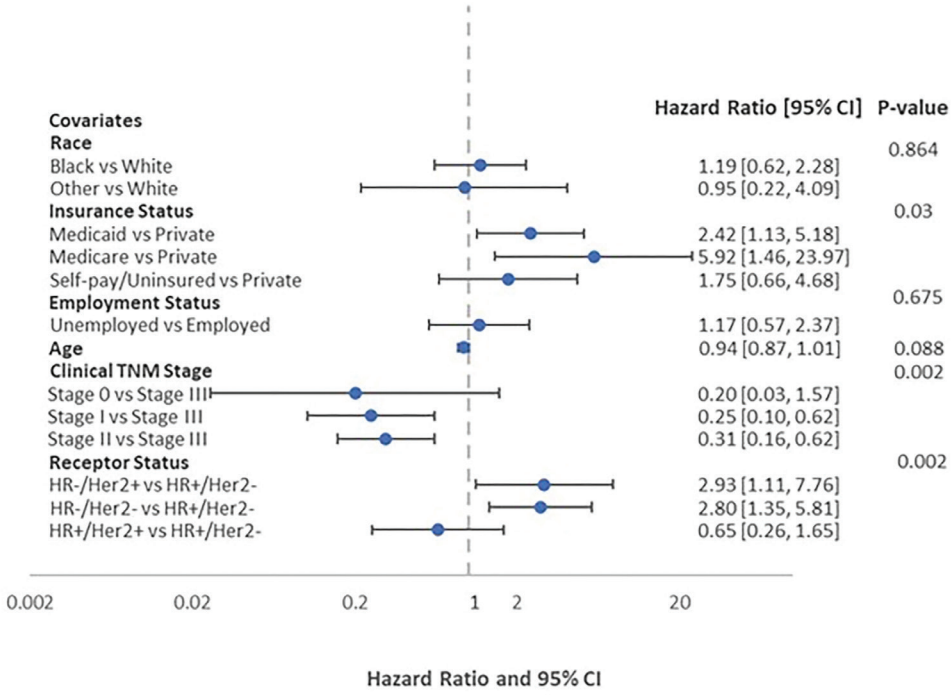

Figure 4. Forest plot depiction of the multivariable model of overall survival

Recurrence-Free Survival

Kaplan-Meier curves show greater RFS in young White patients with breast cancer (p = 0.009; Figure 5A) and in those with private insurance (p = 0.008; Figure 5B). RFS was not significantly associated with employment status (p = 0.35) (Figure 5C). In univariate analysis, young Black women had a significantly increased risk of recurrence compared with young White women (hazard ratio = 1.64; 95% CI, 1.12–2.42; p = 0.01). A statistically significant difference in RFS was observed between Medicaid and private insurance (hazard ratio = 2.02; 95% CI, 1.28–3.20; p = 0.01). There was no significant difference in RFS (p = 0.35) based on employment status. Younger women had an increased risk of recurrence [HR per 1-year increase = 0.94 (95% CI 0.90–0.98); p = 0.006]; however, there was no significant effect of age decade on RFS (p = 0.13). The final multivariable model included race, insurance and employment status, age, diabetes, clinical stage, and receptor status. In multivariable analysis, neither race nor insurance status was associated with an increased risk of recurrence (Figure 6).

Discussion and Conclusion

For young women diagnosed with breast cancer, the choice of surgical procedure is influenced by numerous factors, making it a complex decision. Within our large cohort of young women diagnosed with breast cancer, Black women were more likely to undergo a lumpectomy than White women. However, the surgical approach did not affect OS or recurrence rates. Employment status was associated with neither surgical approach nor survival outcomes. Although health insurance status was not associated with surgical approach among young women with breast cancer, private insurance was associated with improved OS and RFS. A previous study found that 50% of racial disparities could be related to insurance status (14). Other studies have shown that patients with Medicaid and Medicare have worse outcomes—including OS and RFS—than those with private insurance (15-20). These disparities have been linked to factors such as late-stage diagnosis, treatment delays, coverage disruptions, a high comorbidity burden, reduced treatment adherence, and other socioeconomic determinants of health (i.e., transportation, housing, caregiving responsibilities, and work constraints). Unfortunately, many of these individual factors were not captured in our dataset, limiting our ability to further analyze the specific reasons for poor outcomes in our Medicaid and Medicare populations.

Our study has several strengths that support the conclusions drawn. Our Sandra Levine Young Women's Program database represents a large, prospectively maintained source with median follow up of 6.25 years. This allows us to evaluate recurrence and survival over a 5-year follow-up period. This large dataset allows for robust statistical analysis. Additionally, this study builds upon previous work by our group demonstrating no differences in recurrence or survival by surgical approach among young women with breast cancer (15, 16). This report adds to a growing body of literature examining differences in treatment and outcomes of young women with breast cancer.

The study was limited by the retrospective nature of the data review; however, as previously mentioned, the database is prospectively updated and maintained. A large cohort of women (n = 191) had missing ethnicity data, which we presume was due to a lack of clarity in

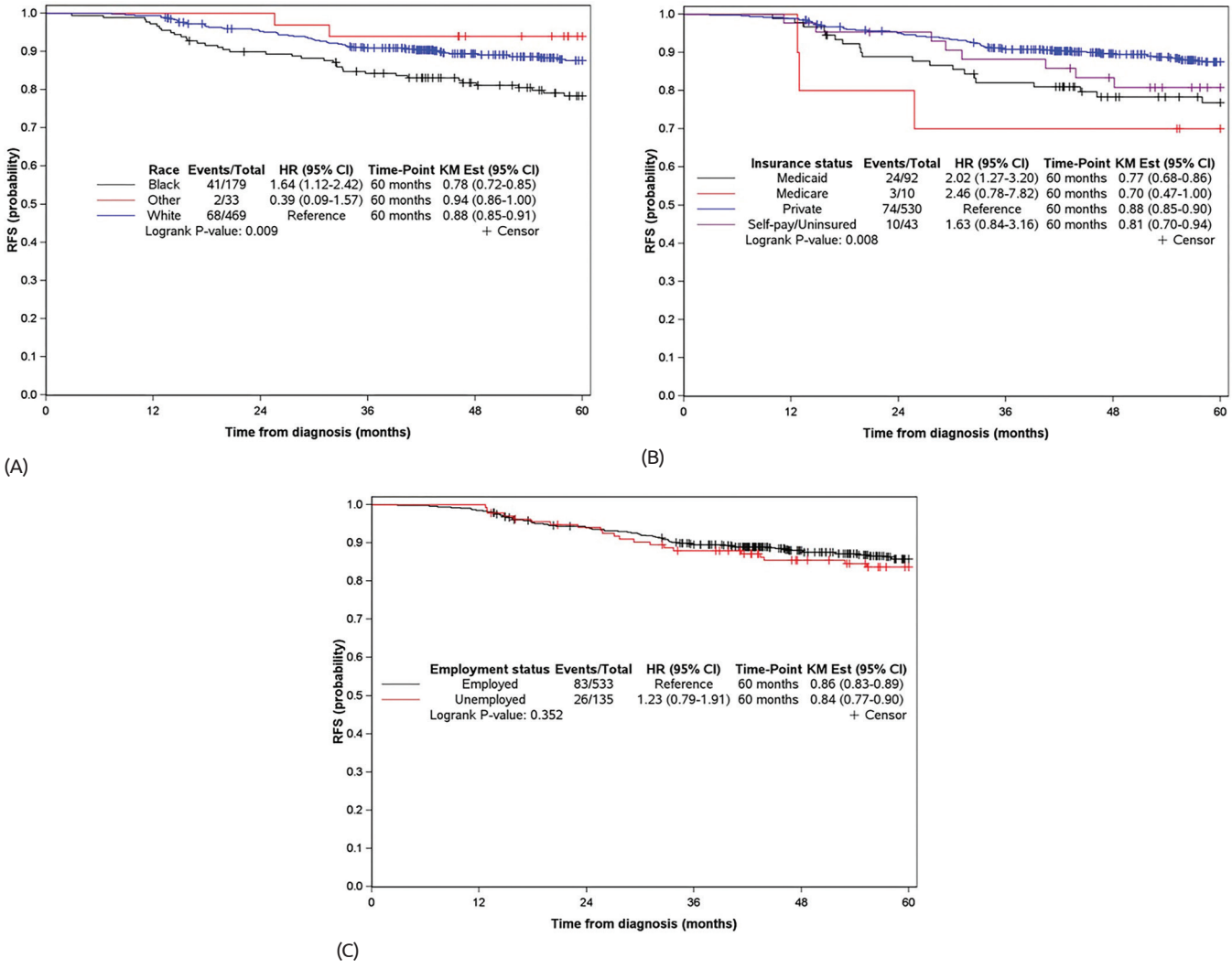

Figure 5. Kaplan-Meier curves of recurrence-free survival by race (A), insurance status (B), and employment status (C)

distinguishing race from ethnicity on intake forms. Despite extensive electronic medical record review, we were unable to accurately identify the ethnicity of these patients. This reflects a broader national challenge faced by many institutions (21-23). In our study, the small number of Hispanic participants and the high proportion of missing ethnicity data limited the interpretability of meaningful analyses of survival outcomes by ethnicity. We have used these findings to strengthen our current intake process by requiring that ethnicity be stated clearly. Unlike race and ethnicity, insurance and employment statuses can change throughout the patient's treatment course. Adjustments to these statuses were not routinely available in the database, with the captured data likely pertaining to the status at the time of diagnosis. Additionally, income and education levels were not captured in the database, and thus may have limited the analysis.

Continued research and emphasis on accurate, inclusive electronic medical record data collection are needed to better understand the effects of patient demographics on surgical approach and subsequent OS and RFS among young women with breast cancer. Hospital systems should prioritize standardized collection of patients' socioeconomic factors, including race, ethnicity, employment, transportation, literacy, education level, insurance, and income. Robust datasets including patients' socioeconomic and demographic factors, disease characteristics, and treatment modalities would provide further insight into the impact of social determinants of health on breast cancer outcomes.

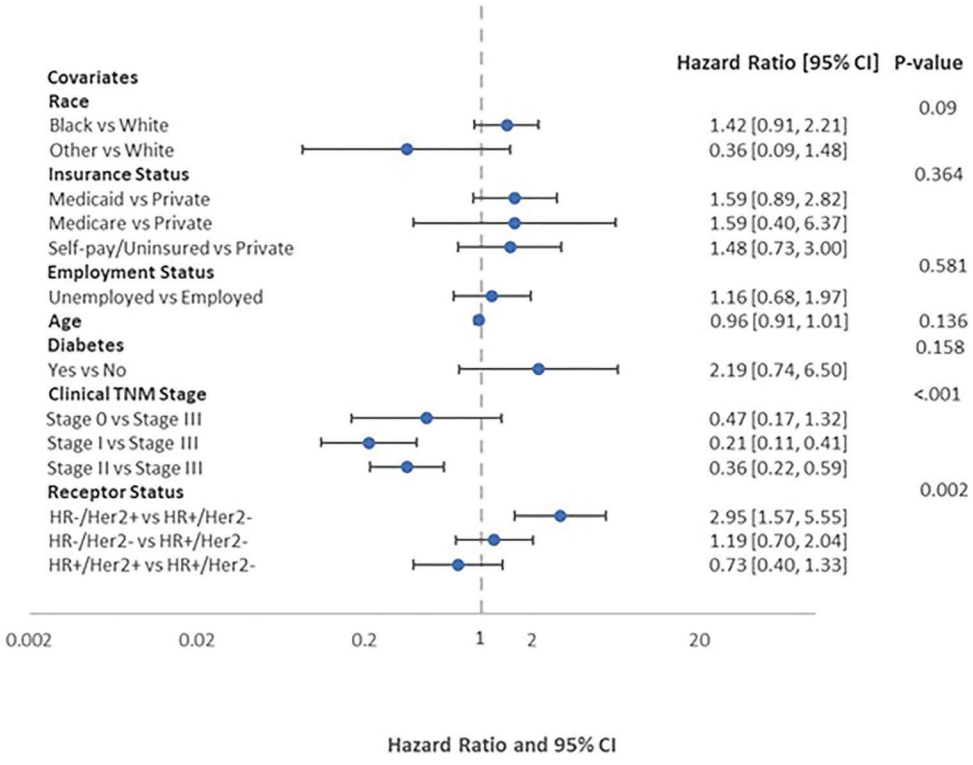

Figure 6. Forest plot depiction of the multivariable model of recurrence-free survival

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Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Not necessary.

Footnotes

Authorship Contributions

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

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

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Original Article

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Financial De-Escalation in T1 Breast Cancers With the Low Magee Equation: An Experience From A Single Institution Without Genomic Testing

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ABSTRACT

Objective: The Oncotype Dx® assay is a validated tool for determining prognosis and predicting benefit from adjuvant systemic chemotherapy in patients with node-negative, early-stage hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER-2)-negative breast cancer. However, genomic testing could incur additional costs, impacting both the patient and the health system. This study aims to explore a subset of patients with a Magee equation score ≤18 who may safely forgo Oncotype Dx® testing.

Materials and Methods: Single institution retrospective analysis of postmenopausal patients with *de novo*, unifocal breast carcinoma that is node negative, Nottingham grade 1, T1, HR positive (>1%), and HER-2 negative. Magee equation 2 (ME2) (https://path.upmc.edu/onlineTools/mageeequations.html) scores were calculated for each patient. The correlation coefficient between Oncotype Dx® and ME2 was determined.

