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Turkish Federation of Breast Diseases Societies

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

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

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European Journal of Breast Health

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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European Journal of Breast Health

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

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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.

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

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

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Review

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New Approaches in Breast Cancer Radiotherapy

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ABSTRACT

Breast cancer stands as the most prevalent malignancy, necessitating a well-established approach to its management due to its sustained prevalence over decades. The implementation of intensive treatments, combining various modalities, has yielded excellent survival outcomes. Consequently, the optimization of quality of life and the mitigation of long-term side effects emerge as critical considerations for clinicians. As a result, discussions regarding treatment de-intensification strategies have been initiated for all treatment modalities, including surgery, radiotherapy (RT), and chemotherapy. RT plays a crucial role in adjuvant therapy. The efficacy of RT in disease control and overall survival across all stages of breast cancer has been demonstrated in numerous clinical trials and meta-analyses utilizing extensive datasets. However, advancements in genetic tumor profiling and improved identification of disease subgroups have prompted a reevaluation of RT omission in low-risk groups as a strategy for treatment de-intensification. Conversely, technological improvements and shortened total treatment times with hypofractionation make RT a secure and feasible option for enhancing local control and survival with minimal impact on the quality of life.

Keywords: Breast cancer; oncotype Dx; radiotherapy; review

Cite this article as: Demircan NV, Bese N. New Approaches in Breast Cancer Radiotherapy. Eur J Breast Health 2024; 20(1): 1-7

Key Points

- Breast cancer is globally the most prevalent cancer type and has a favorable prognosis with a multi-modality approach.
- Radiotherapy plays a crucial role in the adjuvant setting, and its benefit to local control and survival has been demonstrated by numerous randomized trials and meta-analyses with large datasets.
- Recently, most efforts in breast cancer therapy have focused on better understanding the biology and genetics of tumors and de-intensifying treatment accordingly.
- Contemporary studies aim to omit radiotherapy in low-risk patients. On the other hand, with advancements in technology and effective utilization of hypofractionation, evolved radiotherapy emerges as a more feasible option by minimizing radiation-related long-term toxicities and reducing its burden on the national healthcare system.

Introduction

Innovations in Fractionation Schemes

Adjuvant radiotherapy (RT) is not only effective in achieving local control but also contributes to the overall survival of patients at all stages of breast cancer (1, 2). Consequently, adjuvant RT is widely used in breast cancer treatment. However, conventional fractionation necessitates the delivery of a 45–50.4 Gy dose to the whole breast, spread over 25–28 fractions, taking 5–5.5 weeks. In addition to this, a boost dose is required after breast-conserving surgery, which is known to enhance local control rates, usually administered in 4 to 8 fractions, delivering a 10–16 Gy dose (3). This can extend the total treatment time to 7–8 weeks. The prolongation of total adjuvant RT time has led to shifts from breast-conserving approaches to mastectomy for some patients and the omission of RT for others (4). Furthermore, given that breast cancer is the most common cancer type globally, the total treatment time is a significant concern for national healthcare systems and the appointment loads of clinics (5).

However, concerns regarding hypofractionation were raised due to its potential long-term side effects on normal tissues, the inadequacies of previous RT techniques in normal tissue sparing, and the longer life expectancy of breast cancer patients. Nevertheless, advancements in RT technology prompted efforts to shorten the total treatment time for

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early-stage, low-risk breast cancer patients approximately two decades ago. These endeavors yielded local control outcomes that were found to be non-inferior when compared to conventional fractionation. Following initial attempts with moderate hypofractionation (a total of 15–16 fractions without a boost), new schemas evolved into ultra-hypofractionation (a total of 5 fractions), demonstrating their safe applicability in early-stage breast cancer. Some of the studies that have influenced our clinical practice are summarized in Table 1.

While the role of hypofractionation has been established in early-stage breast cancer, data on the use of hypofractionation for chest wall irradiation, regional nodal irradiation, post-neoadjuvant treatment, and patients undergoing reconstruction has not yet matured. However, there is still some data available from the START A and B trials, as well as Chinese and US studies. The START A and B trials were non-inferiority trials comparing hypofractionated whole breast irradiation (HF-WBI) and standard fractionated whole breast irradiation (SF-WBI) for early-stage breast cancer. In these trials, post-mastectomy chest wall RT was administered to 15% and 8% of the patients, respectively. These trials demonstrated that HF-WBI was non-inferior to SF-WBI in terms of disease control and acute and late toxicities. Even though the number of patients receiving post-mastectomy radiotherapy (PMRT) was relatively low compared to the total study population, increased side effects related to mastectomy were not observed in these trials.

In the Chinese study, 820 patients underwent PMRT+RNI (regional nodal irradiation) with a regimen of 43.5 Gy/16 fractions. PMRT was delivered using electron energy, and a 2D technique was employed for irradiation of the supraclavicular field. Internal mammary nodes (IMN) were not included. The study's results indicated similar outcomes for disease control and late adverse effects (such as radiation

Table 1. Randomized studies that have altered the clinical practice

Study	Duration	Patient no	Age	Follow-up (years)	Node positive (%)	RT dose	Local control (%)	Side effects
Ontario CANADA trial (6)	1993-1996	1234	24.7% <50	10	0	50 Gy/25fr vs 42.5 Gy/16fr	93.3 93.8	Similar late toxic effects for skin and breast cosmesis
Royal Marsden (7)	1986-1998	1410	54.5 (mean)	9.7	33	50 Gy/25fr vs 39 Gy/13fr vs 42.9 Gy/13fr	92.1 90.9 92.9	39 Gy arm has the best results for both cosmesis and skin changes, 42.9 Gy arm has the worst results
START-A (8)	1999-2002	2236 (Mastectomy included, 15%)	57 (mean)	9.3	29	50 Gy/25fr vs 39 Gy/13fr vs 41.6 Gy/13fr	93.3 91.9 94.4	Lower rates of late side effects with photographic evaluation and PRO for 39 Gy arm
START-B (9)	1999-2001	2215 (Mastectomy included, 8%)	58 (mean)	10	24	50 Gy/25fr vs 40 Gy/15fr	94.8 96.2	Lower rates of late side effects with photographic evaluation and PRO for 40 Gy arm
HYPO (10)	2009-2014	1854 (DCIS included, 13.3%)	59 (median)	9	9.8	50 Gy/25fr vs 40 Gy/15fr	96.7 97	Skin changes and pain was seen in low rates and similar between dose groups. Patient satisfaction for breast cosmesis was high for both groups. RT boost did not seem to increase breast induration.
FAST (11)	2004-2007	915	62.9 (mean)	9.9	0	50 Gy/25fr vs 30 Gy/5fr vs 28.5 Gy/5fr (once a week for 5weeks)	99 99 98.7	NTE was increased in 30 Gy arm compared to 50 Gy arm. 28.5 Gy has similar results with conventional arm.
FAST-FORWARD (12)	2011-2014	4096 (mastectomy included, 6.4%)	61 (median)	5.9	18.3	40 Gy/15fr vs 27 Gy/5fr vs 26 Gy/5fr (over one week)	97.9 98.3 98.6	Moderate to marked NTEs for dose groups were 9.9%, 15.4% and 11.9% respectively. Twenty-six Gy regimen has similar effects on normal tissue with 40 Gy regimen.

NTE: Normal tissue effects; PRO: Patient reported outcomes; RT: Radiotherapy

pneumonitis, lymphedema, ischemic heart disease, and shoulder), while acute toxicities were significantly better in the HF-PMRT group compared to the SF-PMRT group (3% vs. 8%). An important criticism of this study is that the techniques used in this study are no longer in use in Europe, US, or our country (13).

Another study for HF-PMRT was conducted in the US, designed as a phase II prospective trial, and included 69 patients for PMRT+RNI, with 54% of them including IMN irradiation, at a dose of 36.6 Gy in 11 fractions. High-risk patients (close margins, lymphovascular invasion +, triple-negative, young age) were eligible for the study, and breast reconstruction was performed for 45% of the patients. The 5-year local recurrence rates and grade 2 acute skin toxicity were reported as 4.6% and 24%, respectively. While there were no grade 3 late side effects, the rate of grade 3-4 complications related to reconstruction was reported as 35% with this fractionation scheme (14). The long-term rates of cardiac, pulmonary, and chest wall toxicities were all <1% in all four of these studies (15).

Additionally, numerous retrospective studies in the literature report the safe administration of hypofractionated regimens for PMRT and RNI (15). Despite the encouraging results obtained from these initial efforts, further randomized studies are required to validate the use of hypofractionated schemes for routine application in clinical practice, particularly after breast reconstruction. The results of the FABREC trial recently presented at the 2023 American Society for Radiation Oncology (ASTRO) Annual meeting (16) indicated that both accelerated and standard courses of treatment were equally effective in preventing the recurrences after immediated implant based reconstruction and had the same level of side effects. The RT-CHARM study is still ongoing. FAST Forward nodal substudy is primarily powered to demonstrate non-inferiority in terms of late normal tissue toxicity with an ultrafractionation scheme. Definitive assesment of non-inferiority will be available only at the 5-years analyses (17). Until now there is no data for offering hypofractionated comprehensive nodal RT following neoadjuvant chemotherapy for patients with locally advanced breast cancer.

The Role of Tumor Biology in Breast Radiotherapy

Omission of Radiation Therapy Using Biomarkers After Breast-Conserving Surgery

The low rates of local recurrence observed in breast cancer patients with ultra-low-risk factors raise the question of omitting radiotherapy. Several studies have sought to identify women with early breast cancer who would not derive significant benefit from RT. Long-term outcomes from two randomized trials, namely the CALGB 9343 and PRIME II trials, have indicated increased rates of local recurrence with no impact on survival when radiation was omitted after breast-conserving surgery in women aged 65 years or older (18, 19). Therefore, considering the omission of RT in elderly women with stage I, ER-positive, lymph node–negative disease who are committed to endocrine therapy remains a standard of care option. However, accelerated partial breast irradiation (APBI) or other hypofractionated schedules might serve as alternatives to the omission of RT to enhance local control rates when only endocrine treatment is prescribed. The recently published prospective cohort LUMINA trial focused on breast cancer patients aged at least 55 years who underwent breast-conserving surgery for T1N0, grade 1–2 luminal A subtype of breast cancer, along with adjuvant endocrine therapy. The Luminal A subtype was defined by estrogen receptor positivity of ≥1%, progesterone receptor positivity of >20%, negative Her-2 status, and a Ki-67 index of 13.5% or less. The incidence of local recurrence was found to be 2.3% over 5 years, but longer follow-up will be necessary for a comprehensive assessment (20).

Recent studies focus on using biomarkers such as oncotype DX recurrence score and genetics to guide adjuvant systemic therapy decisions. Numerous prospective studies are underway to evaluate the use of clinicopathologic factors and assays in better identifying low-risk patients for whom adjuvant breast RT may be safely omitted. One such study is the randomized De-Escalation of Breast Radiation trial, which, with an oncotype recurrence score of less than or equal to 18, aims to assess the expansion of RT omission to women aged 50 to 69 years (21). The EXPERT trial is randomizing patients aged 50 years or older with stage I, grade 1 or 2, tumor size 2 cm or less, and a Prosigna (PAM50) assay indicating a luminal A biological subtype into RT and RT omission arms (22).

In addition to these randomized trials, two single-arm prospective trials are ongoing. The IDEA trial targets women between 50 and 69 years with an Oncotype DX score of less than or equal to 18, while the single-arm PRECISION trial focuses on women between 50 and 75 years with T1 tumors and low risk according to the PAM50 molecular profile (23, 24). The novel Profile for the Omission of Local Adjuvant Radiation (POLAR) genomic signature, based on loco-regional recurrence (LRR) biology, may identify patients at low risk for LRR despite not receiving RT and, thus, may be candidates for RT omission (25).

Omission of Regional Nodal Irradiation in Node-Positive Breast Cancer With the Use of Biomarkes Assays

An individual patient data meta-analysis involving 14,324 women across 16 trials revealed that regional node RT significantly reduced breast cancer mortality and all-cause mortality in trials conducted after 1980. Estimated absolute reductions in 15-year breast cancer mortality were 2.7% for individuals with one to three positive axillary lymph nodes (26). Despite the proven benefit of regional irradiation for patients with low axillary involvement, it is crucial to identify subgroups of patients who may not require PMRT or regional nodal irradiation.

In cases of lymph node-positive breast cancer subtypes, such as triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer, systemic therapy is typically administered before surgery. However, for patients with node-positive estrogen receptor (ER)-positive/HER2-negative breast cancer, surgery may be the primary intervention. Several studies have indicated that the oncotype recurrence score (RS) can identify patients at the highest risk for locoregional recurrence in the node-positive setting (27, 28). For instance, the SWOG S8814 trial demonstrated that the estimated cumulative incidence of locoregional recurrence rates over 8.6 years was 9.7% for patients with low-risk RS and 16.5% for those with high-risk RS in ER+, node-positive breast cancer (29).