Results: Oncotype Dx® recurrence score, treatment, and outcomes were analyzed in 126 post-menopausal women diagnosed between 2015 and 2020. The mean tumor size was 1.09 cm, and the mean Oncotype DX® score was 12. The average ME2 score was 13.6. The correlation coefficient between Oncotype and ME2 score was statistically significant (r = 0.3442; p<0.0001). At a median follow-up of 5.03 years, there were no local or distant recurrences or breast cancer-related deaths reported in this patient cohort.

Conclusion: This study suggests that omitting the Oncotype Dx® assay may be feasible in postmenopausal women with early breast cancer and an ME2 score ≤18. Using comparable tools, such as ME2, may reduce financial toxicity in this population and overall costs to the system. Larger study recommended.

Keywords: Breast cancer; cost-effectiveness; hormone receptor-positive; Magee equations (TM); Oncotype Dx

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Key Points

- In this retrospective study of 126 postmenopausal women with grade 1, estrogen receptor-positive, human epidermal growth factor receptor-2-negative, node-negative breast cancer, all patients had low-risk Oncotype DX® recurrence scores (<26).
- Magee equation 2 (ME2) scores correlated significantly with Oncotype DX® results (r = 0.34, p<0.0001).
- Findings support the use of ME2 as a cost-effective alternative to Oncotype DX® testing in this low-risk population.

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Introduction

Adjuvant systemic treatment decisions for early-stage, hormone receptor-positive, node-negative breast cancer (BC) have historically been based on clinicopathologic features such as tumor size, tumor grade, axillary lymph node involvement, and hormone receptor status (1). These factors provide prognostic information regarding the risk of BC (1). Most recently, the incorporation of genomic testing, such as the Oncotype DX® 21-gene recurrence score (RS) assay (Genomic Health, Redwood City, CA), has helped guide treatment recommendations by providing predictive information regarding the potential benefit of adjuvant chemotherapy (2). The prospective Trial Assigning Individualized Options for Treatment (TAILORx) demonstrated that postmenopausal women (aged 50 years and older) with hormone receptor-positive, HER2-negative, axillary node-negative BC, and a 21-gene assay score of 25 or lower may safely omit chemotherapy (3).

Economic models have demonstrated the cost-saving benefits of gene expression assays, such as Oncotype DX®, in early-stage BC because they can help identify patients with low genomic risk who may forgo chemotherapy (1). Consequently, Oncotype DX® has become widely used and is frequently requested by providers to assist in adjuvant treatment decision-making. However, the validation and cost-effectiveness analyses of Oncotype DX® have largely been conducted in patient populations with varying clinicopathologic features and age groups (4, 5). Given that certain postmenopausal women with low-risk clinicopathologic features, such as grade 1 tumors, already achieve an excellent five-year survival rate of nearly 99% with endocrine therapy alone, it remains uncertain whether genomic testing is truly necessary for this subset of patients.

Additionally, both internal and external studies have demonstrated that alternative testing methods, such as the Magee equations (ME), can serve as a cost-effective substitute for the Oncotype DX® RS. The ME are mathematical formulas developed to estimate the Oncotype DX® RS using histopathologic features—including tumor grade, mitotic score, and hormone receptor intensity—and to identify patients who may not require genomic testing (6).

There are three ME: ME1 incorporates the Nottingham score, tumor size, and results for estrogen receptor (ER), progesteron receptor (PR), human epidermal growth factor receptor-2 (HER-2), and Ki-67; ME2 excludes Ki-67; and ME3 uses only ER, PR, HER-2, and Ki-67. A prospective validation study found that patients with an ME score below 25 and a mitotic score of 1 did not require Oncotype DX® testing, resulting in an estimated cost savings of $280,000 per 100 clinical requests (7). Therefore, this study aims to identify a subset of patients who may not require Oncotype DX® testing and to evaluate the potential use of the ME within our institutional cohort.

Materials and Methods

This was a single-institution retrospective analysis of postmenopausal patients with early-stage, ER-positive, HER-2-negative, lymph-node-negative BC whose tumors were classified as Nottingham Histologic Overall grade 1. Only patients with primary breast tumors measuring between 5 mm and 20 mm (American Joint Committee on Cancer 7th edition anatomic stage T1b–T1c) and who had an available Oncotype DX® score were included. Patient data were obtained from the University of Pittsburgh Medical Center Cancer Registry. Postmenopausal status was defined in women as those aged 50 years or older, consistent with the criteria used in the TAILORx study (3). Tumor grading was determined by our pathology department using the Nottingham Histologic score.

Clinicopathologic data obtained included tumor size, lymph node status, hormone receptor staining intensity, Nottingham Histologic score, and Ki-67. Patient demographics and clinical outcomes, including current disease status, were also recorded.

The ME was calculated for each patient using ME2 based on pathology report data, including ER/PR percentage, staining intensity, Nottingham score, and tumor size. In our study, not all patients had an available Ki-67 percentage; therefore, only ME2 was used (https://path.upmc.edu/onlineTools/mageeequations.html). A correlation coefficient was then calculated between the Oncotype DX® RSe and the ME2 score for each patient. This retrospective study was approved by the UPMC Central PA Region Institutional Review Board (approval date: 29.06.2022; decision no: 22E025).

Statistical Analysis

Continuous variables, such as follow-up duration (in days), were reported as the median and interquartile range. The linear correlation between the ME2 score and Oncotype DX® RS was assessed using the Pearson correlation coefficient (r). A p-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 126 postmenopausal women seen between 2015 and 2020 met our selection criteria and were included in the analysis. The mean age was 64.4 years (range: 51–85 years). The median tumor size was 1.09 cm (range: 0.2–2 cm). Patient demographics and tumor characteristics are summarized in Table 1.

The majority of patients underwent partial mastectomies (n=109; 87%), and sentinel lymph node biopsy (SLNB) was performed in 120 patients (95%). After a shared discussion with their surgeons, six patients (age range 71–78; RS range 7–18; ME2 range 7.76–13.84) did not undergo SLNB, in accordance with the American Society of Breast Surgeons' Choosing Wisely Campaign.

Thirty-five patients (28%) did not undergo adjuvant radiotherapy. Of those, 17 patients underwent a total mastectomy; therefore, radiation was not indicated. Eighteen patients underwent partial mastectomies but declined adjuvant radiation. Of those, twelve patients were aged 70–85 years (RS range 3–22; ME2 range 5.42–17.61). Six patients (age range 51–69; RS 11–21; ME2 range 11.12–18.41) declined radiation after it was recommended. Adjuvant endocrine therapy was recommended to all the patients. However, 17% of the patients (*n* = 21; age range 55–78; RS 0–25; ME2, 7.86–24.01) either declined endocrine therapy after discussion or discontinued it due to side effects.

The median follow-up period was 5.03 years (range, 3.88–6.82 years), and no local or distant recurrences or BC-related deaths were observed in this patient cohort. The average Oncotype DX® RS was 12.4 [range: 0–25, standard deviation (SD) = 0.41] and no patients had scores greater than 25. The average ME2 score was 13.6 (range: 5.42–24.01, SD: 4.1), and no patients had an ME2 score above 25. Oncotype DX® RS was <18 in 106 (84%) patients, and ME2 was <18 in 114 (90%) patients. A correlation coefficient of 0.3442 was calculated between the Oncotype DX® RS and ME2 scores, with a statistically significant *p*-value of <0.0001 (Figure 1).

Table 1. Patients' clinic-pathologic characteristics, treatment, and recurrence scores

	Tumor ≤5 mm, T1a (*n* = 4) (%)	Tumor >5 -≤10 mm, T1b (*n* = 64) (%)	Tumor >10-≤20 mm, T1c (*n* = 58) (%)	Recurrence score ≤18 (%)	ME2 score ≤18 (%)
Age (years)	64.3	64.5	64.2		
(Average, range)	(58-69)	(53-78)	(51-85)		
Tumor size average (mm)	5	7.9	14.5		
(± standard)	0	0.16	0.31		
(Range)	(5 to 5)	(5 to 11)	(10 to 20)		
Estrogen receptor status					
Positive	4 (100)	64 (100)	58 (100)		
ER H score average	293	281	278		
Progesterone receptor status					
Positive	4 (100)	61 (96)	56 (97)		
Negative (<1%)	0 (0)	3 (4)	2 (3)		
PR H score average	105	196	278		
Histologic features					
Presence of LVI	0	1 (1)	0		
Presence of PNI	0	0	5 (8)		
Partial mastectomy	4 (100)	53 (83)	52 (90)	92 (84)	99 (87)
Mastectomy	0 (0)	11 (17)	6 (10)	17 (16)	15 (13)
Sentinel lymph node biopsy					
Yes	4 (100)	59 (92)	57 (98)	100 (94)	108 (95)
Omitted	0 (0)	5 (8)	1 (2)	6 (6)	6 (5)
Radiation					
Whole breast	4 (100)	39 (61)	44 (76)	74 (70)	78 (68)
Partial breast	0 (0)	3 (5)	1 (2)	4 (4)	3 (3)
Omitted	0 (0)	22 (34)	13 (22)	28 (26)	33 (29)
Endocrine therapy					
Yes	3 (75)	48 (75)	54 (93)	93 (88)	99 (87)
Omitted	1 (25)	16 (25)	4 (7)	13 (12)	15 (13)

ME2: Magee equation 2; LVI: Lymphovascular invasion; PNI: Perineural invasion; ER: Estrogen receptor; PR: Progesteron receptor

Discussion and Conclusion

Treatment decisions for early-stage, hormone receptor-positive, node-negative BCs have largely relied on the Oncotype DX® RS assay. However, our results suggest that the ME2 may serve as an effective alternative for grade 1 tumors, in which the average Oncotype DX® RS was 12 and the highest RS score in our cohort remained below 26. Our findings demonstrated a statistically significant correlation between a low Oncotype DX® RS and the ME2, although the magnitude of the correlation was modest.

Previous studies have validated the relationship between the ME and the Oncotype DX® RS assay. The original ME was first tested in 2006 in 42 cases with available Oncotype DX® RS results and found to correlate with tumor nuclear grade, mitotic activity, HER2 status, ER, and PR scores (6). Subsequent studies, conducted between 2004 and 2009, further refined the ME using additional cases and ultimately validated their predictive accuracy (6). While the Oncotype DX® RS assay remains a valuable tool for guiding adjuvant chemotherapy decisions, its high cost and overlap with the ME may limit its role in treatment decisions for low-grade BC (8). As our study demonstrates, ME may allow clinicians to omit Oncotype DX® testing, providing a more cost-effective approach to treatment decision-making for grade 1 tumors.

According to Bhargava et al. (7), Oncotype DX® RS testing can be omitted when ME scores are below 18 or above 31. For scores between 18 and 25, testing can be avoided if the mitotic score is 1 because the expected RS would be less than 25. In our cohort, all patients had a mitotic score of 1, and none had an RS above 25, further supporting the omission of Oncotype DX® testing in these patients. The correlation coefficient between Oncotype DX and ME was $r = 0.3442$ ($p<0.0001$), indicating statistical significance.

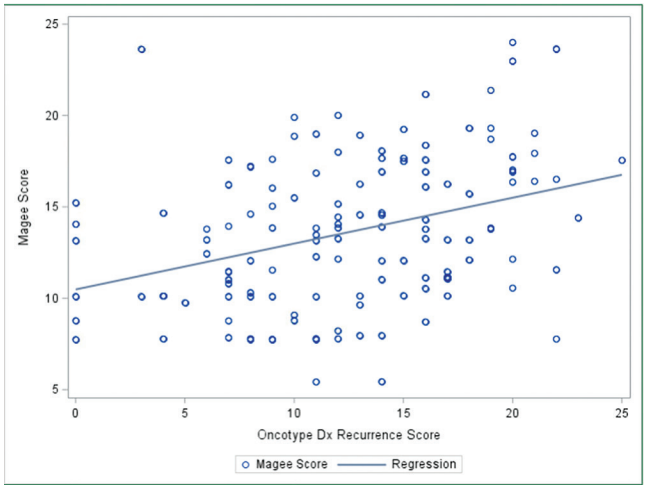

Figure 1. Correlation between Magee equation 2 and Oncotype DX® recurrence score. The Pearson correlation coefficient (r = 0.34; p<0.001) demonstrates a statistically significant but modest positive association

Given these findings, Oncotype DX® RS testing may be selectively deferred in this low-risk patient population based on the ME2 score, resulting in potential cost savings. An average cost of approximately $4,600 per Oncotype DX® RS test represents a substantial financial burden when broadly applied. Therefore, eliminating unnecessary testing could provide a substantial economic benefit. In our patient cohort, the potential cost savings to the health system would be $579,600 if only ME2 scores were used. Additionally, a cost analysis by Reed et al. (9) found that patients who did not undergo Oncotype DX® RS testing had lifetime medical costs $2,692 lower than those who did. Recent budget-impact analyses have similarly shown that Oncotype DX® RS testing is associated with significant health-system costs, with an incremental budget impact of $261,067 for node-negative disease and $56,143 for node-positive disease over 5 years, despite cost offsets from reduced recurrence and chemotherapy use (10). Therefore, an additional $338,192 may be saved in lifetime medical costs for our patient cohort.

Study Limitations

Our study has several limitations. First, given the subjectiveness of histologic grading, there may be a limitation of concordance and interrater reliability amongst various pathologists reviewing pathology samples. Second, most patients lacked Ki-67 data, limiting us to using ME2 to calculate the Magee score. Third, two patients in our cohort were treated in early 2015, before the publication of the TAILORX trial results. If evaluated today, they might not be recommended for chemotherapy. In addition, although Pearson correlation was used to evaluate the association between ME2 and Oncotype DX RS, more comprehensive approaches such as regression or agreement analyses should be applied in larger, multicenter studies to further validate this relationship. Furthermore, because late recurrences may occur in hormone receptor-positive BC, our median follow-up may underestimate long-term recurrence rates.

Several studies have evaluated the omission of radiotherapy in selected patients with low-risk early-stage BC. In a recent prospective IDEA trial, postmenopausal women aged 50–69 years with T1N0, ER(+), PR(+), HER-2(-) BC and Oncotype DX RS ≤18 who underwent partial mastectomy followed by endocrine therapy without radiation were evaluated. At 5 years, recurrence-free survival was 99% (95% confidence interval, 96 to 100) (11). In our study, approximately 10% of patients who underwent partial mastectomy declined radiation. None of these patients developed local or systemic recurrence at the time of follow-up. The role of ME2 in predicting benefit from radiation and endocrine therapy should be explored in future studies.

Our findings suggest that Oncotype DX® RS testing may be omitted in selected postmenopausal women with low-grade, ER-positive, HER2-negative, node-negative BC. Instead, the ME may provide a cost-effective and equally reliable alternative for guiding chemotherapy decisions in this patient population.

Ethics

Ethics Committee Approval: This retrospective study was approved by the UPMC Central PA Region Institutional Review Board (approval date: 29.06.2022; decision no: 22E025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.B, K.L., Y.W., A.S.; Concept: K.B, K.L., Y.W., A.S.; Design: K.B, K.L., Y.W., A.S.; Data Collection or Processing: F.S., B.D., C.E.L., M.S., K.L.; Analysis or Interpretation: F.S., B.D., K.B, C.E.L., M.S., K.L., Y.W., A.S.; Literature Search: C.E.L., M.S., K.L., Y.W., A.S.; Writing: F.S., B.D., K.B, C.E.L., M.S., K.L., Y.W., A.S.

Conflict of Interest: Atilla Soran MD is section editor in European Journal of Breast Health. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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Case Report

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Breast Angiosarcoma: Four Case Series and Literature Review

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ABSTRACT

The mammary angiosarcoma is a rare malignant mesenchymal tumor that develops from the vascular tissue of the breast. It represents 0.004 to 1% of all malignant breast tumors and 8 to 10% of breast sarcomas. It can be primary in a 40-year-old woman or radiation-induced in an older woman who has undergone conservative treatment for breast cancer, including conservative surgery and adjuvant radiotherapy. Herein, we present four cases involving breast angiosarcoma in young and relatively older women and the different treatment they received. Our discussion encompasses the epidemiological, diagnostic, and therapeutic facets of this rare and aggressive tumor type.

Keywords: *BRCA1* and *BRCA2* genes; breast cancer; breast imaging; mammography; primary angiosarcoma

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Key Points

- Mammary angiosarcoma (MAS) is a rare malignant tumor of the breast's vascular tissue, accounting for 8–10% of breast sarcomas. It can be primary (PAS) or secondary to radiotherapy (RAS).
- This is a presentation of four MAS cases with varying clinical features, from localized masses to advanced metastatic forms, requiring surgical and chemotherapeutic management.
- MAS is extremely rare (<0.04% of breast cancers), typically affecting young women (PAS) or elderly patients after radiotherapy (RAS).
- It often presents as a rapidly growing mass, skin lesions, or erythematous plaques, which can be mistaken for benign conditions.
- Mammographic and ultrasound features are non-specific, with magnetic resonance imaging being essential for better assessment and staging.

Introduction

Mammary angiosarcoma (MAS) is a rare malignant mesenchymal tumor arising from the vascular tissue of the breast. It accounts for 8–10% of breast sarcomas (1) and 0.004–1% of all malignant breast tumors (2). In women over 40 years who have undergone conservative treatment for breast cancer, such as breast-conserving surgery and adjuvant radiotherapy, MAS may be either radiation-induced (RAS) or primary (PAS) (3). Despite the use of locoregional conservative treatment, the incidence of subsequent angiosarcomas continues to rise. These tumors usually affect the skin and rarely involve the thoracic wall or mammary parenchyma. The vascular nature of angiosarcomas is confirmed through definitive histological diagnosis (1-3).

In this article, we present four distinct cases of MAS in women of varying ages and clinical contexts, along with a review of the literature to better understand the epidemiological, diagnostic, and therapeutic aspects of this rare entity.

Written informed consent was obtained from the patients for publication of these case series.

Case Presentations

Case 1

The patient was a 36-year-old unmarried, nulliparous woman with a family history of breast carcinoma. She initially presented with a

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rapidly enlarging right breast mass measuring 11 cm, evolving over one month, without associated axillary lymphadenopathy. Breast ultrasound and mammography revealed a large, heterogeneous, and poorly vascularized solid mass occupying nearly the entire right breast, measuring 11×7 cm, and classified as American College of Radiology/Breast Imaging Reporting and Data System 4B (Figure 1). A core needle biopsy revealed a poorly differentiated angiosarcoma. Immunohistochemical staining showed strong positivity for CD31 and factor VIII-related antigen, confirming the vascular endothelial origin of the tumor, and was negative for pancytokeratin, effectively excluding an epithelial malignancy (Figure 2).

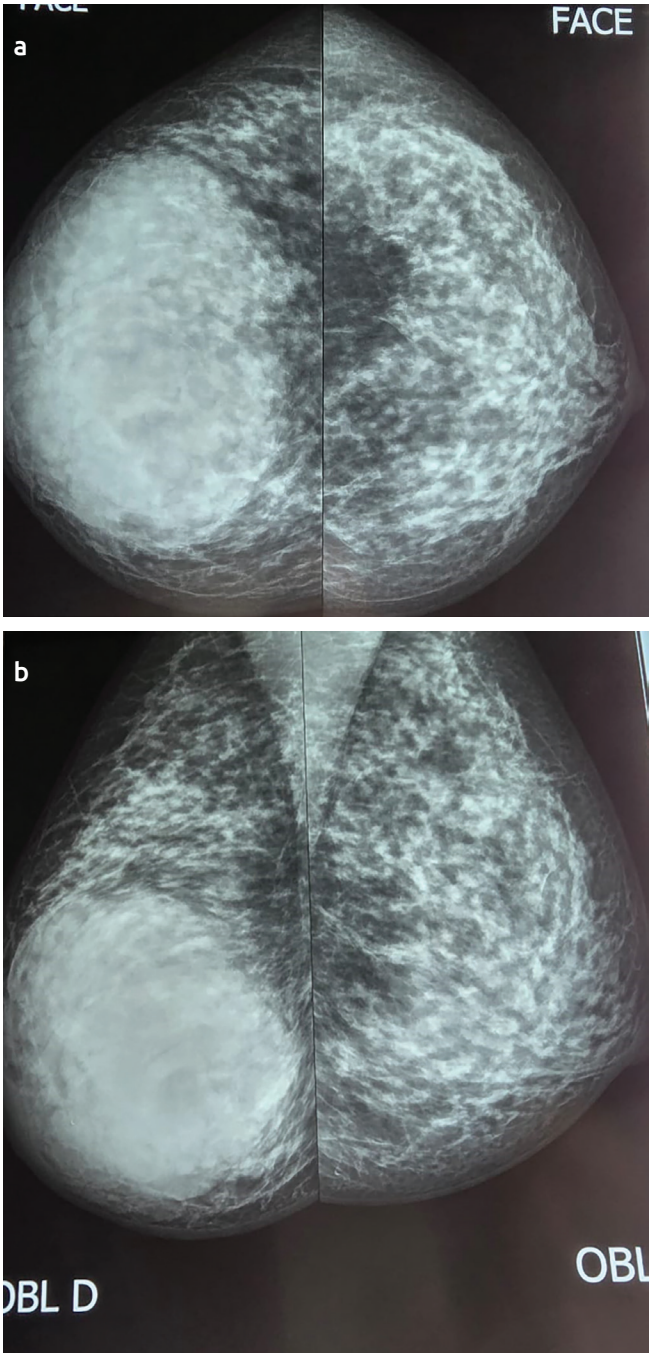

Figure 1. (a+b): Mammography showing a large solid mass occupying nearly the entire right breast (a): Craniocaudal projection, (b): Mediolateral oblique projection

The patient was scheduled for a right mastectomy but was lost to follow-up. Six months later, she presented to the emergency department with a marked deterioration of her general condition and a rapid increase in breast mass volume. Clinical examination revealed a 20 cm exophytic mass involving the entire right breast, with extensive blackish skin discoloration (Figure 3). A thoraco-abdomino-pelvic computed tomography scan demonstrated a large, infiltrative, and necrotic tumor invading the underlying pectoral muscle (Figure 4). The lower portion of the mass contained hydro-aeric components with air bubbles, ulceration, and cutaneous fistulization. In addition, there was right axillary lymphadenopathy and multiple pulmonary (Figure 5) and osseous (Figure 6) metastases.

She was found to have severe anemia (hemoglobin: 1.5 g/dL), necessitating transfusion with eight units of packed red blood cells to achieve a stable condition suitable for major surgery. A right mastectomy was performed, and the defect was reconstructed using a latissimus dorsi muscle flap.

Final histopathological examination confirmed the diagnosis of angiosarcoma, revealing highly irregular, anastomosing vascular channels lined by atypical endothelial cells, with hyperchromatic nuclei and high mitotic activity (Figure 7). The patient was subsequently scheduled for adjuvant chemotherapy and radiotherapy. Unfortunately, she died after four cycles of chemotherapy due to progression of advanced metastases.

Case 2

A 65-year-old patient with a left breast nodule was diagnosed as infiltrating ductal carcinoma. She had undergone conservative treatment followed by postoperative radiotherapy. Ten years later, at the age of 75 years, she underwent reconsultion for the appearance of a 3 cm lump on the same breast corresponding to histologically

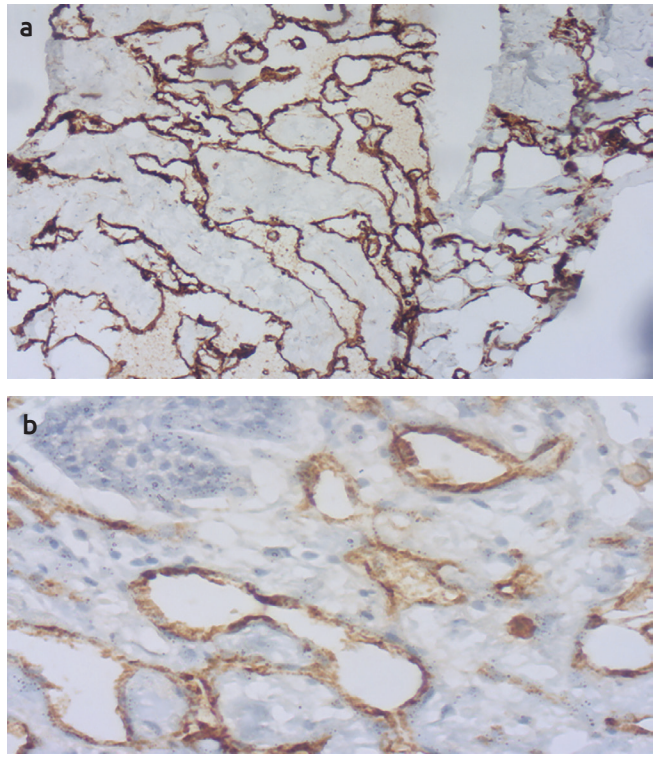

Figure 2. (a): Tumoral cells are positive to CD31, (b): Tumoral cells are positive to fact VIII

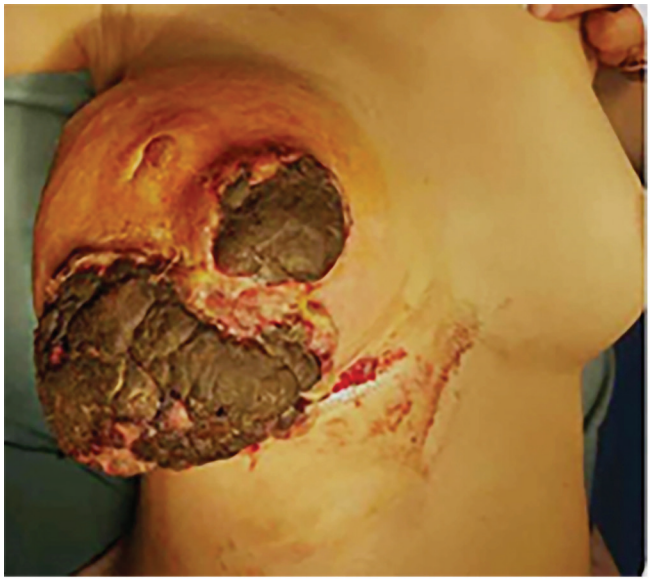

Figure 3. Clinical presentation of an angiosarcoma

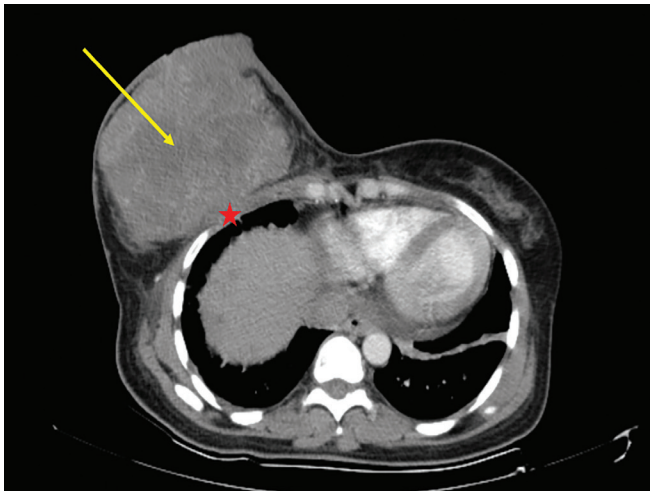

Figure 4. Computed tomography scan showing a large, infiltrative and necrotic tumor of the right breast (arrow) with invasion of the underlying pectoral muscle (asterisk)