Taking into consideration the above data, the Canadian Cancer Trials Group recently initiated the TAILOR RT/MA.39 trial. This trial randomizes lumpectomy or mastectomy patients with one to three nodal macrometastases or micrometastases, or those classified as pT3N0, with an oncotype RS of less than or equal to 25, to receive regional nodal irradiation or not. The objective is to determine whether PMRT or regional nodal irradiation can be safely omitted in this specific group of patients (30).

Technological Advances

Over the course of several decades RT techniques have undergone significant advancements. The initial approach involved 2D planning, which did not incorporate the use of computerized tomography (CT) imaging and the delineation of critical organs. This method was subsequently replaced by three-dimensional conformal radiotherapy (3D-CRT). Following this, the forward planning technique known as Field-in-Field (FINF) was introduced, utilizing the movement of multi-leaf collimators to mitigate the presence of hot spots within the radiation therapy (RT) field. FINF has proven to be instrumental in reducing acute skin complication rates and enhancing breast cosmesis when compared to the conventional 2D RT approach (31, 32).

Subsequently, Intensity Modulated Radiation Therapy (IMRT) with inverse planning became available, clinicians the capability to optimize RT plans according to the specific conditions prior to dose calculation. IMRT has been shown to provide better preservation of breast skin and critical organs and to achieve a more homogeneous dose distribution within the target area compared to 3D-CRT (33). However, the prolongation of treatment duration and the displacement of the breast due to respiratory motion have introduced setup uncertainties. With the introduction of respiratory control systems IMRT can be safely administered for breast, chestwall and comprehensive regional irradiation. The volumetric arc therapy (VMAT) technique, which is essentially rotational IMRT, made possible by the continuous movement of the gantry, has shortened treatment times and enabled the creation of RT plans with similar quality dose distribution to IMRT (34). With the VMAT technique, it is possible to generate more reliable plans in terms of dose distribution and delivery compared to 3D-CRT. This has also been reflected in clinical results, with Grade 1 skin toxicities being reported at around 30%, and physician-reported cosmetic satisfaction rates reaching 98% (35).

Furthermore, a specific technology, helical tomotherapy (HT), can also be utilized in breast irradiation. While it is more successful in terms of hot spots and ipsilateral critical organ protection compared to other techniques, it significantly increases the low-dose area (36). HT's dosimetric advantages are particularly highlighted in bilateral breast and chest wall irradiation. However, due to the extended beam-on-time duration, uncertainties during treatment increase. Therefore, the VMAT technique, which provides results closest to HT, may be preferred for similar patients (37, 38).

Darby et al. (39), examining the results of 2,168 breast cancer patients treated between 1952 and 2001, it was reported that every 1 Gy increase in the mean dose to the heart led to a 7.4% increase in the rate of coronary disease. Although in the present day, deaths from cardiac events in breast cancer are almost non-existent, this study underscores the importance of protecting the heart during radiation therapy. Indeed, current guidelines have limited mean heart doses to <2.5 Gy for breast only RT (40).

The optimal parameter for evaluating cardiac toxicity is a subject of debate. The literature emphasizes the importance of paying attention to doses delivered to the left anterior descending coronary artery (LAD) (41). Given that LAD and the cardiac apex are anatomically located more anteriorly, they are more likely to be exposed to radiation during treatment. Even when mean heart doses are within normal limits, these areas may still receive higher doses.

Reducing heart doses can be challenging, particularly during left breast or chest wall irradiations where internal mammary lymph nodes need to be included in the radiation field. Deep Inspiration Breath Hold (DIBH), hybrid planning, and positioning the patient in the prone position offer solutions to this problem.

DIBH involves holding one's breath during the deep inspiration phase, allowing the heart to move away from the chest wall, thereby achieving the necessary distance for a dose reduction between the target and the heart. It can be applied using surface guidance or a spirometer, with patient compliance being essential (42). While it is generally emphasized in left-sided irradiations, studies have also demonstrated dosimetric advantages for heart and lung parameters in right-sided irradiations (43). In patients treated with this technique, there is a significant dose reduction in level 1–2 axilla that incidentally receive doses from tangential fields (44). Importantly, in the ACOSOG Z0011 and AMAROS studies, which focused on axillary treatment de-escalation in early-stage disease, DIBH was not used. Therefore, when DIBH is applied in this patient group, attention should be paid to the delineation of the axillary target volume intended for inclusion in the RT fields.

Hybrid planning is the term used to describe the combined use of FIF, IMRT, and VMAT techniques. This allows for the optimal utilization of the strengths of each technique while minimizing their weaknesses. Dosimetric studies have shown that hybrid techniques provide a more homogeneous dose distribution and contribute to the reduction of ipsilateral lung and heart doses (45).

Another technique that can be used to reduce doses to critical organs is prone positioning. This method is particularly advantageous for patients with pendulous and large breasts in terms of skin, lung, and heart doses (46). With this technique, average lung doses can be reduced from 3.9 Gy to as low as 0.6 Gy (47). It is known that in breast cancer, smoking increases the risk of developing secondary cancers in the lungs (48). Therefore, minimizing lung doses is of great importance. Additionally, it has been demonstrated that the axillary region can be safely irradiated in the prone position (49).

In addition to innovative technologies, the reduction of treatment volumes has also been considered to minimize treatment toxicity. As a result of studies in this direction, it has been established that APBI can be performed in early-stage low-risk breast cancer. The research initially began with interstitial brachytherapy and was later confirmed with 3D-CRT and IMRT (50-52). Today, according to the guidelines of ASTRO, ABS, and GEC-ESTRO, APBI is recommended for patients with tumors <2–3 cm, estrogen receptor (ER) positive, no lymphovascular invasion, negative surgical margins (>2 mm) and older than 50 years old (53).

In breast cancer, one of the current radiation therapy techniques is intraoperative radiation therapy (IORT), which can be administered using high-dose brachytherapy, low-energy X-rays, or electrons. However, randomized studies investigating IORT have reported a significantly higher rate of local recurrence compared to the control group, which has hindered the widespread adoption of this technique in current practice. Nevertheless, it should be noted that among these studies, TARGIT-A has faced criticism from a statistical perspective, while ELIOT has been criticized for patient selection (54, 55).

Carbon-ion and proton irradiations have a unique feature called the Bragg peak. These beams, characterized by a high linear energy transfer

(LET), do not advance further into the tissue once they reach the maximum dose. As a result, normal tissues located behind the target receive much better protection compared to photon irradiations. In fact, studies involving proton and carbon-ion irradiations have demonstrated their advantages in protecting surrounding organs such as the heart and lungs and minimizing low-dose area. However, initial studies with proton therapy raised concerns about poor cosmetic outcomes (56). While technological advancements in proton therapy have seemingly addressed this issue by increasing the number of radiation fields in treatment plans, excellent dosimetric results can already be achieved with techniques like DIBH and prone positioning. Moreover, considering the cost of proton irradiation, this technique has not yet become a routine practice. On the other hand, the outcomes of proton and photon irradiation for internal mammary chain are currently being evaluated in the ongoing RTOG 3510 trial (57).

Finally, MR-guided radiotherapy (MRgRT) has emerged as a very recent method in the treatment of breast cancer. This system allows for on-couch online adaptive planning before each fraction and the ability to monitor the target online during treatment. Furthermore, MR imaging provides superior soft tissue images. Studies have highlighted the prominence of this technology in prone-positioned APBI applications and preoperative RT applications (58, 59). The patient's time on the treatment table is extended due to routine workflow. Besides, this technology has no superiority compared with other technologies so that it is not suggested to be used in daily practice. However, it is a unique technology that can be safely applied in compliant patients.

Conclusion

Breast cancer stands as the most prevalent malignancy, necessitating a well-established approach to its management due to the sustained prevalence over decades. The implementation of intensive treatments, combining various modalities, has yielded excellent survival outcomes. Consequently, the optimization of quality of life and the mitigation of long-term side effects emerge as critical considerations for clinicians. As a result, discussions regarding treatment de-intensification strategies have been initiated for all treatment modalities, including surgery, RT, and chemotherapy.

RT plays a crucial role in adjuvant therapy. The efficacy of RT in disease control and overall survival across all stages of breast cancer has been demonstrated in numerous clinical trials and meta-analyses utilizing extensive datasets. However, advancements in genetic tumor profiling and improved identification of disease subgroups have prompted a reevaluation of RT omission in low-risk groups as a strategy for treatment de-intensification. Conversely, technological improvements and shortened total treatment times with hypofractionation make RT a secure and feasible option for enhancing local control and survival with minimal impact on the quality of life.

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Review

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Factors Affecting Pathological Complete Response in Locally Advanced Breast Cancer Cases Receiving Neoadjuvant Therapy: A Comprehensive Literature Review

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ABSTRACT

Determining pathological complete response (pCR) could be an important step in planning individual treatment, hence improving the prognosis in terms of survival. Achieving breast pCR not only improves survival but is also linked to a disease-free axilla, therefore increasing the likelihood of avoiding axillary surgery safely. The current trend in de-escalating axillary management surgically or in applying radiotherapy to the axilla is dependent primarily on breast cancer (BC) patients achieving pCR. Studies have demonstrated that certain characteristics can predict pCR, even though it is still difficult to identify these elements. A review of the literature was carried out to determine these factors and their clinical applications. A search was carried out in the MEDLINE database using PubMed, Google Scholar, and EMBASE. This yielded 1368 studies, of which 60 satisfied the criteria. The studies were categorized according to the subject they dealt with. These parameters included age, race, subtypes, clinicopathological, immunological, imaging, obesity, Ki-67 status, vitamin D, and genetics. These factors, in combination, can be used for specific subtypes to individualize treatment and monitor response to therapy. The predictors of pCR are diverse and should be utilized to personalize patient treatment, ultimately inducing the best outcomes. These determinants can also be employed for monitoring responses to neoadjuvant therapy, thereby adjusting treatment. The development of standardized markers for the diversity of BC subtypes still needs additional future research. These factors must be applied in concert in order to provide optimal results.

Keywords: Pathological complete response; neoadjuvant therapy; early breast cancer; pCR biomarkers

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Key Points

- Achieving pathological complete response (pCR) is the desired end result of using neoadjuvant therapy in responders.
- Identifying factors that determine pCR in breast cancer patients can help guide treatment, hence individualizing it.
- Achieving pCR in the breast correlates well with pCR in the axilla; this can result in the de-escalation of axillary surgery.
- pCR determinants should be used in combination to achieve optimal results. Therefore, standardization of these factors is essential.

Introduction

Locally advanced breast cancer (LABC) presents unique challenges in treatment and management, requiring a multidisciplinary approach that may involve surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Neoadjuvant therapy is becoming the treatment of choice for responders, helped by the improvements made in effective drugs. Achieving pathological complete response (pCR) is the aim of neoadjuvant therapy. pCR in the breast correlates well with pCR in the axilla. Current research when dealing with axillary surgery focuses on de-escalation. This is especially true when dealing with patients who present with clinically node-negative (cN0) breast cancer and respond well to neoadjuvant breast therapy, achieving pCR. This can also be applied to clinically node-positive axilla (cN+), as seen in certain studies. Therefore, determining the factors that predict pCR is essential. Patients who show these factors can be expected to have improved outcomes and could avoid axillary lymph node dissection (ALND). Determining pCR could be an essential step in planning individual treatment, hence improving the prognosis. This could also help identify patients who could be candidates for the omission of sentinel lymph node biopsy (SLNB). pCR also correlates well with overall survival. Although it remains challenging to determine these factors, studies have shown certain factors to be associated with pCR. The aim of this review was to identify these factors and investigate them extensively in relation to the evidence available in the literature, emphasizing their clinical applications.

Pathological complete response is defined as no residual disease in either the breast or axillary nodes. Locally advanced breast cancer (LABC) that responds to neoadjuvant therapy correlates well with disease-free

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axilla. The rapid shift now toward de-escalation of treatment for BC, surgically or medically, is gaining acceptance by many authors. With more evidence coming to light, there is a shift in favor of doing more SNLB and avoiding completion of ALND for selected candidates. Moreover, the improvement in neoadjuvant therapy was pivotal in achieving this, as well as improving survival. This de-escalation is further investigated to omit SLNB in clinically node-negative patients (cN0) who achieve pCR (1). These patients are likely to have a lower chance of axillary recurrence, hence avoiding ALND. Omitting ALND not only leads to early recovery but also decreases morbidity and improves quality of life. Furthermore, determining pCR in patients before treatment will help plan and individualize therapy. Post-mastectomy radiotherapy (PMRT) in patients with 1-3 positive lymph nodes who achieve pCR is also a subject of ongoing debate. It is postulated that omitting PMRT in these patients might lead to decreased morbidity, improve quality of life and avoid unnecessary exposure. Factors that determine response to neoadjuvant therapy and hence pCR will help to achieve these goals.