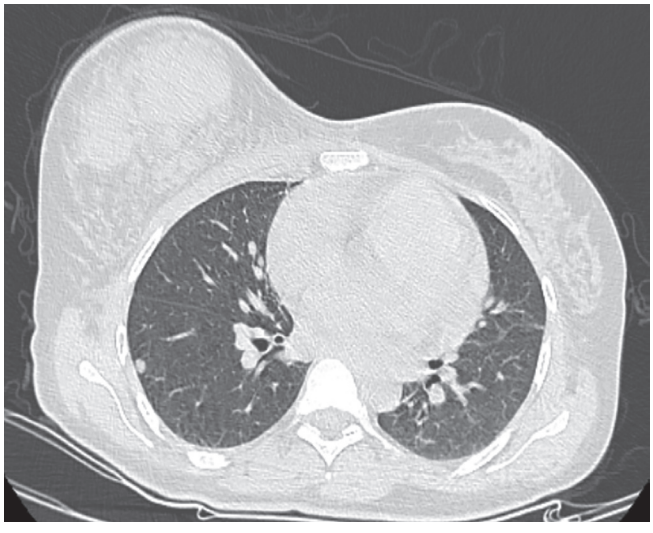

Figure 5. Axial computed tomography scan demonstrating multiple pulmonary metastases

confirmed angiosarcoma of the left breast, necessitating radical treatment with total mastectomy followed by chemotherapy.

Follow-up of the patient revealed no evidence of disease recurrence to date.

Case 3

A 34-year-old woman with no previous relevant medical history consulted for a rapidly growing breast mass measuring 15 cm with

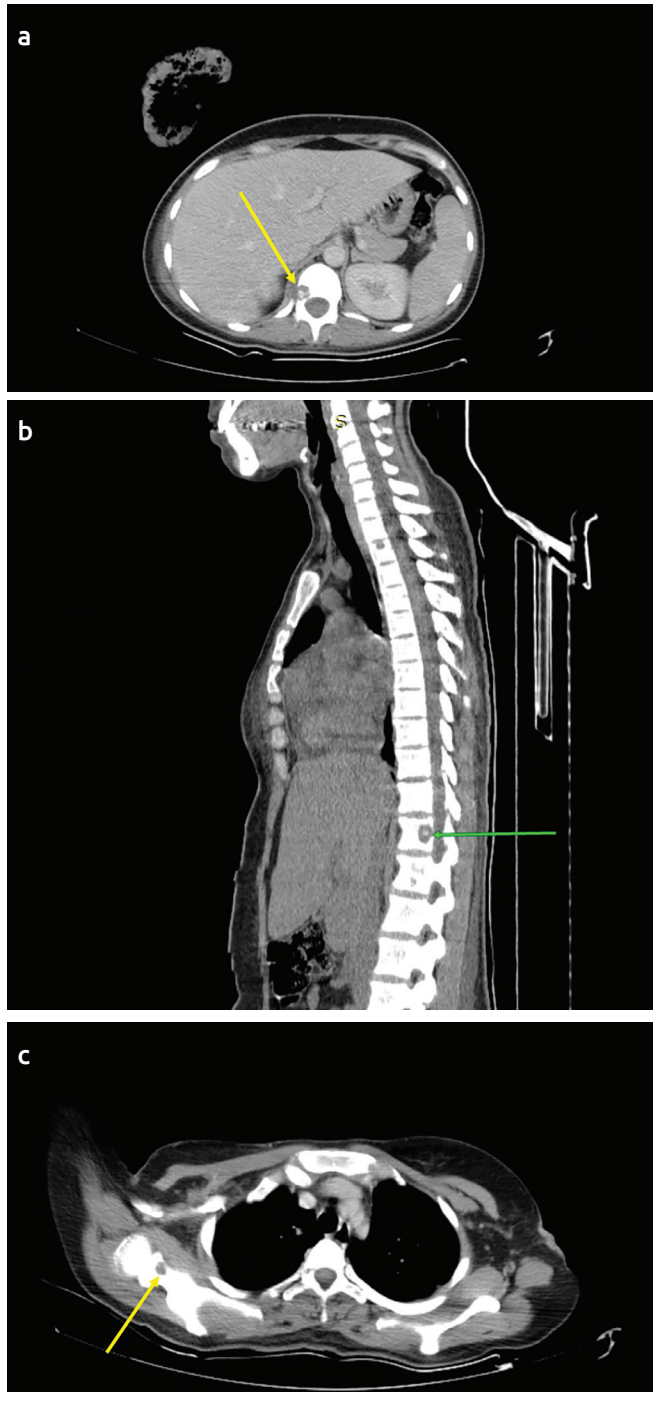

Figure 6. (a): Computed tomography scan axial section demonstrating an osseous metastasis in a thoracic vertebra, (b): Computed tomography scan sagittal section demonstrating an osseous metastasis in a thoracic vertebra, (c): Computed tomography scan sagittal section demonstrating an osseous metastasis in the right scapula

necrotic budding. A biopsy was performed and the result of the histopathology examination showed angiosarcoma of the left breast. She underwent a left mastectomy followed by adjuvant chemotherapy without radiotherapy. The patient has shown no signs of disease recurrence to date during follow-up.

Case 4

A 70-year-old woman presented with a well-circumscribed, 3.5 cm resected mass of the left breast, corresponding to a MAS on histopathology. She subsequently underwent a total mastectomy without receiving chemotherapy or radiotherapy. The patient lived to the age of 79 years and was cancer-free; she died from heart failure secondary to poorly controlled hypertension.

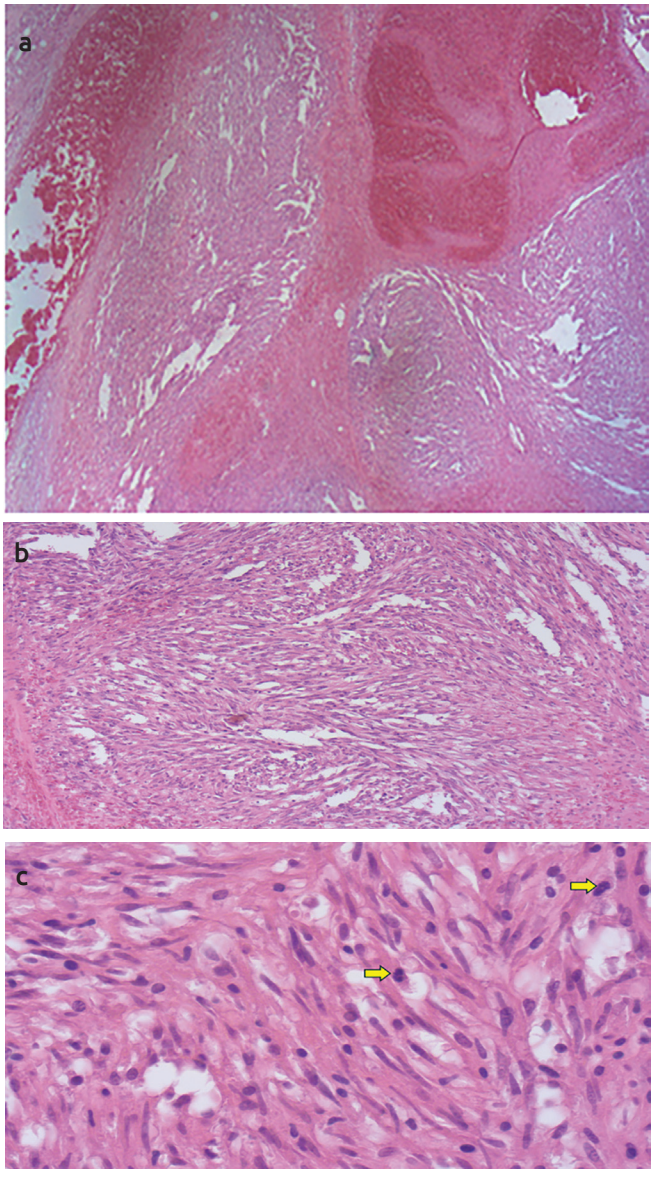

Figure 7. (a): Breast mass composed of anastomosing vascular channels of varying caliber and size, some of which are voluminous and full of blood (HE*10), (b): The vascular channels are lined by atypical endothelial cells (HE*40), (c): Tumoral cells are spindle-shaped with elongated nuclei showing moderate atypia and numerous mitoses (arrows)

Discussion and Conclusion

Epidemiology

Less than 0.04% of all breast cancers are primary breast angiosarcomas (PBAS), an uncommon condition that affects younger women with a median age of 40 years and unknown risk factors. Its frequency is roughly 0.0005% (4). Wang et al. (5) validated its uncommon occurrence in a study that included only 11 instances of MAS, of which only one was a primary MAS, out of a total of over 5,000 cases of breast cancers from 1997 to 2007. There are two types of secondary breast cancer angiosarcomas (SBAS): Post-radiation angiosarcoma and cutaneous angiosarcoma linked to lymphedema. In 1948, Stewart and Treves (6) published the first description of cutaneous angiosarcoma linked to lymphedema. This form typically appears in lymphedematous limbs and chest walls following mastectomy and axillary lymph node dissection. The increased use of sentinel lymph node sampling and breast-conserving therapy has reduced the prevalence of treatment-emergent lymphedema (7). In contrast, post-radiation angiosarcoma typically develops following radiotherapy and breast-conserving treatment. Although it can sometimes form in the breast parenchyma, it primarily affects the breast's dermis in the radiation field in the so-called "twilight zone", where radiation is inhomogeneous and may subsequently invade the underlying breast tissue (7). With a mean age of diagnosis of 70 years, SBAS primarily affects elderly women (4). As more patients are receiving conservative treatment (breast-conserving surgery and adjuvant radiation), its incidence is gradually rising. Although some data suggest that angiosarcoma can develop as early as 1–2 years or as late as 41 years following treatment, the typical interval between radiation and angiosarcoma development is six years (8).

Clinical Presentation

Earlier research reported that SBAS typically manifests as a palpably growing mass that is fast expanding and typically ranges in size from 5.7 cm to 7.3 cm (9). Usually seen in the mammary gland, the tumor can extend to the skin and result in ulceration (10). Rarely, SBAS can manifest as soreness in the breast, a sensation of fullness, or broad induration throughout the entire breast (9, 10).

Furthermore, Kasabach-Merritt syndrome, which is frequently seen in children with large hemangiomas and causes thrombocytopenia and consumptive coagulopathy as a result of platelet sequestration that leads to severe bleeding, may be linked to PBAS. However, rather than a palpable mass, SBAS frequently manifests as skin alterations and lesions in the chest wall or remaining chest parenchyma due to its cutaneous and/or subcutaneous position (5, 11). Erythematous or purplish plaques, nodules, contusions, skin discoloration, erythematous patches, blue to red or black nodules, and edema are the main symptoms of associated skin lesions.

There may or may not be ulceration (11). Diagnosis may be challenging as these lesions may be easily confused with radiodermatitis or other skin conditions.

Imaging Findings

PBAS

In a study into the mammographic features of PBAS, Wang et al. (10) concluded that these findings were non-specific. In particular, the authors describe PBAS as lobulated or oval masses, large diffuse asymmetries with irregular density, skin thickening, locally thickened

arteries, irregular subcutaneous fat density, and changes in the breast's trabecular structure. Notwithstanding these findings, no publication has mentioned the existence of swollen lymph nodes in the axilla. The parenchymal origin of PBAS, as opposed to the ductal structures where calcium is often deposited, and/or their rapid growth may account for the absence of related microcalcifications.

Mammograms may appear falsely normal due to the fact that PBAS primarily affects young women with dense breast parenchyma that may make a lump difficult to see. Naka et al. (12) reported that 33% of the angiosarcomas in their dataset were not detected on mammography. Momand et al. (13) found that 19% of patients had tumors that were apparent on magnetic resonance imaging (MRI) and ultrasonography, but were not evident on mammography. When a palpable anomaly is discovered, ultrasound can be helpful in verifying a mass, particularly in young women with dense breast parenchyma. On color Doppler, masses are typically vascularized and poorly delineated.

Angiomatous pseudo-stromal hyperplasia, galactocele or lactating adenoma, ductal ectasia, apocrine metaplasia, lipoma, angiolipoma, hematoma, seroma, fat necrosis, silicon granuloma, sebaceous or epidermal inclusion cyst, abscess, and ductal ectasia are among the largely benign breast angiosarcomas that can be identified by ultrasound (14).