Materials and Methods

The MEDLINE database was searched using PubMed, Google Scholar, and EMBASE up to and including September 2023. The search words included pathological complete response, breast cancer, response to neoadjuvant therapy in breast cancer, and genetic mutations in breast cancer. Inclusion criteria were factors determining pathologic complete response including neoadjuvant therapy, race, age, BC subtypes, genetic mutations, and imaging. Exclusion criteria included case reports, incomplete data, specific treatments, correspondence, papers other than in English, and repetitive topics.

Results

Out of 1368 manuscripts, 60 satisfied the inclusion criteria. Full texts were obtained and analyzed. Factors were identified and grouped individually for discussion (Figure 1). The areas that were most covered and had an abundance of research papers were, subtypes, biomarkers and imaging. Although there were enough studies on most of the subjects to form an opinion, some lacked adequate numbers. This included race, plasma fibrinogen and the use of anti-lipids. In order to be as relevant as possible, the studies used were the most recent.

Although it is challenging to determine the factors that favor pCR, the factors discussed below are well-established and supported by numerous studies. Furthermore, identifying these factors will help improve treatment, hence improving prognosis in terms of disease-free survival and overall survival. However, not all patients achieve pCR due to the biological nature of BC. Therefore, it is essential to identify these patients and improve their response to neoadjuvant therapy. This will also avoid using these cytotoxic drugs in patients who otherwise will not benefit and will require other modes of treatment. The factors that influence pCR are categorized below.

Race

Terman et al. (2) looked at 2196 black and white women treated in Chicago over the past 20 years for early breast cancer. Of the 397 women receiving neoadjuvant chemotherapy (NACT), 47.5% of young white women achieved pCR, compared to 26.8% of young black women. They concluded that black women had a poorer outcome than white women, particularly in the young age group. Hence, the response to NACT and achieving pCR is significantly higher in white women, which might indicate a different pathological process. This racial disparity was also confirmed in another study (3). The disparities and lower pCR achievement were across all subtypes and correlated with poorer survival. Both studies highlighted the need to understand the disease process in black women in order to improve outcome and survival.

These findings call for further research into young black women to understand why this disparity exists and help introduce effective treatment.

Age

Verdial et al. (4) identified 1383 women with stage I-III BC treated with NACT and subsequent surgery. pCR and breast/axillary downstaging rates were assessed and compared across age groups. Younger women were significantly more likely to have ductal histology, poorly differentiated tumors, and *BRCA* mutations; 35% of tumors were hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR-positive/HER2-negative), 36% were HER2-positive, and 29% were triple-negative breast cancer (TNBC) patients, with similar subtype distribution across age groups. Overall, pCR rates did not differ by age. However, among patients with TNBC tumors, younger women had higher pCR rates (52% vs. 35% among those aged 41–60 years and 29% among those aged ≥61 years). They were more likely to have tumors with high tumor-infiltrating lymphocyte (TIL)

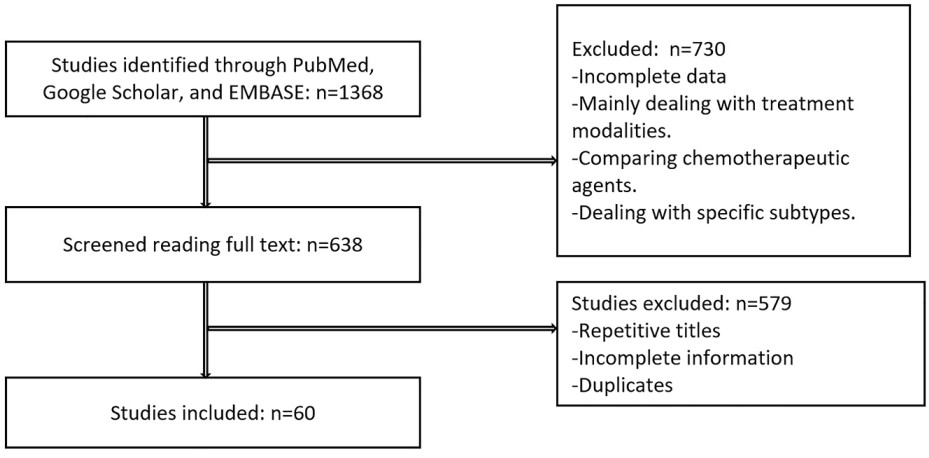

Figure 1. Consort diagram showing the number (n) of studies excluded and included

concentrations. They concluded that younger women undergoing NACT for axillary downstaging were more likely to avoid ALND across all subtypes. Despite equivalent breast downstaging and breast-conserving surgery (BCS) eligibility rates across age groups, younger women were less likely to undergo BCS.

Subtypes, Tumor Size, and Grade

The subtypes that have been shown by studies to be favorable to achieving pCR include HER2-positive and TNBC subtypes. The former two are superior for attaining pCR compared to hormone receptor-positive BC. Patients with these subtypes who achieve pCR have a very high chance of avoiding surgery. Those who do not respond tend to have a poor prognosis. pCR achievement is also related to disease-free survival (DFS), particularly for HER2-positive and TNBC (5). Overall, factors related to pCR were nonluminal subtype, high grade, and HER2 overexpression. Residual tumor and nodal stage after NACT significantly correlated with DFS and OS. Similarly, pCR after NACT showed significantly better DFS, particularly for HER2-positive, TNBC, and HER2-positive luminal B profiles (6). Luminal B (HER2-positive) subtype, HER2 overexpression subtype, and TNBC subtype were factors in predicting pCR (7). HER2-low BC patients represent roughly half of the cases treated with neoadjuvant therapy and have poor treatment responses. In the absence of pCR, HER2-low BC patients have a dismal prognosis, especially when their primary tumor hormone receptor status is negative. Therefore, studies are needed to define the biology of these tumors for new therapeutic targets and to incorporate HER2-targeting agents in early-stage treatment (8). Recent studies have reported several subtypes of TNBC, distinguishable by gene expression analysis, that may respond differently to treatment. Furthermore, novel agents, including pertuzumab or T-DM1 for HER2-type BC, bevacizumab or PARP inhibitors for TNBC, or combination regimens with these novel agents, are expected to achieve higher pCR rates and improve patient prognosis (9). Achievement of pCR led to significantly better overall survival in women with HER2-positive tumors and also to significantly better locoregional survival in women treated for TNBC. Predictive factors of pCR were a high pathologic grade, the HER2 molecular subtype, positive estrogenic hormonal receptors, and a positive HER2 receptor (10). Assessing nearly 14,000 women from a contemporary United States database, Haque et al. (11) examined the relationship between response to NACT and molecular subtype. Women with luminal A disease are the least likely to undergo pCR, with the highest rates of HER2 disease. The degree of response is associated with OS, especially in luminal B, HER2, and TNBC patients. Despite the comparatively higher likelihood of achieving pCR in TNBC cases, they found that this subgroup may still experience a survival disadvantage. pCR rate in ER expression also varies. The rate of low ER-positive tumors was similar to that of ER-negative tumors but significantly different from the rate of moderately ER-positive and high ER-positive tumors. Patients with pCR had an excellent prognosis regardless of their ER status. In patients with residual disease (no pCR), the recurrence and death rates were higher in ER-negative and low ER-positive cases compared with moderate and high ER-positive cases (12). When considering HER2-positive/HR-negative and HER2-positive/HR-positive patients, HER2-positive patients achieved more significant benefit from HER2-targeted treatment, although the efficacy of neoadjuvant therapy was relatively poor (13). Patients with TNBC and HER2-positive BC have the highest rates of BCS and pCR after neoadjuvant chemotherapy. Patients with these subtypes are most likely to be candidates for less invasive surgical approaches after chemotherapy (14). Furthermore, tumor size does not impact response to neoadjuvant therapy or pCR rate across all subtypes (15).

Obesity

Obesity is considered a risk factor for BC and is associated in some studies with a low pCR rate; other studies, as discussed below, found no association. There seems to be evidence from the numerous studies of the association of BC with obesity, which warrants further prospective research. Studies have reported that BMI was not found to influence the rate of pCR (16, 17). On the contrary, in other studies, it was found that obesity had a negative impact on pCR. Rasmy and Sorour (18) found that 58.3% of patients who failed to achieve pCR had a BMI above the normal level; they also had higher relapse rates and lower survival rates compared with normal BMI patients. It was observed that obesity was a significant independent prognostic factor that has an adverse effect on pCR (19, 20).

Vitamin D

Numerous studies have explored the relationship between vitamin D and BC incidence, progression, prognosis, and pCR rate. Vitamin D regulates the expression of genes essential in the development and progression of BC. The effect of vitamin D on the pCR rate has been looked at in numerous medical trials. Vitamin D deficiency was defined as <20 ng/mL. Vitamin D deficiency is associated with the inability to reach pCR in patients with BC undergoing NACT (21). Other studies have found no association between vitamin D and pCR (22). However, it is essential to normalize vitamin D pre- and post-therapy to maintain skeletal health. The discrepancies in the role of vitamin D warrant further clinical trials on a larger scale.

Serum Lipids

Serum lipid alteration may play a role in BC progression and achieving pCR. High density lipoprotein (HDL) cholesterol has been linked to a reduced risk of BC incidence, while low density lipoprotein (LDL) cholesterol and triglycerides have shown associations with increased risk. Chemotherapy increased the levels of triglycerides, total cholesterol, and LDL cholesterol but decreased the level of HDL cholesterol. Preoperative dyslipidemia was significantly associated with the axillary pCR rate. Dyslipidemia deteriorated after chemotherapy. Thus, the full-course serum lipid level may serve as a blood marker for predicting BC prognosis (23). The administration of anti-lipids such as simvastatin combined with chemotherapy showed improvements in pathological response in patients with LABC (24).

Plasma Fibrinogen

Elevated levels of plasma fibrinogen have been linked with increased tumor aggressiveness, metastasis, and poor prognosis in various malignancies, including BC. Low plasma fibrinogen pretreatment levels have been associated with higher rates of achieving pCR. This is potentially attributed to reduced tumor cell proliferation and angiogenesis. Low pretreatment plasma fibrinogen (<3.435 g/L) is an independent predictive factor for pCR to NACT in BC patients (25).

Biomarkers

Biomarkers play a pivotal role in predicting pCR in patients undergoing neoadjuvant therapy. While several biomarkers have shown promise,

their clinical application requires further specification. Combining two or more biomarkers might be necessary to enhance predictive value. They can be employed to initiate individualized treatment strategies, such as adding targeted therapies for certain subtypes.

Ki-67

Ki-67 is a nuclear protein used for assessing cell proliferation in BC. High Ki-67 expression is associated with ER negativity and HER2 positivity. The level of Ki-67 expression is a prognostic factor predicting disease-free and overall survival. A high Ki-67 level was significantly associated with breast pCR in BC patients receiving NACT (26). The cut-off of Ki-67 expression has been suggested at greater than 35% (27). Ki-67 expression was found to be a prognostic independent factor across all subtypes, including HR-negative (28). The expression level has also been shown to be associated with pCR of the axilla in HR-positive patients and can guide treatment options. This will improve downstaging of the axilla, leading to the avoidance of axillary surgery, as is the case with HER2-positive and TNBC (29). Although Ki-67 has a significant role in pCR prediction and treatment, it is limited by representative tissue sampling, staining, and interobserver variability. Therefore, it is essential to have standardized guidelines for its clinical application. Ki-67 remains a multifaceted approach to treatment and should be looked at in the context of other biomarkers.

Tumor-Infiltrating Lymphocytes and other Immunological Factors

The tumor microenvironment in BC consists of various immune cell populations, including T lymphocytes (CD4+ and CD8+), B lymphocytes, natural killer cells, and tumor-associated macrophages. These cells play pivotal roles in modulating the immune response of the tumor. TILs are predictive for response to neoadjuvant chemotherapy in HER2-positive and TNBC patients. A pooled analysis of 3771 patients carried out by Denkert et al. (30) found that pCR was consistently higher in higher TIL in luminal-HER2-negative, HER2-positive, and TNBC. TILs were also associated with a survival benefit in HER2-positive BC and TNBC. In contrast, increased TILs were an adverse prognostic factor for survival in luminal HER2-negative BC, suggesting a different biology of the immunological infiltrate in this subtype. Increased levels of TILs were associated with increased rates of response to NACT and an improved prognosis for the molecular subtypes of TNBC and HER2-positive BC but not for patients with HR-positive BC. A threshold of 20% TILs was the most potent outcome prognosticator of pCR (31). The platelet-to-lymphocyte ratio (PLR) has also been found to predict pCR. Low PLR is found to be favorable for achieving pCR (32-34). The neutrophil-to-lymphocyte ratio has been suggested as a predictive factor for pCR in Luminal B/Her2-negative and postmenopausal subgroups. It was found to be significantly higher in those patients who achieved pCR (35).

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are small, noncoding RNA molecules that play a crucial role in post-transcriptional gene regulation. Emerging evidence suggests that dysregulation of miRNA expression patterns in BC is associated with treatment response, particularly in achieving pCR following therapy. miRNAs are believed to predict the response to NACT. Therefore, establishing biomarkers that identify responses to NACT is imperative to personalizing treatment strategies. miRNAs, in combination with other biomarkers, hold great promise. A prospective study carried out by Davey et al. (36) found that reduced circulating miRNA was a predictor of pCR.

Circulating Tumor DNA (ctDNA)

Circulating tumor DNA (ctDNA) is a fragmented DNA released into the bloodstream by tumor cells. The noninvasive analysis of ctDNA is emerging as a significant predictor of response to treatment in BC. ctDNA levels correlate with tumor burden, stage, and genetic alteration in BC patients. ctDNA monitoring during and after therapy gives a good indication of the response to therapy. A reduction in ctDNA during treatment may predict a higher likelihood of achieving pCR. Lack of ctDNA clearance was a significant predictor of poor response and metastatic recurrence, while clearance was associated with improved survival even in patients who did not achieve pCR. Personalized monitoring of ctDNA during NACT of high-risk, early BC may aid in real-time assessment of treatment response and help fine-tune pCR as a surrogate endpoint of survival (37). Detection and persistence of ctDNA during therapy may have the potential to negatively predict response to neoadjuvant treatment and identify patients who will not achieve pCR (38). Therefore, integrating ctDNA profiling into the management of LABC patients might improve clinical outcomes (39).

Genetics

BRCA 1 and 2 are genes that are crucial in maintaining genomic stability. Mutations in these genes have been linked with an increased risk of developing BC and TNBC in particular. *BRCA* mutations have been associated with the likelihood of achieving higher rates of pCR (40). This response to chemotherapy is attributed to various factors, including defective DNA repair mechanisms and increased sensitivity to certain chemotherapeutic agents, such as platinum-based drugs. This fact may guide treatment decisions, leading to more personalized therapeutic strategies for patients with *BRCA* mutations. TNBC has the highest percentage of *BRCA* mutations among the BC subtypes. In TNBC patients, platinum-based NACT is associated with significantly increased pCR rates. Platinum-based NACT may be considered an option for TNBC patients (41). Therefore, it is reported that *BRCA1/2* mutation status leads to better responses to NACT in BC (42). NACT is not frequently used in ER-positive or HER2-negative BC because around 10% of patients achieve pCR. Since NACT can result in cancer downstaging both in the breast and axilla and prevent morbid surgery, a score to predict pCR in this population will be crucial to identify patients who can benefit from this approach. Oshi et al. (43) looked at the 5-gene score to predict pCR in HR-positive and HER2- patients, and they concluded that the 5-gene score reflects cancer cell proliferation and immune cell infiltration and predicts pCR after NACT in ER-positive and HER2-negative BC.

Neoadjuvant Therapy

The choice, combination, and dose of chemotherapeutic agents play a pivotal role in achieving pCR. The addition of targeted treatment, as in HER2-positive patients, can also increase the rate of achieving pCR. A combination of therapies, including targeted therapy, as in HER2-positive subtypes, has yielded greater results in pCR rates, hence improving the prognosis. Therefore, identifying the right dose and combination for the different subtypes is crucial to achieving these goals. This can be demonstrated as an example in TNBC. Predicted rates of pCR for TNBC treated with sequential taxane/anthracycline

regimens range from 35% to 48%. With the addition of a platinum agent, pCR rates of 55% are predicted. Further increases have been observed with the addition of immune checkpoint inhibitors to this standard chemotherapy backbone (44). In the pivotal KEYNOTE-522 clinical trial, pCR rates of 65% and 69% were reported for chemotherapy plus pembrolizumab in the overall and PD-L1-positive subgroups, respectively (45).

Imaging

The use of imaging in predicting pCR is very challenging and may be used in association with other biomarkers. It provides a noninvasive option but is limited to certain subtypes. The most commonly used imaging technique for predicting pCR is magnetic resonance imaging (MRI). Mammography has been employed to look at breast density and its association with pCR. The findings suggest that although mammographic density can be associated with HR positivity and these patients are unlikely to achieve pCR, its role in determining pCR independently is limited (46). However, microcalcification has been reported to be a predictor of poor NACT response and hence a poor rate of pCR (47). The TIL-ultrasonography (US) score determined through characteristic US findings has predictive performance for lymphocyte-predominant breast cancer. TILs-US scores can be used to evaluate the therapeutic effect of NACT and may be used as a noninvasive, convenient, and alternative method to assess stromal TILs in pretreatment biopsies; this is particularly true for HER2-positive and TNBC (48). Choudhery et al. (49) suggested an MRI radiomics by looking at the median volume, median longest axial tumor diameter, and median longest volumetric diameter among tumor subtypes of luminal, HER2-positive, and TNBC, in which there was a significant difference. There was also a significant difference in minimum signal intensity and entropy among the tumor subtypes. Additionally, sphericity in HER2-positive tumors and entropy within luminal tumors were significantly associated with pCR. Multiple features demonstrated a significant association with pCR and these authors suggested that MRI radiomics features are associated with different molecular subtypes of BC and pCR. These features may be noninvasive imaging biomarkers to identify cancer subtypes and predict responses to NACT. Radiomics based on pretreatment staging contrast-enhanced computed tomography has also been developed and validated for individualized prediction of pCR to neoadjuvant therapy in BC, which could assist clinical decision-making and improve patient outcomes (50).

Conclusion

The factors that are well established and supported by ample clinical research include BC subtypes, Ki-67, ctDNA, and TIL, among others. However, despite the suggestions and future potential use of certain factors, they remain in their infancy and require more studies. Such factors include anti-lipids, plasma fibrinogen, and vitamin D. Although race is suggested as a pCR predictor, it has only been looked at in specific populations and has to be applied as such. The predictors of pCR are diverse and should be utilized to personalize patient treatment, ultimately inducing the best outcomes. These determinants can also be employed for monitoring responses to neoadjuvant therapy, thereby adjusting treatment. The development of standardized markers for the diverse subtypes still needs additional future research. These factors must be applied in concert in order to provide optimal results.

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Original Article

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Mastalgia - The Burden Beneath

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ABSTRACT

Objective: Mastalgia is the most common breast-related complaint. A multitude of hormonal changes and lifestyle associated factors have been implicated in its causation. A long list of treatment modalities have been tried with varying success rates. To identify the most common risk factors and the most effective management strategies for mastalgia in our clinic population.

Materials and Methods: A total of 100 women between 18–65 years of age presenting to the breast clinic with mastalgia were followed throughout their course of diagnosis and management. Stepwise treatment was provided, starting with reassurance and breast support and progressing to include pharmacological measures, when necessary. The risk factors and outcomes of treatment were analysed.

Results: The majority (66%) were aged 25–47 years and the left breast was found to be most frequently involved. Involvement of the upper outer quadrant was significantly more common. Lump/nodularity was the most prevalent risk factor. Most patients showed a positive response to non-steroid anti-inflammatories (NSAIDs) in addition to reassurance, breast support and dietary changes.

Conclusion: A detailed history and clinical examination helps to identify the risk factors and the best approach for the management of mastalgia. Educating women regarding breast self-examination at regular intervals helps in early presentation and diagnosis of the underlying condition. Reassurance, breast support and lifestyle changes are the first line treatment and have good results in a significant number of patients. In our practice topical and oral NSAIDs, evening primrose oil and vitamin E were frequently used as additional treatments to non-pharmacological methods.

Keywords: Centchroman; mastalgia; menarche; risk factors

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Key Points

- Majority of the patients were premenopausal, in the age group of 25–47 years.
- Lump/nodularity was the most prevalent risk factor.
- The diagnostic accuracy was 84.9% on the basis of history and clinical examination alone.
- The pretreatment average pain score was 4.45±1.59 and after treatment was 0.69±0.88.
- Reassurance, breast support and lifestyle changes are the first line treatment followed by topical and oral NSAIDs, EPO and vitamin E as needed.

Introduction

One of the cornerstones of the diagnosis of breast disease and management is an accessible dedicated breast clinic. It not only heightens awareness about breast cancer but also educates the patients about the various risk factors and the benefits of breast self-examination (BSE) so that they can themselves note any changes and approach the healthcare system whenever required. It also provides an emotionally secure environment for the patients when the examination is carried out by female doctors.

"Mastalgia","mammalgia" or "mastodynia" is the most common breast-related complaint with a prevalence in working women and may be defined as "pain in the breast of sufficient severity for a woman to seek medical advice" (1, 2). Although mastalgia can be broadly classified as cyclical or non-cyclical, various conditions such as costochondritis (Teitze's or Tiitze's disease), herpes zoster infection and cervical spondylitis cause extramammary (non-breast) pain that can mimic mastalgia (3), as can pain due to non-chest wall pain causes such as ischemic heart disease, peptic ulcer or biliary colic. A well localized

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pain precipitated by touch, known as "trigger point pain", may be seen in patients with duct ectasia or periductal mastitis (2).

Increased estrogen production along with deficient progesterone production and hyperprolactinemia leads to changes in breast tissue that may precipitate mastalgia (4). Aberrations of normal development and involution (ANDI) may also lead to mastalgia in the reproductive age group (5). Mastalgia is also linked to certain lifestyle associated factors, such as high dietary lipid intake (6), obesity (BMI >30 kg/m^2) (7, 8), smoking (9) and excessive consumption of methylxanthine-containing products such as tea, coffee and chocolate (4, 7). Mastalgia has been considered to be a part of psychosomatic disorder (10), as demonstrated by Hafiz et al. (7), where depression and anxiety scores were higher in mastalgia patients.

Reassurance, breast support, topical and oral non-steroidal anti-inflammatory drugs (NSAIDs), evening primrose oil, vitamin E, tamoxifen, centchroman, danazol, bromocriptine, lisuride maleate, oral and topical progesterone are, to name a few, among the long list of tried and tested treatments across the world, each with a varying success rate and a rather unpredictable side effect profile (7, 11). The objectives of this study were to investigate the most common risk factors and the most effective management strategies for mastalgia in our clinic population.

Materials and Methods

This was a prospective study which included 100 women, aged between 18–65 years who came to the Breast Clinic, Government Medical College and Rajindra Hospital, Patiala with a complain of mastalgia. After a detailed history and clinical examination using visual analogue scale (VAS) scores, Cardiff breast pain charts, and Hamilton anxiety and depression scores, patients were given treatment sequentially while evaluating the cause of mastalgia and modifying the treatment accordingly.

Results

The majority of the patients with mastalgia were aged 25–47 years (66%) whereas the least affected age group was aged 58–65 years (6%). The left breast was found to be involved more than the right breast with overall incidence of mastalgia being higher than lump/nodularity. Most of the women (41%) had diffuse breast pain and the most commonly involved quadrant was the upper outer quadrant (UOQ; 36%). Around 75% of patients had a parity of 2 or less. Various risk factors were found to be associated with mastalgia and are listed in Table 1. Table 2 shows the findings of clinical examinations while Table 3 shows the various final outcomes of provisional diagnoses. The Kappa value of 0.849 signifies that the accuracy between the provisional and final diagnosis was 84.9% on the basis of history and clinical examination alone. Among the 32% of patients with a discrete lump, 19% had a lump <2 cm in size whereas lump >5 cm was seen in only 4% of the women, of which 2% had a giant fibroadenoma and 2% had histologically confirmed carcinoma. Patients having fibroadenoma underwent excision whereas those having carcinoma underwent modified radical mastectomy. Table 4 shows the various treatment modalities given to patients on the basis of their symptoms, pain scores and investigations.

Discussion and Conclusion

Mastalgia is one of the most common complaints in women worldwide. A variety of risk factors have been implicated in the causation of mastalgia and varying treatment strategies have been attempted for its resolution in the past. We found that most of the women suffering with mastalgia were premenopausal, and tended to be in the second or third decade of life. Similar results were seen in studies done by Memon et al. (5), Kalyanasundarabharathi (4), Koçoğlu et al. (8) and Sabry et al. (12). This can mostly be attributed to the increased estrogen to progesterone ratio, and hyperprolactinemia leading to changes in the breast tissue, especially the mammary stroma, that leads to mastalgia.