In situations when MAS is suspected, MRI may be helpful for differential diagnosis and determining the extent of the disease, given the prevalence of false-positive and non-specific results with conventional imaging techniques. A heterogeneous mass with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images is visible in angiosarcoma MRI scans. Higher-grade lesions may have irregular regions of strong T1 signal, which indicate venous lacunae or hemorrhages. MRI helps with surgery planning and is useful for determining the size of a tumor. Moreover, MRI can detect any disease that remains after an incisional biopsy (14, 15).

SBAS

Skin changes during radiation therapy, such as thickness, retraction, and architectural distortion of the breast parenchyma, can obscure or cause angiosarcoma-related skin alterations to be misinterpreted on mammograms. Poorly defined asymmetric masses may be seen in the subset of instances with parenchymal involvement. However, it is important to realize that mammograms can produce false-negative readings. According to Lim and Goei (16), a fully normal mammogram may be evident in about 33% of angiosarcoma cases linked to radiation therapy. Consequently, it is important to remember that skin thickness often declines two years following radiation therapy while monitoring patients undergoing breast-conserving therapy (17).

Beyond this point, any additional increase in skin thickness should raise the possibility of a malignant disease, such as angiosarcoma or carcinomatous mastitis. It can be challenging to differentiate skin lesions from post-radiation skin thickening on ultrasonography. Heterogeneous regions with disturbance of normal tissue planes are recognized as intraparenchymal masses (18). A plateau or washout with delayed imaging and fast gadolinium enhancement are MRI characteristics comparable to those of primary angiosarcoma. Of note, it has been demonstrated that MRI is the most sensitive method for identifying radiotherapy-associated sagittal angiosarcoma (15).

Histopathology

The pathogenesis of angiosarcoma, especially MAS, is complex. *BRCA1* and *BRCA2*, two important genes in breast and ovarian cancer, are thought to play a part in the development of SBAS because they are essential for maintaining cellular equilibrium and protecting DNA from radiation-induced damage. Cases of SBAS have been reported in people with *BRCA1* and *BRCA2* mutations by researchers such as West et al. (19). Both animal models and MAS patients exhibit signs of angiosarcoma development linked to the transcription factor p53 and its inhibitor MDM2 (18). Increased expression of vascular endothelial growth factor may also be involved in this particular mechanism (12, 13, 18). In order to differentiate invasive carcinomas from MAS, immunohistochemistry investigations are essential. Angiosarcoma can be indicated by endothelial markers, including CD34, CD31, and factor VIII. A poorer prognosis is linked to a higher ki-67 index (20). A thorough histological and immunohistochemical examination of the entire material is important following surgical excision and is regarded as the gold standard for diagnosis (20). Fine-needle aspiration and needle biopsy can result in false-negative results for malignancy, estimated to occur in 37% of cases because of well-differentiated histological types or the presence of necrotic tissue, fat, or bleeding.

Angiolipomas, hemangiomas, and benign proliferative lesions are examples of the differential diagnoses for low-grade angiosarcomas. Mastitis, fibromatosis, and especially invasive breast cancer are factors to take into account for higher grade angiosarcomas (21). Abnormal endothelial cells in blood vessels proliferate rapidly in MAS. These cells frequently infiltrate the surrounding breast tissue, resulting in necrotic and hemorrhagic patches. Although the cells of well-differentiated angiosarcomas resemble normal endothelium, they also have aberrant vascular patterns and atypia.

Histologically, poorly differentiated types may be more challenging to identify due to their unclear vascular development. MAS typically has a poor prognosis due to its high rate of local recurrence and tendency for hematogenous dissemination. There are three categories of MAS: Low grade, which has well-formed vascular channels; intermediate grade, which has prominent neoplastic vascular development; and high grade, which has localized hemorrhage, infarction, and necrosis (18).

Treatment

For both primary and secondary MAS, surgical excision with mastectomy is usually the accepted course of treatment. For minor primary lesions, breast-conserving treatment may be an option. The rate of local recurrence may be decreased by chemotherapy, and docetaxel shows promise in the treatment of secondary angiosarcoma (22). Hyper fractionated radiation therapy has been demonstrated to be successful in lowering cell repopulation in quickly expanding high-grade secondary angiosarcomas, despite the paucity of available evidence (22).

Prognosis

Although 5-year survival rates may be higher than those of other types of cutaneous angiosarcoma, secondary angiosarcomas often have a dismal prognosis. The completeness of surgical resection affects the outcome. Local recurrence is frequently linked to distant metastases and is a poor prognostic indication (7).

In summary, MAS, both primary and secondary, are uncommon diseases. The clinical presentation may be skin discoloration, skin plaques or nodules, a palpable mass, or a combination of these symptoms. The diagnosis may be delayed if discoloration is confused with bruising. Findings from ultrasonography and mammography are not specific for angiosarcoma. Particularly in high-grade tumors, MRI can be used to determine the extent of the lesion and can show a rapidly enhancing heterogeneous mass with bleeding or blood pooling. The incidence of post-irradiation angiosarcomas is increasing as breast-conserving therapy is used more often to treat breast cancer. Early intervention, which is important for treatment of this aggressive malignancy, depends on prompt recognition.

Ethics

Informed Consent: Written informed consent was obtained from the patients for publication of these case series.

Footnotes

Authorship Contributions

Surgical and Medical Practices: I.B., S.F., H.A., E.G., D.C., S.B., B.B.; Concept: I.B., H.A., E.G., S.B., B.B.; Design: I.B., H.A., E.G.; Data Collection or Processing: S.F., H.A., E.G.; Analysis or Interpretation: S.F., D.C., S.B., B.B.; Literature Search: I.B., S.F., H.A., E.G.; Writing: H.A., E.G.

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

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Case Report

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Bilateral Gestational Gigantomastia Complicating Pregnancy: A Challenging Case Refractory to Conservative Management

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ABSTRACT

Gestational gigantomastia (GG) is a rare condition characterized by excessive and rapid breast enlargement during pregnancy, resulting in significant physical discomfort, functional limitations, and significant psychological impact. We present a case of a 33-year-old multiparous woman in her third pregnancy, who developed severe bilateral GG by 16 weeks of gestation. Despite initial conservative management, including analgesia and pharmacological (bromocriptine) therapy, the condition worsened causing functional impairment and recurrent mastitis requiring repeated hospital admissions. The pregnancy was electively induced due to physical limitations at 35 weeks of gestation; however, the labour was complicated by obstruction, necessitating an emergency Cesarean section. Postpartum the patient developed severe lactational mastitis complicated by sepsis necessitating intensive care unit admission. After recovery and cessation of breastfeeding, she elected to undergo Wise-pattern bilateral reduction mammoplasty with free nipple-areolar complex grafting four months into her postpartum period. The procedure provided substantial functional relief and a favorable esthetic outcome. This case highlights the potential complexity of managing GG and the need for individualized care. Although conservative treatments may offer temporary relief, surgical intervention is often necessary in severe cases.

Keywords: Gestational gyganomastia, breast feeding, lactational mastitis, reduction mammoplasty

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Key Points

- Gestational gigantomastia is a rare and debilitating condition that can lead to severe physical and psychological impairment during pregnancy often requiring multidisciplinary care.
- Conservative treatments, including pharmacotherapy with bromocriptine may be ineffective in severe cases, necessitating surgical intervention for long term relief.
- Postpartum reduction mammoplasty with free nipple areolar complex grafting offers a safe and effective solution for patients with no future fertility plans, improving both function and aesthetics.

Introduction

Gestational gigantomastia (GG) is a rare condition characterized by rapid and excessive breast enlargement during pregnancy, often due to an exaggerated hormonal response to oestrogen and progesterone (1). While the exact causes are not fully understood, factors such as hormonal imbalance, increased hormone sensitivity, and genetics are believed to contribute (2). GG typically affects younger women, especially during their first pregnancy, with an incidence peak between ages 18 and 30 years (3). Though it occurs in only about 1 in 100,000 pregnancies, GG can cause significant symptoms, such as breast pain, skin damage, infections, and functional impairment (4). Risk factors include obesity, a family history, and multiparity (5).

Management strategies typically commence with conservative approaches, which include analgesia, mechanical support, and psychological counseling (6). Pharmacological therapy using dopamine agonists (e.g., bromocriptine) or anti-oestrogens may be trialed during pregnancy in more severe cases (7). However, definitive treatment may necessitate surgical intervention, including breast reduction or mastectomy, particularly when complications arise or conservative measures fail (8). Postpartum surgical management is

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frequently indicated if hypertrophy persists (9). This report describes a case of bilateral GG managed with bilateral reduction mammoplasty and free nipple-areolar complex (NAC) grafting following failure of conservative treatment, highlighting clinical decision-making, surgical technique, and outcomes.

Case Presentation

A 33-year-old woman, with a history of two uncomplicated pregnancies, presented with severe bilateral GG during her third pregnancy. Her pregnancy was uneventful until 16 weeks, when she developed rapid breast enlargement, increasing her bra size from 28B to 38E over 12 weeks, making it difficult to find suitable support garments. The excessive breast size severely limited her mobility, and by late pregnancy, she needed help with daily activities (Figure 1). In addition, she experienced severe mastalgia, skin breakdown, hyperpigmentation, striae distensae, and erythema.

The patient's condition required frequent medical attention, and she was managed by a medical team including an obstetrician-gynecologist, a breast surgeon, antenatal care midwife, and a psychologist throughout this period. Ultrasonography and core biopsy of a clinically abnormal area revealed findings consistent with mastitis and pregnancy-related changes without evidence of malignancy or acute infection. Hormonal evaluation revealed normal pregnancy-related values except for elevated prolactin. Therefore, the medical team initially opted for conservative management with pain relief, supportive garments, and psychological counseling. Consequently, pharmacological therapy with bromocriptine, a dopamine agonist, was initiated to reduce breast size. Despite conservative measures, her condition deteriorated, significantly affecting daily life. She was hospitalized three times for recurrent mastitis and treated with intravenous antibiotics. Following obstetric consultation, early induction at 35 weeks was attempted but failed due to obstructed labor, necessitating emergency Cesarean section.

Despite medical advice, the patient continued breastfeeding postpartum. Six weeks later, she developed sepsis from lactational mastitis, requiring intensive care unit admission. Ultrasound showed multiple breast collections, which were drained. Cultures confirmed *Streptococcus viridans* infection. After recovery, surgical intervention was offered and scheduled four months postpartum. Breast volume had decreased following cessation of lactation, making surgery more feasible (Figure 2A). She underwent bilateral Wise-pattern reduction mammoplasty with free NAC grafting. A total of 3.4 kg of breast tissue was excised. The surgical team opted for free nipple grafting, as a very long pedicle would compromise the blood supply for the NAC. Her postoperative course was uncomplicated. She was discharged on day 3, with drains removed on day 6, following adequate reduction in output (<50 mL/24 h) (Figure 2B).

Outpatient reviews were conducted biweekly for three months with good healing and satisfactory cosmetic outcome (Figure 3).

Figure 1. Gestational giganotomastia giving rise to significant discomfort

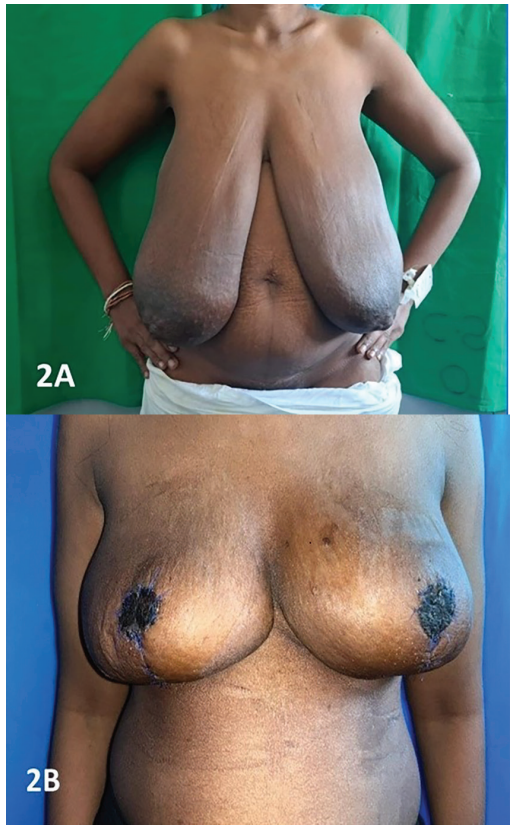

Figure 2. Pre op image (2A), post op 2 weeks image (2B)

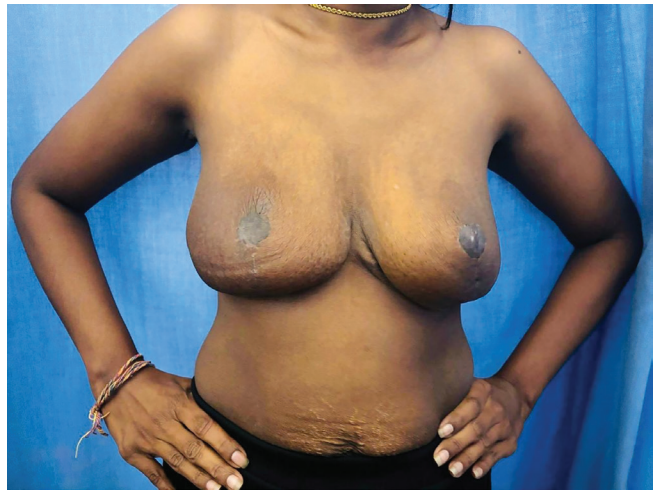

Figure 3. Post-op 3 months image

Informed written consent was given by the patient for clinical details and anonymized images for data collection and publication purposes.