Breast asymmetry and right sided predominance lead to frequent screening of the left breast. Due to this, unilateral involvement of the left breast is a frequent presentation among women, as was seen in our study where, 76% patients had unilateral left breast pain. Similar trends were seen in study done by Ayaprasad (13). In study done by Khanna et al. (14) 45.8% patients had bilateral breast pain compared to 24% in the present study. The most common manifestation

Table 1. Comparison of risk factors causing mastalgia

Risk factor	n	%
Lump/nodularity	72	72
History of cyclical mastalgia	41	41
Parity and lactation frequency >2	28	28
History of wearing ill-fitting bra	27	27
Weight gain in last 5 years	24	24
Age at menarche <12 years	22	22
Similar illness in the past	21	21
Psychiatric illness (anxiety/depression)	21	21
Excessive caffeine intake	17	17
History of OCP consumption	15	15
Nipple discharge/retraction	14	14
Family history	14	14
History of smoking	0	0

Table 2. Findings of clinical examination

Examination	Percentage involvement		
Lump/nodularity	Lump	Nodularity	Absent
	32	40	28
Nipple involvement	Discharge	Retraction	
	13	1	
Skin involvement	Present	Absent	
	10	90	
Temperature	Raised	Normal	
	4	96	
Tenderness	Present	Absent	
	25	75	
Axillary lymph nodes	Palpable	Not palpable	
	6	94	
Arms and thorax involvement	Present	Absent	
	0	100	

Table 3. Various outcomes of provisional diagnoses

Provisional diagnosis Benign breast disease		Final diagnosis				
		Cancer	Idiopathic mastalgia	Infection	Traumatic	
Benign breast disease	67	62	5	0	0	0
Cancer	3	0	3	0	0	0
Idiopathic mastalgia	21	1	0	19	1	0
Infective	7	0	1	0	6	0
Traumatic	2	0	0	0	0	2
Total	100	63	9	19	7	2
Kappa	0.849					
p-value	<0.001					

of ANDI is mastalgia with or without associated nodularity (10). Kalyanasundarabharathi (4), Koçoğlu et al. (8) and Khanna et al. (14) have demonstrated a correlation between pain and the presence of lump/nodularity. In the present study, the majority had an associated lump/nodularity, with nodularity (37%) being slightly more common than a discrete lump (32%).

Pain can also be due to dilated milk ducts (9) and nipple involvement and was seen in 14% of the patients in the present study. Peters et al. (15) and Memon et al. (5) investigated the correlation between mastalgia and duct ectasia and prolactin levels, respectively. A positive family history plays an important role in the causation of breast disorders, and this is especially true in breast carcinoma, where genetics and syndromic associations are known to play an important role. Colak et al. (16) reported that 11.7% of women with mastalgia had first-degree relatives with a history of breast cancer whereas a positive history of similar breast disease was found among 14% women in our study.

Studies done by Jhonson et al. (17), Kanat et al. (18), Eren et al. (19) and Katar and Başer (20) have shown a positive correlation between psychological factors, such as stress, anxiety, and depression and mastalgia. In the present study, 6% had a history of psychiatric illness, 18% were found to have anxiety and 9% were found to have depression. Psychoeducation has been shown to be effective in patients with severe pain refractory to any form of treatment (2015) (21).

Other risk factors in decreasing order of frequency were: lactation frequency >2 (28%), history of wearing ill-fitting brassiere (27%) and excess weight gain in the last five years (24%). An early age at menarche is also one of the factors implicated in the pathogenesis of mastalgia. We found that 89% of the women who presented with mastalgia, attained menarche before 15 years of age whereas only a minority (11%) were over 16 years of age, indicating that as age of menarche increases, the incidence of mastalgia may decrease.

Cyclical mastalgia is the onset of bilateral breast pain one to two weeks before menses, owing to the exposure of breast tissue to increased levels of estrogen. Khanna et al. (14), Colak et al. (16), Eren et al. (19), Koçoğlu et al. (8), Katar and Başer (20) all showed that cyclical mastalgia was more common than non-cyclical mastalgia, which is in contrast to the findings of the present study (41% versus 59%, respectively). Yıldırım et al. (22) and Kalyanasundarabharathi (4) showed increased prevalence of non-cyclical mastalgia.

Table 4. Various treatment modalities given

Treatment given	Number	Percentage
NSAIDs	84	84.0
Evening primrose oil	77	77.0
Vitamin E	75	75.0
Surgery	32	32.0
Incision and drainage	6	6.0
Lump excision	21	21.0
Modified radical mastectomy	5	5.0
Antibiotics	8	8.0
Local anaesthetic injection	1	1.0
Centchroman	1	1.0

NSAIDs: Non-steroid anti-inflammatories

The increased number of live births have been associated with a significant decreasing trend in benign breast diseases. This may be attributed to the decline in progesterone levels which, in turn, have been associated with changes in breast structure leading to mastalgia (2). Colak et al. (16) reported the average number of live births to be 1.7 which was similar to the average parity (1.79) in the present study. Wearing of an ill-fitting brassiere and subsequent active breast movement on weak suspensory breast ligaments may also contribute to mastalgia (7, 8). This was the case in almost a third of the women in the present study. Eren et al. (19) and Koçoğlu et al. (8), found that a BMI >30 kg/m^2, use of excessive salt, weight gain in the last five years, and using a poorly fitted brassiere for their body habitus were risk factors for mastalgia.

A detailed history and appropriate clinical evaluation gives a fair idea to the physician regarding the management of patients presenting with mastalgia. Most patients respond to non-pharmacological treatment approach that include reassurance, breast support with a sports brassiere, weight reduction, regular exercise, reduction in caffeine intake (3) and diclofenac gel massage to the painful area. Pharmacological management may include the use of NSAIDs, evening primrose oil and vitamin E for symptomatic pain relief.

In the present study, while majority of patients were treated using conservative measures such as reassurance, breast support and dietary changes, drugs such as NSAIDs were used liberally to provide symptomatic relief and capsules of vitamin E and evening primrose oil were given to treat the breast pathology, as needed. For patients with severe pain, centchroman was given. Where these measures failed or in cases of breast carcinoma, surgery was the mainstay of treatment.

Koçoğlu et al. (8) reported that women gave a mean VAS pain score of 4.54±2.1. In the present study, before treatment the average pain score was 4.45±1.59, similar to that of the earlier study, and after treatment this had reduced significantly to 0.69±0.88. There was a significant statistical difference between pain scores before and after treatment.

Mastalgia is one of the most common complaints in women of reproductive age. A detailed history helps to identify the risk factors that may be responsible in each individual patient, along with clinical evaluation, which aids the physician in selecting the best approach for the management of the condition. Educating women regarding BSE at regular intervals will help in early presentation and diagnosis of the underlying condition. This can be achieved in a dedicated breast clinic which not only improves the reach among women but also provides a supportive environment to alleviate their stress regarding breast pathologies, especially cancer. Reassurance, breast support and lifestyle changes are the first line treatment and have good results in significant number of patients. Topical and oral NSAIDs, evening primrose oil and vitamin E can be used frequently as an addition to non-pharmacological methods. Visits to the pain clinic may be necessary in patients with persistent refractory mastalgia, despite all measures.

Ethics Committee Approval: Our study was reviewed and was exempted from ERC approval.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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The Clinical and Pathological Characteristics That Differentiate Cases With "Low Estrogen Receptor Expression" From Triple-Negative Breast Cancer

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ABSTRACT

Objective: Estrogen receptor (ER) expression is an immunohistochemical marker that is examined in all invasive breast cancers and has prognostic and predictive value. ER-positive breast cancers refer to those that show positivity for ER at 1% cellular expression or higher. The American Society of Clinical Oncology/College of American Pathologists guidelines suggest using the term "low ER-positive breast cancer" for tumors with ER expression between 1% and 10%. Low ER-positive breast cancers exhibit similarities, in terms of disease-free survival and overall survival rates, to triple-negative breast cancers (TNBCs) rather than ER-positive breast cancers. In this study, our aim was to compare the clinicopathological characteristics of low ER-positive breast cancer cases diagnosed and followed in our clinic with TNBCs.

Materials and Methods: A total of 26 cases of low ER-positive breast cancer diagnosed at University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital between 2010 and 2016 were retrieved from hospital records. The relevant histopathology slides and blocks were retrieved and re-evaluated retrospectively through microscopic examination. Thirteen cases that met the criteria were included in the study. Additionally, a consecutive series of 13 TNBC cases that did not receive neoadjuvant treatment within the same time period were identified.

Results: In the low ER-positive group, the presence of tumor necrosis, as well as histological grade, nuclear grade and Ki-67 proliferation index were significantly lower compared to the TNBC group. Ductal carcinoma *in situ* (DCIS) was significantly more common in the low ER-positive group compared to the TNBC group. There were no significant differences between the two groups in terms of tumor size, histological tumor type, axillary lymph node involvement, tumor margins, peritumoral and intratumoral inflammation, local recurrence, distant metastasis, survival, and other characteristics.

Conclusion: Although our study consisted of a small number of cases, some features showed significant differences between low ER-positive breast cancers and TNBCs. Histological and nuclear grades, as well as the presence of a DCIS component, were associated with low ER-positive breast cancer. In contrast, the presence of tumor necrosis, as well as Grade 3 features and a high Ki-67 proliferation index indicated TNBC.

Keywords: Low ER-positive breast carcinoma; triple-negative breast carcinoma; histopathological findings; clinicopathological features; survival

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Key Points

- Preanalytical and analytical processes play a crucial role in accurately molecular classification of tissue samples containing breast cancer and directing patients to appropriate treatment. Proper handling of samples such as needle biopsies or excision materials is essential.
- Low estrogen receptor (ER)-positive breast cancer has lower histological grade, nuclear grade, and Ki-67 proliferation index compared to triple-negative breast cancer (TNBC).
- Low ER-positive cancers are less likely to have tumor necrosis and more likely to have a higher percentage of intraductal carcinoma component compared to TNBC.

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Introduction

In 2018, approximately 2.1 million new cases of breast cancer were reported worldwide in women, accounting for a quarter of all female cancer cases (1). Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in more than 100 countries worldwide (1). The incidence of breast cancer and cancer-related deaths are increasing in developing countries, including Turkey. According to data from the Ministry of Health in Turkey, the incidence of breast cancer was reported as 48.5 per 100,000 in 2015 (2). In European Union countries, the incidence of breast cancer was 142.8 per 100,000 in 2020 (3).

Estrogen receptor (ER) expression is a marker that should be immunohistochemically examined in all invasive breast cancers due to its prognostic and predictive value. ER-positive breast cancers refer to tumors that show positive staining for ER at 1% or higher using immunohistochemistry. The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines recommend the term "low ER-positive breast cancer" for invasive breast cancers with ER expression between 1% and 10% (Figure 1) (3-7). The term low receptor-positive is applicable only to invasive breast tumors and the level of ER receptor expression. It is not valid for progesterone receptor (PR) expression levels or *in situ* carcinoma foci (7). Studies have shown that low ER-positive breast cancer cases constitute a heterogeneous group and share similarities with triple-negative breast cancer (TNBC) rather than ER-positive breast cancer in terms of clinical, histopathological, and molecular characteristics (4).

In this study, our aim was to re-evaluate cases diagnosed with invasive breast carcinoma at our center, which were initially classified as low ER-positive based on immunohistochemical (IHC) examination and compare them with cases of TNBC, in order to highlight the differences between the two diagnostic groups.

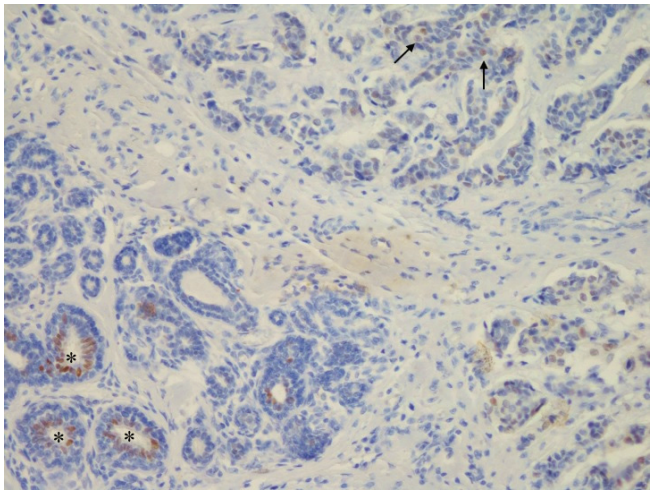

Figure 1. Low ER-positive breast cancer (ER immunohistochemistry, x200)

* Internal control: Presence of nuclear staining with ER in benign ductal luminal epithelial cells

→ Invasive tumor showing a small number of weakly intense nuclear staining with ER (between 1% and 10%)

ER: Estrogen receptor

Materials and Methods

Cases diagnosed with invasive breast carcinoma at University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pathology between 2010 and 2016 were identified. The ER and PR IHC staining profiles of these cases were checked, and a total of 26 cases that met the criteria for low ER positivity were identified. Hematoxylin and eosin (HE) and IHC stained slides (ER, PR, CerbB2, Ki-67) belonging to these cases were retrieved from the archive and re-evaluated. Histopathological features and clinical follow-up information from the cases were noted. During the re-evaluation, the ER expression level was assessed as <1% in 3 cases and >10% in 5 cases. HE-stained slides and paraffin blocks could not be retrieved from the archive for 3 cases, and 1 case was excluded due to receiving neoadjuvant chemotherapy, while 2 cases were excluded due to the absence of internal control in the ER and PR immunostains. Thus a total of 13 cases of low ER positivity were included in the study, all of which were Luminal-B molecular subtype. All cases with low ER positivity had breast-conserving surgery and adjuvant chemotherapy + radiotherapy + hormone therapy. For comparison, 13 consecutive TNBC cases, diagnosed within the same time period and without a history of neoadjuvant treatment, were identified. All TNBC cases had a history of breast-conserving surgery and adjuvant chemotherapy and radiotherapy. HE-stained slides and IHC stains of TNBC cases were retrieved from the archive and re-evaluated. Cases with negative ER and PR hormone expression in the invasive tumor, confirmed with internal control, were included in the study. Then, these two groups were compared in terms of tumor size, histological type, histological grade, nuclear grade, presence of lymph node metastasis, presence and severity of peritumoral/intratumoral inflammation, presence of extensive necrotic areas accompanying the tumor, presence of a ductal carcinoma *in situ* (DCIS) component, pattern of DCIS, percentage and intensity of ER staining, percentage and intensity of PR staining, CerbB2 staining score, Ki-67 proliferation index, local recurrence, distant metastasis, and survival parameters. The time from the initial diagnosis to death was evaluated as overall survival. The time from surgery to death or disease recurrence was evaluated as disease-free survival.

Statistical Analysis

Histopathological and clinical data were analyzed using SPSS, version 25 (IBM Inc., Armonk, NY, USA). Chi-square and Kaplan-Meier statistical methods were used for evaluation.

Results

Significant differences were observed between the two groups in terms of tumor necrosis, histological grade, nuclear grade, presence of DCIS component, and Ki-67 proliferation index (Table 1). In the low ER positive invasive breast carcinoma group, the presence of necrotic areas in the tumor was less common, and the histological grade and nuclear grade were lower (Grade 2). Although tumor metastasis in axillary lymph nodes was more common in the low ER positive group, this difference was not significant (p = 0.09).

There were no significant differences between the two groups in terms of patient age, tumor size, histological tumor type, presence and severity of peritumoral/intratumoral inflammation, pattern of DCIS, CerbB2 score, local recurrence, distant metastasis, overall survival, and disease-free survival.

Table 1. Clinicopathological features

	Low ER positive				**Triple negative**				***p*-value**
Age (Median)	53 (28-77 age)				49 (32-81 age)				
Tumor size (cm)	2.9				3.2				
Histological type	Ductal	Lobular	Ductal+lobular	Metaplastic	Ductal	Lobular	Ductal+lobular	Metaplastic	0.22
	12	0	1	0	10	0	0	3	
Nuclear grade	Grade 2		Grade 3		Grade 2		Grade 3		0.005
	7		6		0		13		
Histological grade	Grade 2		Grade 3		Grade 2		Grade 3		0.002
	8		5		0		13		
Peritumoral inflammation	Absent		Present		Absent		Present		1
	1		12		0		13		
Intensity of peritumoral inflammation	Absent	Mild	Moderate	Significant	Absent	Mild	Moderate	Significant	0.166
	1	5	5	2	0	2	4	7	
Intratumoral inflammation	Absent		Present		Absent		Present		0.48
	2		11		0		13		
Intensity of intratumoral inflammation	Absent	Mild	Moderate	Significant	Absent	Mild	Moderate	Significant	0.18
	2	5	5	1	0	4	4	5	
Necrosis	Absent		Present		Absent		Present		0.005
	10		3		2		11		
Presence of ductal carcinoma *in situ*	Absent		Present		Absent		Present		0.039
	8		5		12		1		
ER staining intensity	Negative	+	++	+++	Negative	+	++	+++	
	0	11	1	1	13	0	0	0	
PR staining intensity	Negative	+	++	+++	Negative	+	++	+++	
	9	2	1	1	13	0	0	0	
HER2 status*	Negative		Positive		Negative		Positive		
	7		6		13		0		
Ki-67 (mean)	36%				53%				0.036
Local recurrence	Absent		Present		Absent		Present		1
	12		1		13		0		
Lymph node metastasis	Absent		Present		Absent		Present		0.097
	2		11		7		6		
			N1: 8 N2: 0	N3: 3			N1: 5 N2: 0	N3: 1	
Distant metastasis	Absent		Present**		Absent		Present***		1

Table 1. Continued

	11	2	10	3	
Survive/exitus	Survive	Exitus	Survive	Exitus	
	9	4	10	3	
Disease-free survival	Mean	Median	Mean	Median	0.054
	96.6 month	101 month	78.7 month	97 month	
Overall survival	Mean	Median	Mean	Median	0.098
	104 month	102 month	83 month	98 month	

*HER2-negative group: Cases with an immunohistochemistry score of 0 or 1, and cases with a score of 2 but negative FISH result.
** Distant metastasis sites: One case in the liver and one case in the sacrum.
*** Distant metastasis sites: One case in the liver + brain; one case in the brain + lungs + abdominal wall; one case in bone + liver metastasis

Discussion and Conclusion

In this study, the group of patients with low ER-positive breast cancer was compared to a group of TNBC cases in terms of various clinicopathological features. It was found that the low ER-positive cases were associated with Grade 2 histological and nuclear characteristics, necrosis in the invasive tumor was less common, and there were lower levels of Ki-67 proliferation index. Although axillary lymph node metastasis, disease-free survival, and overall survival durations were higher in the low ER-positive group, these differences were not significant.

It is recommended to perform hormone receptor expression (ER, PR) and CerbB2 immunostaining in all newly diagnosed primary invasive breast carcinomas, as well as in recurrent or metastatic breast carcinomas (7, 8). In cases of multiple invasive breast tumors, immunostaining for ER, PR, and CerbB2 should be performed on the largest tumor. In the presence of multiple invasive tumor foci, if different histological types and higher grades are identified, these foci should also be separately evaluated for ER, PR, and CerbB2 staining. The aim of this practice is to identify possible expression differences among invasive tumors and determine the appropriate treatment regimen (7, 8). The ASCO and CAP guidelines highlight various pre-analytical and analytical factors that can affect the results of immunostaining in tissues (7). These factors include cold ischemia time, type of fixative, duration of tissue fixation, decalcification process, adequacy of tissue sample, and the clone of the primary antibody used (7, 9). Cold ischemia refers to the time from tissue removal to its placement in buffered formalin. If this time is unavoidably extended, the tissue sample can be stored in a refrigerator at +4 degrees Celsius for up to one hour (7, 9). The type of fixative is important in tissue fixation, and the use of buffered formalin is preferred. IHC stains should be evaluated in tumor foci that contain an adequate invasive tumor area. Foci with suspicious invasion or rare invasive tumor cells are not suitable for evaluation. In addition, if possible, FDA-approved and guideline-recommended clones of antibodies used for ER and PR immunostaining should be selected, and only nuclear staining should be considered. Epithelial cells in normal breast parenchyma carry ER and PR receptors, thus exhibiting varying degrees of nuclear staining. The presence of this staining in normal breast parenchyma serves as an "internal control" for evaluating staining in invasive tumor foci (7, 9). Factors that may lead to "false-negative" immunostaining results in tissues are briefly summarized in Table 2 (7). Knowing these factors and taking necessary precautions will ensure the accurate characterization of an invasive tumor as "ER-positive", "low ER-positive", or "ER-negative" and facilitate the correct guidance of treatment.

Table 2. Factors that may lead to "false ER negative" results in invasive breast carcinoma

Exposure of tumor cells to heat, such as during cautery
Prolonged cold ischemia time (causes a decrease in antigenic properties and reduces immunoreactivity)
Short or long fixation time (fixation time less than 6 hours or more than 72 hours reduces immunoreactivity)
Use of inappropriate fixatives (the use of buffered formalin is ideal. Acidic fixatives such as B5 or Bouin's solution are not suitable as they degrade ER)
Decalcification (reduces immunoreactivity)
Antibody clone used for ER (FDA-approved clones recommended by guidelines should be selected if possible)
Dark Hematoxylin background staining can obscure weak nuclear ER staining in tumor cells

ER: Estrogen receptor; FDA: Food and Drug Administration

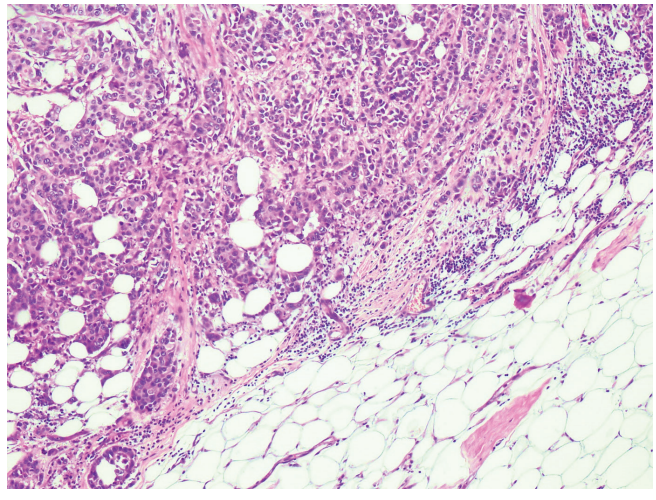

Figure 2. Invasive breast carcinoma (TNBC) showing a growth pattern characterized by solid islands of varying sizes, H&E x100

TNBC: Triple-negative breast cancer; H&E: Hematoxylin and eosin

Approximately 75–80% of invasive breast carcinomas are positive for ER and PR expression (7). Within this group, a small subset, around 2–3%, shows ER expression in 1 to 10% of tumor cells (9). The ASCO/CAP guidelines recommend reporting ER immunoreactivity between 1% and 10% as "low ER-positive". This suggested threshold represents the point at which patients derive clinical benefit from endocrine therapy. The success of hormone therapy in cases with weak nuclear staining intensity in the low ER-positive group remains controversial (6). Therefore, there is a need for studies investigating the relationship between ER staining intensity and hormone therapy.

Fei et al. (4) identified ER staining intensity as positive (+) in all 97 patients (100%) in their study on the low ER-positive group (3). In our study, we found ER staining intensity to be three positive (+++) in one case (7.7%), two positive (++) in one case (7.7%), and one positive (+) in the remaining eleven cases (84.6%) in the low ER-positive group. In the same study, Fei et al. (4) observed that the prognosis in the low ER-positive group was better than that in the TNBC group

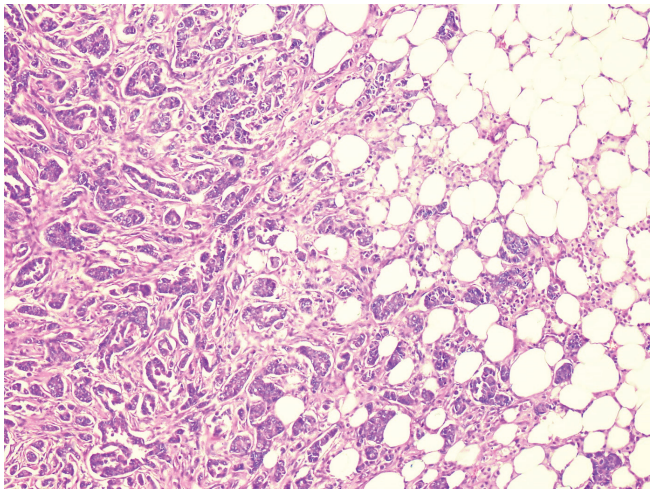

Figure 3. Invasive breast carcinoma (low-ER positive) displaying glandular structures, H&E x100

ER: Estrogen receptor; H&E: Hematoxylin and eosin

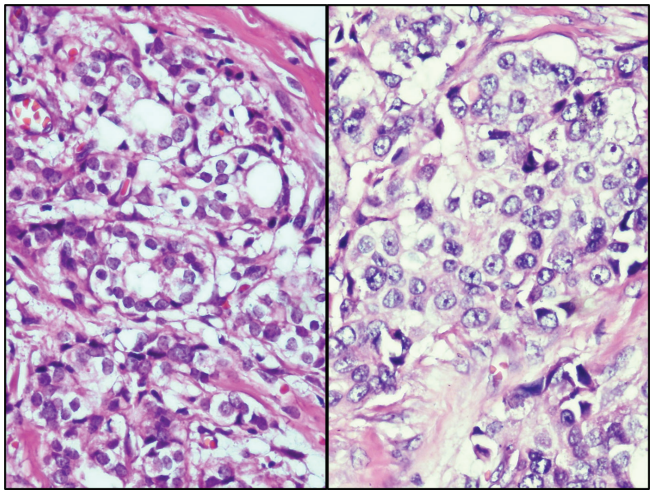

Figure 4. On the left side, tumor cells with round-oval nuclei and nuclear enlargement of moderate degree, showing nuclear grade 2 features (low ER-positive breast carcinoma); on the right side, tumor cells with large nuclei, prominent nucleoli, and nuclear grade 3 features (TNBC) (H&E x400)

TNBC: Triple-negative breast cancer; H&E: Hematoxylin and eosin

and emphasized the need for confirmation of this observation through larger cohort studies. In our study, although the difference between the two groups was not significant, disease-free survival and overall survival tended to be longer in the low ER-positive group compared to disease-free survival and overall survival in the TNBC group. In our cohort, we believe that the association between shorter survival and the TNBC group could be attributed to the higher histological and nuclear grades (Grade 3) (Figure 2), increased necrosis, and higher Ki-67 proliferation index in the TNBC group. Additionally, we observed a case of local recurrence in the low ER-positive group, while no recurrence was observed in the TNBC group. We speculate that the presence of extensive DCIS foci accompanying the invasive tumor in this recurrent case could be associated with local recurrence. Similarly, our more frequent detection of DCIS foci in the low ER-positive group may be associated with the lower Ki-67 proliferation exhibited by this group of tumors. In tumors with slower proliferation, it becomes easier to detect the tumor at the *in situ* stage. In our study, the mean Ki-67 proliferation index was 36% in low ER-positive breast carcinoma cases compared to 53% in the TNBC group (p = 0.036).