Discussion and Conclusion

GG requires consideration of several key factors, including the patient's age, pregnancy-related complications, and the timing and management of the condition (2). Although GG most commonly presents during the first or second pregnancies, this patient developed symptoms during her third gestation, with onset and escalation in the second trimester, notably earlier than the third trimester onset commonly cited (10). The rapid increase in breast size-rising from 28B to 38E within 12 weeks-demonstrates the potential severity of GG and its substantial impact on quality of life, consistent with prior reports (4).

Elevated prolactin levels in the patient support the suggestion of a correlation between prolactin and GG, though the role of hormone sensitivity at the tissue level may be more influential than absolute hormone concentrations (11). Despite bromocriptine therapy, symptoms persisted, aligning with literature indicating that medical therapy offers limited benefit in severe GG (12).

Obstetric complications, particularly preterm labor and obstructed delivery, are documented in GG cases due to the mechanical challenges posed by enlarged breasts (5). The patient's emergency Cesarean section after failed induction reinforces this association. Postpartum complications are also common, as seen with her episode of lactational mastitis progressing to sepsis, a serious but known risk in GG (13).

Surgical intervention remains the definitive treatment when conservative therapies fail or complications arise (8). Mastectomy and reduction mammoplasty are the primary options, with the choice dictated by severity, patient preference, and reproductive plans (14). As with our patient, for women with no desire for future fertility, reduction mammoplasty is often preferred due to its ability to preserve the breast contour and provide a more esthetically acceptable result (9). In this case, free NAC grafting was employed given the compromised vascularity anticipated with a traditional pedicle technique, which is corroborated by existing surgical guidelines (15).

Delaying surgery until several months postpartum is consistent with best practice to reduce risk of complications, such as delayed wound healing and nipple necrosis, particularly common due to the increased vascularity of the breast in the immediate postpartum period (13). The four-month delay allowed for tissue involution and decreased congestion, resulting in a smoother surgical course and improved cosmetic outcome.

GG is a rare but potentially severely debilitating condition with the potential for significant physical, psychological, and obstetric complications. This case highlights the need for multidisciplinary management and an individualized approach, beginning with conservative management and transitioning to surgical intervention when appropriate. A carefully tailored management strategy can significantly enhance overall quality of life and long-term patient satisfaction. This is especially relevant, given that GG primarily affects young women.

Ethics

Informed Consent: Informed written consent was given by the patient for clinical details and anonymized images for data collection and publication purposes.

Footnotes

Authorship Contributions

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

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

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Case Report

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Isolated Ileocecal Metastasis from Lobular Carcinoma of the Breast: A Case Report

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ABSTRACT

Invasive lobular carcinoma (ILC) is the second most common histologic subtype of invasive breast cancer, accounting for 5–15% of this type. Though its unique propensity to metastasize to the extra-hepatic gastrointestinal tract is well known, isolated colonic metastasis without disseminated or locoregional recurrence is rare. These isolated lesions may be amenable to curative treatment with a better prognosis. Here we present the diagnostic challenge faced while managing the case of a 62-year-old female who was treated for estrogen receptor-positive ILC of the breast 10-years previously, who presented with an ileocecal mass, which on biopsy revealed metastatic ILC. She was treated with laparoscopic hemicolectomy followed by hormonal therapy and remained asymptomatic at 18-months follow-up.

Keywords: Colonic breast metastasis; extrahepatic gastrointestinal metastasis; ileocecal metastasis; invasive lobular carcinoma; lobular carcinoma breast

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Key Points

- Isolated colonic metastases from invasive lobular carcinoma are rare and manifests with subtle clinico-radiological findings.
- A high index of suspicion and repeated deep biopsies are important for early diagnosis.
- A close follow-up is essential to monitor for the development of multifocal or disseminated disease.

Introduction

Invasive lobular carcinoma (ILC) is the second most common histologic subtype of breast cancer after invasive ductal carcinoma (1). Breast cancers tend to metastasize to the lung, bone, liver and brain, whereas ILC has a higher propensity to spread to the extra-hepatic gastrointestinal (GI) tract (2). Herein, we report the challenges faced during the diagnosis of a rare case of ILC which manifested as isolated colonic metastasis without locoregional symptoms, a decade after initial diagnosis.

Case Presentation

A 62-year-old female presented with on-and-off colicky abdominal pain with vomiting and abdominal distension for 3-months. In her past medical history she had been treated for ILC of the right breast (stage T2N3M0) 10-years earlier with modified radical mastectomy, adjuvant chemotherapy, radiotherapy to the chest wall and regional lymph nodes followed by hormone therapy with Anastrozole for 5-years. She remained well in follow-up for 10-years until the onset of her present symptoms. There was no current clinical evidence of locoregional recurrence or distant metastasis and her screening mammogram of the opposite breast and abdominal examination were also normal.

On investigation, complete blood count and renal function tests were normal. Though ultrasonography of the abdomen revealed no abnormalities, contrast enhanced computed tomography showed mucosal thickening of the terminal ileum with an edematous serosal surface. Colonoscopy showed a bulky ileocecal junction but biopsy from the lesion was non-specific. She was managed conservatively but she remained symptomatic and presented with features of subacute intestinal obstruction. A repeat colonoscopy was done, which showed an edematous ileocecal junction with ulcerations and multiple deep biopsies were taken (Figure 1). Histopathological

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examination showed small intestinal mucosa infiltrated by dyscohesive monomorphic tumor cells scattered within the colonic mucosa with signet ring cell morphology, infiltrating into the submucosa. These cells were immunopositive for cytokeratin, mammaglobin and GATA-3 and exhibited loss of E-cadherin, compatible with metastasis from ILC. Further immunohistochemistry showed estrogen receptor positive (5/8), progesterone receptor and human epidermal growth factor receptor 2 negative disease, with a Ki-67 index of 7–8% (Figure 2). A whole-body PET CT also revealed mildly fluorodeoxyglucose (FDG)-avid, non-enhancing, irregular circumferential wall thickening of the terminal ileum and ileo-cecum with partial luminal narrowing, suggestive of malignancy. There were no other foci of FDG uptake in the body (Figure 3).

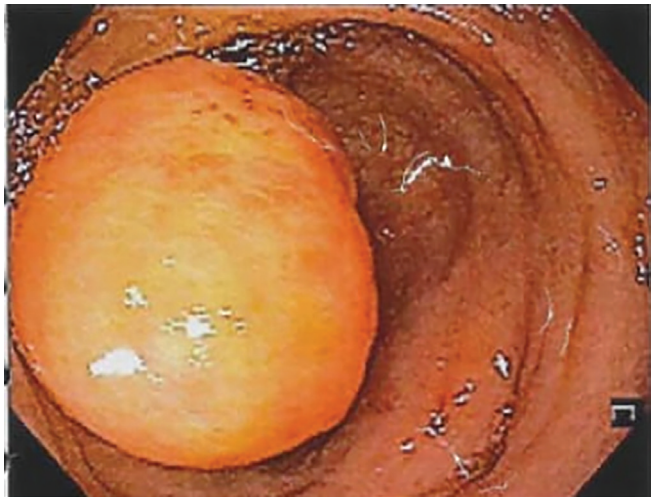

Figure 1. Colonoscopic image showing an oedematous ileocecal junction with superficial ulcerations

Diagnostic laparoscopy and curative resection of the isolated colonic metastasis of ILC was planned. Intraoperatively, there was no evidence of peritoneal deposits, liver metastasis or ascites and laparoscopic-assisted radical right hemicolectomy and ileo-transverse colon anastomosis was performed. The post-operative period was uneventful and the patient was discharged on post-operative day 3. Histopathology of the resected specimen showed an ulcero-proliferative and infiltrative tumor, involving the cecum and distal ileum, measuring 2.5x2.5x1.0 cm, showing features of lobular carcinoma with transmural involvement and focally involving the serosa with perineural invasion. Six out of 12 resected lymph nodes showed metastatic deposits, with the largest one measuring 8 mm.

After discussion with the multidisciplinary team, the patient was started on Ribociclib and Anastrozole, with 3-monthly denosumab, calcium and vitamin D supplementation. She was switched to Palbociclib, due to a hypersensitivity skin reaction from Ribociclib, which she tolerated well. A repeat PET-CT scan was done in follow-up at 6-months and 1-year was normal. Informed consent was obtained from all individual participants included in the study.

Discussion and Conclusion

ILC has several unique characteristics, such as presentation with a vague ill-demarcated lump, a higher rate of multifocal or multicentric disease with a greater chance of involving the contralateral breast. ILC may be missed on screening mammograms due to subtle clinico-radiological features (3). During treatment, achieving a negative surgical margin is challenging, resulting in increased mastectomy rates and a propensity for late local recurrences (4). ILC typically metastasizes to the extra-hepatic GI tract, retroperitoneum, peritoneum and unusual sites, such as the genito-urinary system (5).

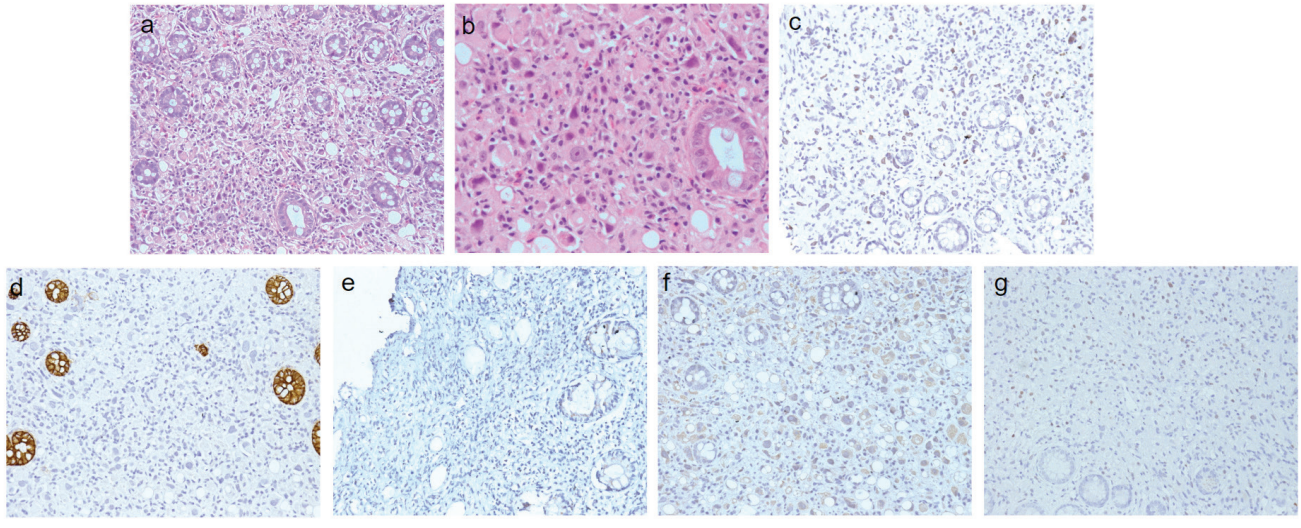

Figure 2. a. Section shows dyscohesive monomorphic tumor cells scattered within the colonic mucosa (H&E x200), **b.** Shows scattered tumor cells with vesicular nuclear chromatin, prominent nucleoli and moderate eosinophilic cytoplasm (H&E x400), **c.** Tumor cells showing nuclear immunopositivity immune-stain (GATA3 x200) **d.** Loss of immunoexpression in tumor cells (E-cadherin x200), **e.** Tumor cells show nuclear immunopositivity of moderate intensity (score 2) in 11-33% of tumor cells (score 3) (ER x200), **f.** Tumor cells are immune-negative (PR x200), **g.** Tumor cells are immune-negative (HER2/neu x200)

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; H&E: Hematoxylin and eosin

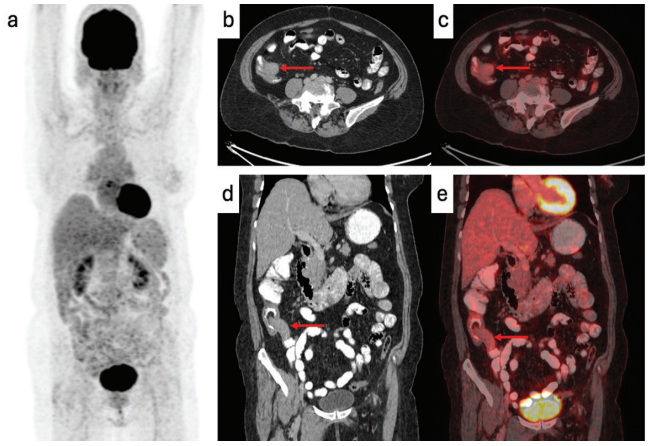

Figure 3. This is the maximum intensity projection image **a.** of F-18 FDG PET/CECT of the patient with invasive lobular carcinoma of right breast. Axial CECT, PET/CECT images **b, c.** &; coronal CECT, PET/CECT **d, e.** images show mildly FDG avid non-enhancing irregular circumferential wall thickening involving the terminal ileum and ileo-cecum with partial luminal narrowing (red solid arrow)

CECT: Contrast enhanced computed tomography; FDG: Fluorodeoxyglucose; PET: Positron emission tomography

Loss of E-cadherin molecules by lobular breast cancer cells leads to dedifferentiated, non-cohesive tumor cells resulting in diffuse infiltration and a pattern of spread different from invasive ductal carcinoma (6, 7). While most of these metastases are multifocal or disseminated and associated with locoregional recurrence, isolated bowel metastasis is rare. Usually, breast carcinoma spreads to the abdomen by subdiaphragmatic lymphatics resulting in disseminated peritoneal involvement, whereas isolated GI involvement**,** as in this case, may be explained by hematogenous spread and seeding of tumor cells in the GI tract.

Initial ILC deposits in the intestine are difficult to detect by both endoscopy or radiography because of its appearance as smooth bowel wall thickening that can mimic peristalsis. Colorectal linitisplastica is the term used for diffuse infiltration of all the layers of the colon by ILC, similar to that of the stomach, where a concentric ring or the "target sign" is seen on cross-sectional imaging. FDG avidity of these tumor cells is also comparable to normal tissues, and so can be easily overlooked. It is imperative to take deep and repeated biopsies in these scenarios as the deposits are primarily submucosal and more superficial biopsies remain normal in around half of the patients, as in our case (8).

Most of the cases of ILC with GI metastasis reported to date either had multifocal GI involvement or were associated with locoregional recurrence and distant metastasis (9-13). Switzer et al. (9) described the largest case series of 21 patients and the most frequent sites of involvement were stomach (52%), peritoneum (38%), omentum (19%), esophagus (10%), duodenum (5%), jejunum (5%), transverse colon (5%), and pancreas (5%) with multiple GI site involvement seen in six (28.6%) patients. Presence of isolated colonic metastasis after a decade of initial diagnosis, in the absence of other metastatic sites confirmed thorough metastatic evaluation, thus enabling curative treatment is unique to our case.

Management options for isolated ILC metastasis include complete resection with adequate margins and regional lymph nodal basins. However, attempts at complete resection should always be preceded by a thorough work-up to rule out evidence of multifocal or disseminated disease. Adjuvant treatment with aromatase inhibitors and CDK4/6 inhibitors or Fulvestrant may delay disease progression. However, given the limited literature in this regard, long-term outcomes and prognosis of such patients are yet to be elucidated and close follow-up is required (14, 15).

Isolated colonic metastases from ILC are rare and manifest subtle clinico-radiological findings. A high index of suspicion and repeated deep biopsies are important for early diagnosis as this may facilitate complete surgical resection which, along with adjuvant therapy, may lead to favourable outcomes. A close follow-up is essential to monitor for the development of multifocal or disseminated disease.

Ethics

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Footnotes

Authorship Contributions

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

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

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Case Report

Eur J Breast Health 2026; 22(1): 106-109
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Mammographic Breast Pseudocalcifications Associated With Topical Betamethasone Dipropionate

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ABSTRACT

Screening mammography plays a critical role in the early detection of breast cancer. Suspicious breast calcifications on mammography often prompt further diagnostic evaluation due to concern for malignancy, worrying physicians and patients alike. Here, we present a case of a woman in her 70s whose annual screening mammogram with digital breast tomosynthesis demonstrated two new groups of microcalcifications, confirmed after recall with magnification views. However, because of their superficial location, biopsy was thought to be too technically challenging and short follow-up was recommended. At 6-month mammographic follow-up, there was interval non-visualization of both calcifications. Additional clinical history interrogation revealed that due to a diffuse pruritic rash, the patient had been applying topical betamethasone dipropionate daily to her entire body, including her breasts, when she received her initial mammogram. This case illustrates how corticosteroid ointments and lotions may mimic suspicious calcifications on mammography, reinforcing the importance of guidelines recommending avoidance of topical products on the day of imaging.

Keywords: Breast cancer screenings; breast imaging; mammography; pseudocalcifications

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Key Points

- Deodorant, powders, lotions, or ointments for the breast and axillae can all confound screening mammography and cause pseudocalcifications.
- Less commonly considered sources such as topical steroids must be considered as potential sources of pseudocalcifications on screening mammography.
- Early detection of indeterminate microcalcifications play a critical role in breast cancer screening; thus, further awareness regarding pre-imaging preparation among physicians, technologists, and patients must be achieved.

Introduction

The American College of Radiology (ACR), UK National Health Service (NHS), and American Cancer Society (ACS) all recommend avoidance of deodorant, powders, lotions, ointments, or creams on the day of a screening mammogram. These products may contain metallic substances, such as zinc or aluminum, that mimic breast parenchymal calcifications, prompting further diagnostic evaluation due to concern for malignancy. Given the critical role of screening mammography in the early detection of breast cancer in women, ensuring accurate imaging is essential to patient care. Though there are several case reports detailing the presence of pseudocalcifications due to skin products, to the best of our knowledge, none associated with betamethasone dipropionate have been previously described.

Case Presentation

A woman in her 70s presented to a designated comprehensive breast imaging center for her annual mammogram. The patient reported no personal history of breast cancer. However, she did report a family history of breast cancer in her mother in her mid-60s and her sister in her 50s. Prior mammograms demonstrated stable findings with no suspicious calcifications for the past 5 years (Figure 1). On the day of her mammogram, the patient disclosed a one-month history of diffuse pruritic rash, which involved both breasts. Her mammogram demonstrated two groups of microcalcifications in the left upper central breast and left upper outer breast (Figure 2). Due to their superficial location, they would likely not be amenable to stereotactic breast biopsy and were thought to potentially represent dermal calcifications. Short interval mammographic follow-up in six months was recommended. On her follow-up mammogram of the left breast, there was complete interval non-visualization of the previously seen superficial grouped calcifications, suggesting resolution of dermal calcifications versus the presence of residue from skin products (Figure 3). The patient was informed of the results in the clinic at the time of the exam and was questioned about any use of topical agents during her prior mammogram. The patient revealed that due to her rash, she had been applying topical betamethasone dipropionate, USP 0.05%

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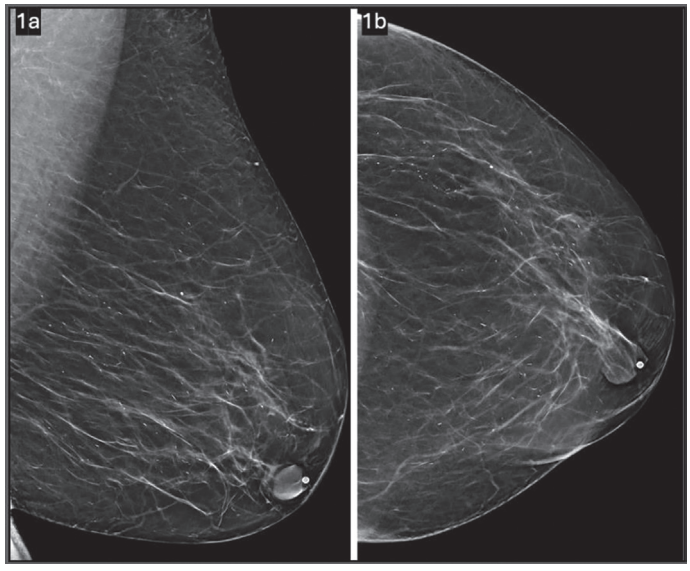

Figure 1. One year prior to the described presentation, digital mediolateral oblique (1a) and craniocaudal (1b) views of the bilateral breasts were obtained with tomosynthesis

The patient's annual screening mammogram one year before the episode described demonstrated breast tissue with scattered areas of fibroglandular density and no suspicious mammographic findings

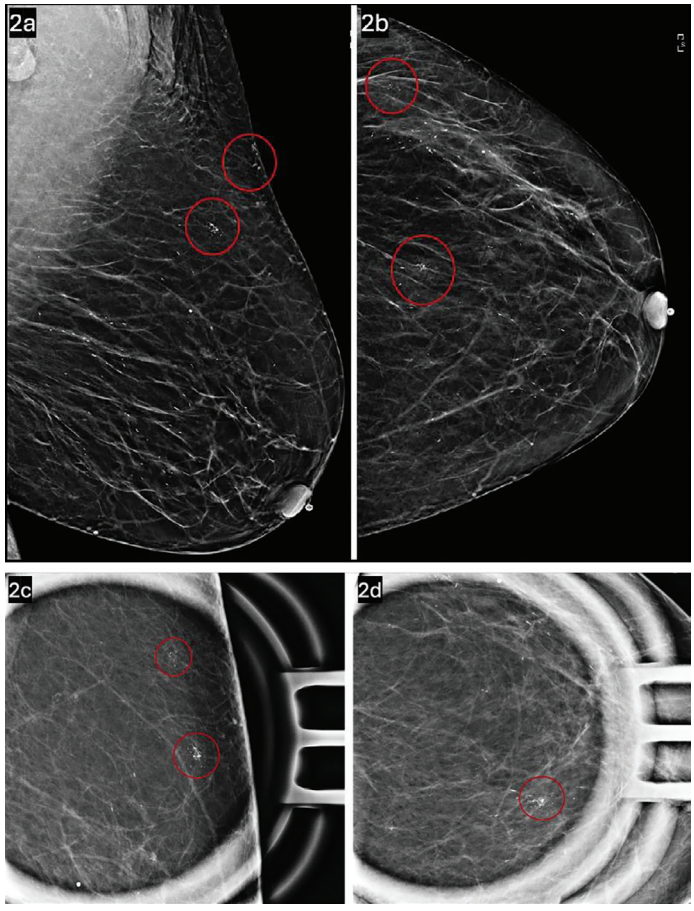

Figure 2. Digital mediolateral oblique (2a) and craniocaudal (2b) views of the left breast were obtained with tomosynthesis. Mediolateral (2c) and craniocaudal (2d) magnification views of the left breast were also obtained

This mammogram revealed a new group of amorphous and coarse heterogeneous calcifications in the left upper central breast at posterior depth, spanning up to 0.8 cm. There was also an additional new group of amorphous calcifications in the left upper outer breast, at posterior depth, spanning up to 0.5 cm. Both groups of calcifications were superficial, possibly representing dermal calcifications. Moreover, due to the superficial location, they were not amenable to stereotactic breast biopsy. The findings corresponded to a Breast Imaging Reporting & Data System category 3, and therefore short-interval follow-up at 6 months with left diagnostic mammography was recommended

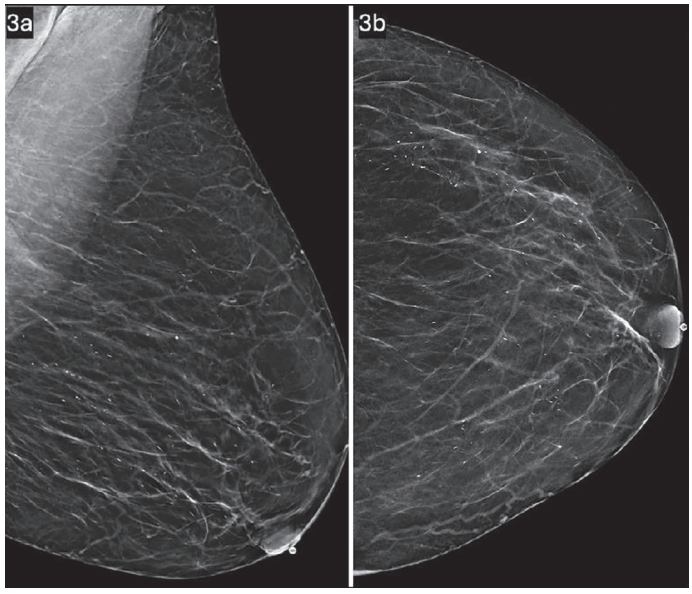

Figure 3. Short interval (six month) follow-up mammogram, digital diagnostic mediolateral oblique (3a) and craniocaudal (3b) views of the bilateral breasts were obtained with tomosynthesis

There was complete interval non-visualization of the grouped coarse heterogeneous and amorphous calcifications in the upper central and upper outer left breast

ointment and lotion to her body, including her breasts. The patient had frequently been treated with topical betamethasone dipropionate for her chronic dermatitis. She did not realize this could affect the outcome of her mammogram, but considered this once she was informed that the superficial calcifications just vanished. The patient was advised to return to routine annual mammographic screening and avoid wearing topical ointments during the day of her mammogram.

Discussion and Conclusion

This case highlights the diagnostic challenge of pseudocalcifications on mammography and underscores the importance of adherence to pre-imaging guidelines and careful consideration of clinical history. Pseudocalcifications on mammography are imaging artifacts that mimic true parenchymal breast calcifications, which are frequently associated with malignancy. As opposed to true calcifications, they are transient, frequently superficial, opacities caused by external radio-opaque particles from topical residues on the skin of the breast. The ability to distinguish between true parenchymal calcifications and pseudocalcifications is important, given that most cases of ductal carcinoma *in situ* are associated with suspicious microcalcifications (1, 2), often warranting further diagnostic imaging, short interval follow-up, and/or stereotactic breast biopsy, the latter particularly relevant in cases of new indeterminate calcifications, as in the presented case. Thus, the ability to distinguish true calcifications from pseudocalcifications or prevent them, will avoid unnecessary diagnostic work-up and follow-up.