It has been reported that low ER-positive breast cancers show similarities with basal-like breast cancer or Human epidermal growth factor receptor 2-enriched breast carcinoma in molecular subtyping (3, 10). Low ER-positive breast cancers have been found to be less associated with Luminal B and Luminal A molecular subtypes (3).

In estrogen-positive tumors, the receptor activated by ER binds to target DNA and leads to changes in cellular gene expression, including PR. The expression levels of ER and PR determine the patient group that will receive endocrine therapy and are important predictors of the response to endocrine therapy. If the ER percentage threshold for deciding on treatment is lowered, more patients can receive the less toxic option of endocrine therapy. However, if patients in the low ER-positive group do not benefit from endocrine therapy, they may be exposed to unnecessary daily medication and the adverse effects of these treatments. Therefore, although the recommended threshold for hormone therapy in low ER-positive breast cancers is 1%, different clinics may choose different percentage levels (such as 5–10% and 20%) as the threshold for treatment (4). Molecular studies have suggested that chemotherapy may be more effective in these cases due to the small proportion of low ER-positive cases being luminal and the majority being basal-like molecular subtype (11). In a study by Gloyeske et al. (6), 90% of cases in the low ER-positive group were found to be negative for PR receptor. In our study, 69.2% of cases in the low ER-positive group were negative for PR receptor expression. The relationship between the response to hormone therapy in the low ER-positive group and PR levels may be suitable for further study.

Chen et al. (12) reported that in cases of low ER-positive breast carcinoma, the tumor size was smaller and the tumor was better differentiated compared to TNBC cases. Similarly, in the present study, the low ER-positive breast carcinoma group showed more nuclear and histological grade 2 characteristics, which were lower than those in the TNBC group (Figure 3). However, there was no significant difference in tumor size between the two groups. This could be due to the small number of cases in our study.

In a study conducted at MD Anderson Cancer Research Center, the incidence of *BRCA* germline mutations was investigated in 314 patients, and similar frequencies were found in the TNBC group (36.1%) and

the low ER-positive breast carcinoma group (39.5%) (13). In both groups, *BRCA1* germline mutation was reported more frequently than *BRCA2* mutation. Currently, the use of PARP inhibitors in treatment is determined by identifying the *BRCA1/2* germline mutation status in all recurrent or metastatic breast cancer cases (8). Therefore, the low ER-positive patient group should also be considered in terms of the frequency of *BRCA* germline mutations. In the present study, *BRCA1/2* mutation results were unavailable as the cases included in the study period have not yet been evaluated. Yoder et al. (14) compared the low ER-positive breast carcinoma group with the TNBC group and found no significant differences in clinical, demographic, germline *BRCA1/2* mutation prevalence, and chemotherapy use between the two groups. Additionally, they did not report any differences in disease-free survival and overall survival after a median follow-up period of 3 years. This study highlighted that although breast carcinomas showing low ER expression resemble TNBCs in terms of biological characteristics, they are deprived of current treatment options used in TNBC cases (such as immunotherapy) (14).

The predictive and prognostic characteristics of low ER-positive breast cancers have not yet been clearly defined. It is crucial to distinguish these patients from TNBC and obtain accurate clinicopathological data to select the appropriate patient group for hormone therapy. The importance of preanalytical processes, such as cold ischemia time, improper fixative use, or short or prolonged fixation, in determining the ER receptor expression level in breast cancer biopsy samples should be kept in mind. Factors that could negatively affect the process should be identified, and precautions should be taken. Additionally, correlation with tumor morphology should be established during IHC evaluation. In this study where we compared low ER-positive breast cancer cases with TNBC, we found that low ER-positive breast cancers were associated with histological and nuclear grade 2 features (Figure 4), less necrosis in invasive tumors, lower Ki-67 proliferation index, and more accompanying DCIS foci. The limitation of this study was the small number of cases. Further extensive case series are needed to identify low ER-positive breast cancers, which constitute a small proportion (2–3%) of invasive breast carcinomas and exhibit heterogeneous characteristics.

Ethics Committee Approval: Ethical approval has been obtained from the University of Health Sciences Turkey, Izmir Faculty of Medicine Tepecik Education and Research Hospital Ethics Committee (approval number: 2023/02-40, date: 08.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: C.K., S.S.; Design: C.K., C.K.T.; Data Collection and/or Processing: C.K., C.K.T.; Analysis and/or Interpretation: C.K., M.E., M.D., M.K., S.S., C.K.T.; Literature Search: C.K., M.D., M.K., C.K.T.; Writing: C.K., M.E., C.K.T.

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

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Original Article

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Treatment of Granulomatous Mastitis With Steroids: Should the Decision to End the Treatment be Made Radiologically?

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ABSTRACT

Objective: Idiopathic granulomatous mastitis (IGM) is a benign inflammatory breast disease of unknown etiology that affects women in their reproductive period. The most commonly preferred option as first-line treatment is steroids, but the lack of a standard treatment protocol and high recurrence rate after treatment constitutes a recurring challenge during its management. The aim of this study was to investigate whether the decision to end the treatment should be made radiologically or clinically.

Materials and Methods: This retrospective cohort study included IGM patients who had complete clinical recovery with steroids and were followed for a minimum of 30 months. Patient demographics, disease severity and findings, treatment regimens and duration, and magnetic resonance imaging (MRI) findings at clinical recovery were assessed for their relation to recurrence.

Results: Eighty-nine patients who were clinically completely healed after steroid treatment for IGM were included in the study. At the time of clinical healing, 51 (57.3%) patients had a complete radiological response and 38 (42.7%) had a partial radiological response (PRR) on MRI. Overall, recurrence developed in 22 (24.7%) patients after a median 38.6-month follow-up. Patients who experienced recurrence were significantly older and had PRR when their treatment was stopped upon clinical healing.

Conclusion: During the process of clinical healing, the imaging findings revealed that the remaining disease seems to be a significant predictor for recurrence in IGM patients. In patients with PRR, extending the treatment with either prolonged steroid therapy or by surgical excision of the occult residual disease may prevent recurrences in IGM patients.

Keywords: Granulomatous mastitis; steroid treatment; recurrence; MRI

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Key Points

- Although idiopathic granulomatous mastitis responds well to steroids, relapse rates are high after discontinuation.
- In all studies published to date, treatment has been discontinued based on clinical response.
- We identified residual radiological disease in almost half of patients with complete clinical response.
- We found that radiological residual disease was associated with recurrence after steroid therapy.
- Prolonging steroid treatment until achieving a complete radiological response or excision of the radiologically detected residual disease could lower the recurrence rate.

Introduction

Idiopathic granulomatous mastitis (IGM) is a benign inflammatory breast disease of unknown etiology that affects women of reproductive age (1). The lack of a standard protocol for its treatment, high anxiety among patients due to its mimicking of malignancy with clinical and radiological findings, and the high recurrence rate after treatment are the challenges of managing this disease. Although it has endemic proclivity in Middle Eastern and Asian countries mainly, these challenges also constitute a problem for Western clinicians due to immigration. In general, diagnosis is not difficult for physicians in

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endemic areas. Although physicians can diagnose IGM easily, they deal with challenges when managing the disease owing to its presentation as well as after recurrence.

Surgery was the primary treatment for many years, even after the effectiveness of steroids was reported and proven in 1980 (2). However, the clinical efficacy of steroids as a first-line treatment, rising to 90%, was somewhat undermined by recurrence rates of up to 46% following treatment discontinuation (3). In addition, the side effects of steroids during the long-term treatment reduce compliance with the treatment for the patients (4). Given these factors, surgery has again become the preferred first-line treatment (5-7). However, reported recurrence rates of surgical excisions are similar to those found after steroid therapy, therefore limiting its feasibility (8,9). Moreover, either repetitive interventions or wide surgical excisions may be required to achieve remission, which leads to poor cosmetic results. The complexity of the management of IGM has prompted investigation of the factors associated with disease recurrence.

Although there have been many studies considering the dosage, time, and methods used to apply steroids, to date there had not been a study regarding the optimal end-point to discontinue treatment. Complete clinical response (CCR) was the criterion to discontinue the treatment in the search for the effectiveness of steroid treatment, in accordance with the studies to date (10). However, there is no standardized and objective definition of CCR. In addition, it has been shown that there are residual findings of disease that are only evident on imaging which were present in up to 50% of the patients with CCR (4).

Imaging modalities such as ultrasound (US) and contrast-enhanced magnetic resonance imaging (MRI) are used routinely in the diagnosis of IGM (11, 12). US possesses the distinct advantages of high sensitivity, non-invasiveness, and is valuable in screening patients in cases of mild disease. In contrast, MRI is a useful imaging modality for the differential diagnosis of breast cancer and it may also be more useful for indicating active lesions and locate the extent of the lesions (13). Therefore, MRI has been used in the evaluation of the response to steroid treatment (4, 13).

The aim of this study was to investigate if the decision to end treatment should be made radiologically or clinically and to assess the factors which may have an impact on recurrence after steroid treatment in a cohort of IGM patients who had undergone steroid treatment and also had long-term follow-up.

Materials and Methods

Study Design

The study was planned as a retrospective cohort design and conducted at a tertiary breast care unit. The study protocol was approved by the institutional ethics committee. Patients with a diagnosis of IGM who were treated with steroids as first-line treatment and had achieved CCR were included in the study. IGM patients who did not receive their steroid treatment according to the planned regimen or did not have a satisfactory response to the treatment or had a follow-up of less than 30 months after clinical recovery or did not have an MRI exam at the time of clinical recovery were excluded from the study (Figure 1). The minimum follow-up period of 30 months was chosen as this was the time of latest recurrence of IGM in our records after full clinical recovery among all IGM patients who only received steroid therapy.

Study Groups

Following CCR, the reappearance of clinical symptoms and/or findings, such as palpable mass, erythema, fistula-formation, skin ulceration, and abscess formation suggesting IGM in the same breast was regarded as recurrence.

The patients were grouped according to their radiological findings at the termination of steroid therapy when patients became symptom-free. The patients who had the findings suggesting residual IGM disease on MRI (abscess formation, heterogeneous mass, skin thickening, unresolved fistula tracks, contrast-enhanced appearances) were designated Group partially radiological response (PRR), whereas those with no such radiological findings were designated Group complete radiological response (CRR).

Study Outcomes

The primary aim was to assess the impact of MRI findings at the time of CCR on predicting the recurrence in IGM patients who only received steroids as their treatment. Therefore, the rate of recurrence in both study groups was compared. As a secondary outcome, demographic and clinical variables related to IGM which may have an independent impact on the recurrence were also analyzed.

Variables

Patients' features and demographics, clinical findings and extension of the disease, treatment history including the type of agents and their duration, and MRI findings at the end of the treatment were collected from patient files for univariate and multivariate analysis.