In this case, the patient presented with new grouped amorphous, coarse, heterogeneous calcifications on screening mammography, findings frequently associated with malignancy. On follow-up diagnostic mammogram after a six-month interval, the complete non-visualization of the calcifications strongly favored the diagnosis of dermal pseudocalcifications due to an undisclosed topical agent. These transient, calcifications may be caused by radiopaque metallic particles found in deodorants, antiperspirants, talcum powders, lotions, and ointments. In the case of pseudocalcifications associated with betamethasone dipropionate lotion and ointment, the thickness and density of the applied topical treatments, the active ingredient itself, the emollients, the preservatives, and/or trace radiopaque metallic compounds may be contributing factors and require further investigation. Another type of pseudocalcification artifact may be seen when a synthesized 2D reconstruction produced from digital breast tomosynthesis source images enhances dense parenchymal tissue in a way that produces the appearance of calcifications in the reconstructed 2D. However, this type of pseudocalcification artifact would not be reproduced on 2D magnification views.

Though there are ample examples of deodorants and antiperspirants mimicking calcifications in the literature, there are relatively few reported cases associated with dermatological treatments. One case described a 72-year-old woman with pseudocalcifications secondary to zinc-containing ointment (3). Similar to our patient, the complete interval resolution of the calcifications was highly suggestive of an external radiopaque material, and the patient's provided clinical history confirmed this. Suen et al. (4) reported a case of pseudocalcifications on screening mammography of a woman using calamine lotion. In terms of larger studies, one retrospective analysis of 34 patients in Korea identified topical *go-yak*, a Chinese herbal medicine for breast abscesses, as a possible source of pseudocalcifications (5). Another individual example is an Australian case report of pseudocalcifications associated with tungsten particles in a topical skin treatment (6). To the best of our knowledge, however, this is the first case report published on a topical corticosteroid associated with mammographic pseudocalcifications.

Overall, this case reinforces the importance of adhering to pre-imaging guidelines regarding topical products and maintaining an index of suspicion for pseudocalcifications when multiple groups of superficial calcifications are seen, particularly if the patient reports a current

history of a body rash, as in this case. With the ACR, UK NHS, and ACS all recommending avoidance of deodorant, powders, lotions, or creams on the day of a screening mammogram, breast imaging professionals must be vigilant and consider dermatologic treatments, such as betamethasone dipropionate, as a possible confounding factor causing calcific artifacts (7-10). This will be important for both improved quality of screening and reducing unnecessary patient distress, diagnostic work-up and intervention. Further awareness among physicians, technologists, and patients alike will help prevent the presence of exogenous pseudocalcifications and ensure accurate imaging interpretation.

Ethics

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.P., J.S., P.S.A., C.P-T.; Concept: H.P., J.S., P.S.A., C.P-T.; Design: H.P., J.S., P.S.A., C.P-T.; Data Collection or Processing: H.P., J.S., P.S.A., C.P-T.; Analysis or Interpretation: H.P., J.S., P.S.A., C.P-T.; Literature Search: H.P., J.S., P.S.A., C.P-T.; Writing: H.P., J.S., P.S.A., C.P-T.

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Letter to the Editor

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Aromatase Inhibitor-Related Alveolar Hemorrhage or ANCA-Associated Vasculitis?

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Cite this article as: Büyükavcı R. Aromatase inhibitor-related alveolar hemorrhage or ANCA-associated vasculitis? Eur J Breast Health. 2026; 22(1): 110-111

Dear Editor,

A 64-year-old woman who had undergone a mastectomy for left breast cancer three years earlier and had been treated with aromatase inhibitors (AIs) (anastrozole 1 mg/day) postoperatively. Two years after treatment, she presented with diffuse arthralgia and myalgia persisting for three months, followed by increasing dyspnea and massive hemoptysis. Computed tomography (CT) showed bilateral reticular formation, ground-glass shadows, and diffuse hemorrhage areas in the lung fields (Figure 1). A differential diagnosis was made for alveolar hemorrhage syndromes (AHS), and no finding suggesting vasculitis was found. With this presumed drug-induced pathology, the relevant treatment was discontinued, and corticosteroid treatment was started. A rapid clinical response and laboratory and radiologic improvements were evident. However, during a routine follow-up, areas of alveolar hemorrhage and a ground glass appearance were observed again on the thoracic CT. Anti-proteinase 3 anti-neutrophil cytoplasmic antibodies (PR3 ANCA) sent one year later was positive. The patient was diagnosed with ANCA-associated vasculitis six months prior to the time of writing, and steroid+rituximab treatment was started. Radiologic improvement was observed on CT, and PR3 ANCA became negative (Figure 2). AI treatment was continued with letrozole 2.5 mg/day. Among the side effects of AIs, drug-induced AHS should be kept in mind, but the patient should be closely monitored for other primary diagnoses. The patient is still under follow-up.

AIs are recognized as the first-line treatment for the long-term treatment of breast cancer in postmenopausal women (1). Adverse effects frequently encountered during treatment with AIs include generalized arthralgia and myalgia, bone loss, and effects on the cardiovascular system and blood lipids (2, 3). In patients with breast cancer, inflammatory rheumatic diseases related to both the drugs used and the disease itself are relatively common (3). AHS refer to all the clinical-pathologic disorders resulting from bleeding into the alveolar space due to alveolar capillary basement membrane damage. Bleeding into the alveolar space can occur in the setting of medications, infections, autoimmune rheumatologic diseases, vasculitis, or idiopathically. Alveolar hemorrhage is alarming for both the patient and their healthcare provider, especially when it leads to hemoptysis. Hemoptysis may be minimal or may present with different clinical conditions ranging from life-threatening to massive hemoptysis. Therefore, rapid diagnosis and treatment are required. AHS should be considered in the presence of hemoptysis, anemia, and bilateral/unilateral infiltration on chest radiography (4). Among the side effects of AIs, of the vasculitides cutaneous vasculitis and Henoch-Schonlein purpura were the most commonly reported in the literature. Vasculitis is the most common adverse skin event reported for both tamoxifen and AIs (5). However, to the best of our knowledge there is no published report of AI-associated medium/large vessel vasculitis.

Systemic evaluation, detailed laboratory tests and radiological imaging are invaluable in patients with AHS. Since the patient had a history of malignancy and AI use and there were no findings supporting a rheumatologic diagnosis, primary drug-induced vasculitis was considered the most likely cause. AI treatment was interrupted.

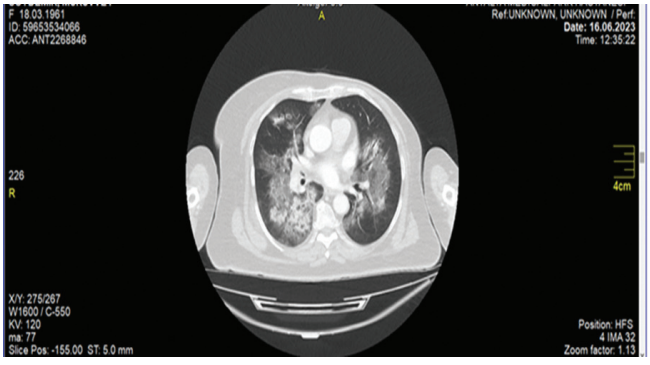

Figure 1. Thorax computed tomography with bilateral alveolar hemorrhage

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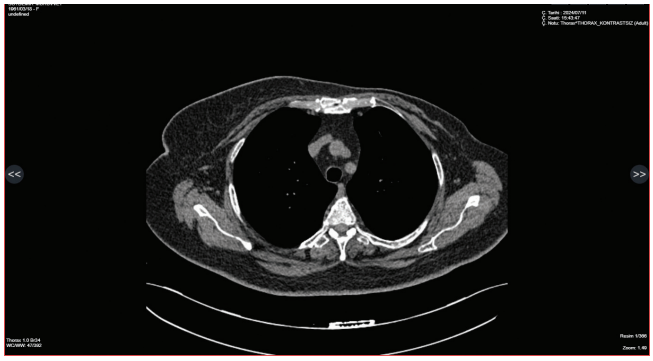

Figure 2. Thorax computed tomography after treatment

As a result of alveolar microhemorrhages that developed later and ANCA positivity, the patient was diagnosed as ANCA-associated vasculitis and appropriate treatment was initiated while AIs were restarted.

Footnotes

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

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Letter to the Editor

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Comment on "Prognostic Importance of PTEN and P53 in Aggressive Luminal A Subtype Breast Cancers"

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Dear Editor,

We read with great interest the study by Gemci et al. (1), which investigated the prognostic significance of phosphatase and tensin homolog (PTEN) and tumor protein p53 (p53) in aggressive Luminal A (LumA) subtype breast cancers. While the study attempted to identify histopathological predictors in a subtype generally associated with favorable outcomes, several analytical limitations require critical examination.

The classification of "aggressive LumA" based solely on recurrence or metastasis within five years, introduces the risk of misclassification due to the absence of genomic validation. Although molecular testing is not always available in clinical settings, reliance on immunohistochemical surrogates lacks the granularity provided by gene expression assays such as prediction analysis of microarray 50 (2). Notably, four of the five recurrent LumA cases exhibited features such as multifocality, lobular carcinoma *in situ*, or extensive intraductal component, which are known to confound subtype designation and may mimic LumA phenotypes despite underlying biological divergence (3).

Second, while all five recurrent LumA tumors showed low PTEN immunoreactivity score (<6), the comparison with non-recurrent LumA tumors failed to achieve statistical significance. The high overall prevalence of PTEN loss in the cohort (77.1%) limits its specificity, and no molecular confirmation through PTEN sequencing or methylation analysis was performed. These constraints diminish the ability to infer PTEN's prognostic independence.

Third, the interpretation of p53 histoscore (H-score) lacks biological validation. Assigning H-scores <10 as null-type p53 expression is inaccurate; such low scores can still reflect wild-type expression unless confirmed with sequencing. The threshold of <50 was used without genomic correlation, and most recurrent LumA tumors had H-scores <10. However, immunohistochemistry alone is insufficient to distinguish between wild-type, missense, and loss-of-function mutations (4). Without tumor protein p53 sequencing, these findings remain speculative.

In addition, tumor-infiltrating lymphocyte (TIL) density was evaluated using an arbitrary cutoff without reference to standardized scoring criteria, such as those proposed by the International Immuno-Oncology Biomarker Working Group. Although lower TIL density was observed in recurrent LumA tumors, the sample size of only five cases precludes robust inference. Moreover, the absence of multivariate modeling limits the ability to assess the independent contributions of each biomarker to recurrence risk (5).

In summary, while the study offers initial insight into the pathological features of aggressive LumA subtype breast cancers, the small sample size, absence of genomic validation, and non-standardized biomarker thresholds limit the reliability of its prognostic claims. Future work should incorporate multivariate analysis and molecular subtyping to establish the independent prognostic utility of PTEN and p53.

Footnotes

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

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Letter to the Editor

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Prognostic Significance and Molecular Classification of Triple Negative Breast Cancer: A Systematic Review

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Cite this article as: Aziz OBA. Prognostic significance and molecular classification of triple negative breast cancer: a systematic review. Eur J Breast Health. 2026; 22(1): 114

Dear Editor,

I appreciate Dogra et al. (1) for their systematic review on the prognostic significance and molecular classification of triple-negative breast cancer (TNBC). It takes a lot of time and effort to collect and analyse this amount of data. The results provide valuable insight into different subtypes of TNBC along with their prognosis. However, I wish to bring your attention to some of the issues in the methodology and data extraction.

Systematic reviews and meta-analyses are generally not included in conducting systematic reviews as these are secondary data, unless it's a "meta-meta-analysis" or "review of review". Alternatively, if systematic reviews are included, then studies of the same period should be excluded from the search. Where the authors did mention that review articles were to be excluded, the inclusion criteria included systematic reviews and meta-analyses.

The Study selection process lacks clarity. The authors claim that 421 studies were finally included for meta-analyses after completing the selection process. However, as per Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) flowsheet, 708 articles were removed out of 771 leaving only 63 articles. The study selection process does not cater for the specifically mentioned "studies included in quantitative synthesis (n = 58)" in the PRISMA flow diagram. The PRISMA flow diagram includes 50 studies from other sources but study selection procedure does not include them.

As per the PRISMA 2020 flow diagrams for systematic reviews, excluded studies are lateralized from the main flow of remaining studies to keep things clear. This is not the case in this study as excluded studies are presented in the same flow making it difficult to understand. The studies from other sources also need to be presented in a different stem which joins the main stem at the end. This again is not the case in this study (2).

A breakdown of included studies on the basis of the study types such as randomized controlled trials (RCTs), clinical trials, cohort studies, case-control studies, and systematic reviews/meta-analyses is not mentioned. This also entails that the number of RCTs undergoing RoB and observational studies undergoing NOS is not made part of this study which is considered an essential in systematic reviews/ meta-analyses.

This review however provides useful information about this complex heterogenous disease and its implications for therapeutic strategies. Understanding molecular diversity is crucial in opting the right treatment modality in TNBC leading to better patient outcomes.

I really liked the segment of current gaps and future directions where authors admit a lack of consensus on molecular classification criteria leading to challenges in development of standardized clinical guidelines for each molecular subtype. This to date remains a controversial area.

The sole purpose of this input is to stimulate further discussion for clarity and improvement in future systematic reviews.

Footnotes

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