Steroid Treatment Protocol

Patients in the study cohort received three different regimens of steroids. Some patients received only topical, some others received only

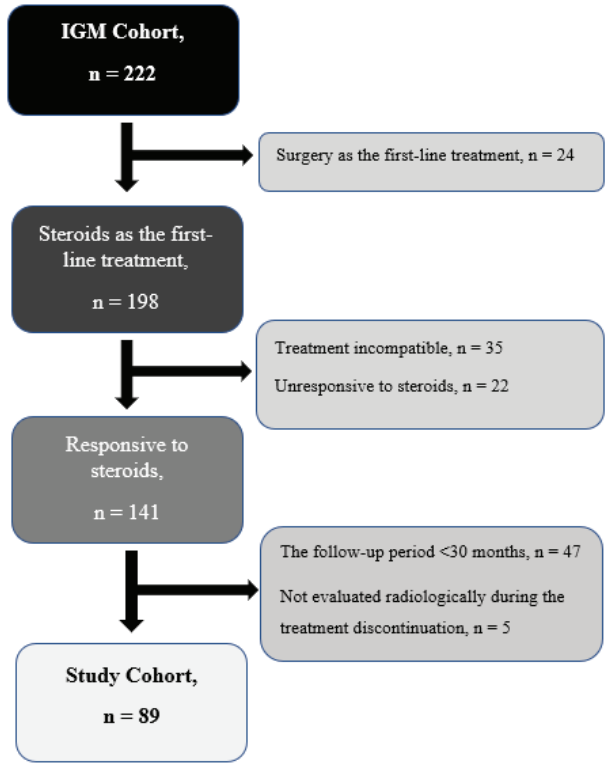

Figure 1. The creation of the study cohort

IGM: Idiopathic granulomatous mastitis

oral steroids and the rest received both. The choice of the treatment regimen was at the physician's discretion.

Topical steroid administration: Prednasinolone 0.125% pomade (Prednol pomad; Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey) was applied topically by the patients to the affected breast, twice a day on weekdays with breaks during weekends (1-week cycle).

Treatment with oral steroid: Postprandial 0.8 mg/kg oral methylprednisolone (Prednol tablet, Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey) was given once daily.

Combined steroid therapy: Postprandial 0.4 mg/kg oral methylprednisolone was given once daily and Prednasinolone 0.125% pomade – with the same pharmaceutical agent - was applied topically to the diseased breast as described in the topical steroid administration protocol.

Steroid treatment according to the unit protocol was continued until the first signs of disease amelioration were observed. Then the treatment was tapered in patients who received oral methylprednisolone. Topical treatment cycles were ended when CCR was obtained.

Decision for Completion of Steroid Treatment

Following tissue diagnosis and before starting steroid treatment, all patients underwent MRI in order to assess the extent of the disease within the breast. Thereafter, the response to treatment was assessed by physical examination and breast US.

The decision to stop steroid treatment was given according to the clinical responses. The lack of palpable mass and erythema on physical examination, and healing of the skin with the closure of ulceration, and fistula were considered CCR. Patients were also assessed by breast MRI at the end of steroid treatment when CCR was achieved. The lack of image findings indicative of persistent IGM on MRI was regarded as CRR. Any remaining image findings suggesting IGM, such as heterogeneous mass, skin thickening, unresolved fistula tracks, and contrast-enhanced appearances were regarded as PRR (Figure 2).

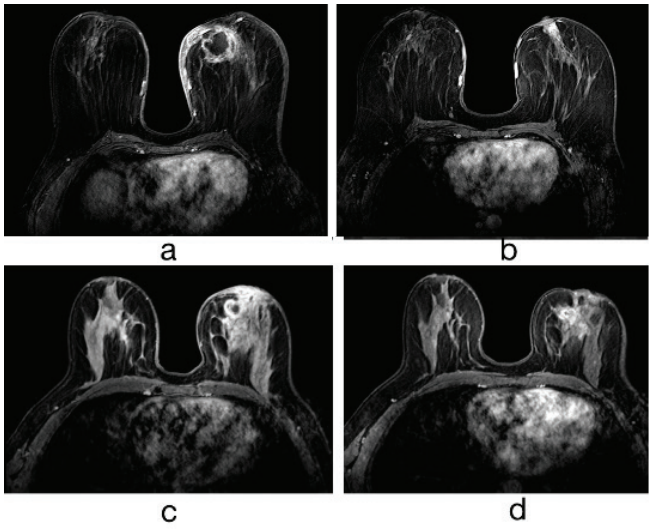

Figure 2. a. Patient with IGM at 36 years old. Abscess formation of 42 mm with enhancement at the wall, on medial site of left breast. b. MRI findings of the same patient on the third month following the end of combined steroid treatment. Abscess formation and the thickness of skin have disappeared. The complete radiological response was observed. There was no recurrence with the follow-up of 42 months. c. Patient with IGM at 37 years old. Retroareolar abscess formation of 20 mm with peripheral enhancement, at left. d. Partial radiological response was observed following systemic steroid therapy for 4 months. Recurrence was observed on the fifth month of follow-up with a palpable mass with pain, and the patient underwent surgery

IGM: Idiopathic granulomatous mastitis; MRI: Magnetic resonance imaging

Follow-up

During the course of treatment, patients were examined for findins suggestive of IGM. After termination of treatment, patients were followed on the first, third, and sixth months, and every six months thereafter. At each visit, a physical examination and breast US were performed to assess the patient for recurrence.

Statistical Analysis

Data were analyzed with Statistical Package for Social Sciences software (SPSS) version 24.0 (IBM Inc, Armonk, NY, USA). Pearson's chi-square test and Fisher's exact test were used to compare qualitative data. Normality for the distribution of quantitative variables was analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Student's t-test was used to compare normally distributed data. Mann-Whitney U test was used to compare the variables without normal distribution. Multivariate logistic regression analysis was performed to assess variables that may be associated with recurrence. Based on the result of the analysis, a $p<0.05$ was considered to be statistically significant.

Results

Study Cohort

The study included 222 patients who were diagnosed with IGM between September 2014 and October 2019 at the Breast Unit in Kartal Dr. Lütfi Kırdar Training and Research Hospital.

Among these, surgical treatment was performed as first-line treatment in 24 patients, and the remaining 198 patients received steroid therapy. Of these 198, 89 (44.9%) patients who fulfilled the inclusion criteria remained in the cohort for the current study (Figure 1). Some of the patients in the current cohort were also included in our previous trials with different outcomes and the results were published elsewhere (4, 14).

The mean age of the cohort was 33.2±6.4 years, and 87 (97.8%) patients were of reproductive age. The most common finding was palpable mass (n=85, 95.5%), followed by erythematous appearance (n=72, 80.9%).

MRI Findings at Clinical Recovery

When CCR was achieved and steroid treatment was stopped, 51 (57.3%) had CRR and 38 (42.7%) had PRR on MRI.

Recurrence Rate and Associated Factors

Recurrence was observed in 22 (24.7%) patients after a mean follow-up of 42±10.3 months. Patients who had recurrence were significantly older than those who did not (35.8±6.8 *vs.* 32.4±6, $p = 0.03$). Most recurrences were seen in the Group PRR group, as follows: PRR n = 19 (86.4%) *vs.* CRR group n = 3 (13.6%) and this difference was significant ($p<0.001$) (Table1).

Multivariate analysis revealed that each one-year increase in age significantly increased the probability of recurrence by around 1.1 times [odds ratio (OR) (95% confidence interval (CI) 1.11 (1.01,

Table 1. Patients' variables and their associations with recurrence

	Study cohort, n = 89	Recurrence		p
		No, n = 67	Yes, n = 22	
Age; mean ± standard deviation (years)	33.2±6.4	32.4±6	35.8±6.8	0.03
Smoking; n (%)	18 (20.2)	13 (19.4)	5 (22.7)	0.8
Oral contraceptive use; n (%)	18 (20.2)	14 (20.9)	4 (18.2)	0.8
Number of live births; median (range)	2 (0-7)	2 (0-7)	2 (1-5)	0.3
Total breastfeeding time *	36 (0-120)	36 (0-120)	36 (9-120)	0.7
Affected side; n (%)				0.61
Right	48 (53.9)	37 (55.2)	11 (50)	
Left	39 (43.8)	28 (41.8)	11 (50)	
Bilateral	2 (2.2)	2 (3)	0 (0)	
Previous treatments; n (%)				
Antibiotics ± abscess drainage	54 (60.7)	43 (64.2)	11 (50)	0.24
Steroids	13 (14.6)	10 (14.9)	3 (13.6)	0.88
Presence of breast mass; n (%)	85 (95.5)	65 (97)	20 (90.9)	0.25
Presence of skin fistula; n (%)	45 (50.6)	32 (47.8)	12 (54.5)	0.6
Presence of skin ulceration; n (%)	15 (16.8)	12 (17.9)	3 (13.6)	0.75
Presence of abscess; n (%)	56 (62.9)	42 (62.7)	14 (63.6)	0.94
Extent of breast involvement; n (%)				0.8
Single quadrant	53 (59.5)	39 (58.2)	14 (63.6)	
Two or more quadrants	36 (40.4)	28 (41.8)	8 (36.4)	
Retroareolar involvement; n (%)	16 (18)	11 (16.4)	5 (22.7)	0.5
Co-occurrence of EN; n (%)	7 (7.9)	4 (6)	3 (13.6)	0.25
Steroid treatment protocol				0.3
Topical	35 (39.3)	29 (43.3)	6 (27.3)	
Systemic	26 (29.2)	17 (25.4)	9 (40.9)	
Combined	28 (31.5)	21 (31.3)	7 (31.8)	
Duration of treatment *	5 (1-10)	4 (1-10)	5 (2-9)	0.25
Radiological response; n (%)				<0.001
CRR	51 (57.3)	48 (71.6)	3 (13.6)	
PRR	38 (42.7)	19 (28.4)	19 (86.4)	
Follow-up time *	38.6 (30-66)	38.1 (30-66)	43.7 (30-62)	0.14

* median month (range)
Student t, Mann-Whitney U, and chi-square tests were used
EN: Erythema nodosum; PRR: Partial radiological response; CRR: Complete radiological response

Table 2. The multivariate analysis of the factors associated with recurrences

Variables	Multivariate analysis		
	Odds ratio	95% CI	p
Age	1.11	1.01–1.22	0.029
Radiological response			
PRR vs. CRR	18.25	4.48–74.34	<0.001

Binary Logistic Regression was used
OR: Odds ratio; CI: Confidence interval; PRR: Partial radiological response; CRR: Complete radiological response

1.22), $p = 0.029$]. Furthermore, PRR at the end of treatment increased the probability of recurrence by more than 18 times [OR (95% CI) 18.25 (4.48, 74.34), $p<0.001$] (Table 2).

For the whole cohort, recurrences were observed at a median of 3.5 months after stopping treatment. Recurrences developed significantly earlier in those patients who had PRR [median 3 months (range:1–30)] than in those who had CRR [median: 15 months (range:15–20), $p = 0.03$].

Discussion and Conclusion

A 24.7% recurrence rate was observed in our IGM cohort, which comprised patients with long-term follow-up, in whom steroids were used as first-line treatment, and treatment was discontinued based on clinical responses. Radiological residual disease at the time of

discontinuation and age was an independent risk factor for recurrence in univariate analysis and persisted on multivariate analysis. Each one-year increase in age significantly increased the probability of recurrence by around 1.1, and PRR at the end of treatment increased the probability of recurrence by more than 18 times. Notably, we found that recurrences developed significantly earlier in those patients who had PRR than in those who had CRR.

To the best of our knowledge, the decision to discontinue medical treatment has been made clinically in all studies to date (10). However, there was no standard definition of complete remission in the treatment of IGM. Complete remission was defined as the absence of pain, swelling, erythema, tenderness, and lump after treatment (15-17), but the radiological responses were never addressed in the decision to cease the treatment. This is the first study investigating the relationship between the radiological responses and recurrences while the decision of treatment discontinuation was made. The long-term follow-up of our series is longer than the ones in the literature and thus has strengthened the results of our study.

Retrospective design and use of different treatment modalities with different time periods-even though all cases were treated with steroids successfully-were the most important limitations of our study. Moreover, recurrence was not found to be related to different treatment modalities and different periods in our series. Another limitation of our study was the use of MRI instead of US, which is more sophisticated and expensive in comparison to the US. MRI is useful for evaluating possible residual disease after treatment or for monitoring the disease in patients who underwent conservative treatment (18, 19).

In our study, the overall recurrence rate with steroid treatment was 24.7%, consistent with the literature. More specifically, it was 5.9% (3/51) in the CRR group and 50% (19/38) in the PRR group. Wang et al. (6) reported a lower recurrence rate in the group with surgical excision following systemic steroid treatment than the group with only systemic steroid treatment (5.1% vs. 22.7%). The high total recurrence rate could be explained by long follow-up intervals and different treatment protocols in our cohort. The patients who received wide surgical excision following systemic steroids in the study of Wang et al. (6) showed similar characteristics to the CRR group in our series in terms of the recurrence rate. Gurleyik et al. (20) reported a similar recurrence rate of 5.3% in 19 patients with local excision following 8 weeks of oral methylprednisolone treatment, in a retrospective cohort. Additionally, Lei et al. (10) reported that management with surgery following treatment with steroids resulted in the lowest recurrence rate (4%) in a meta-analysis. Recurrence rates were low and similar in regard of the patients with CRR in our series. In our opinion, the similarity of the lower recurrence rate is related to the removal of residual disease following steroid treatment.

To the best of our knowledge, there are two studies in the literature investigating the relationship between age and recurrence in IGM (21, 22). Although Yılmaz et al. (22) reported a higher mean age of patients with recurrence (40.1 vs. 38.4 years), there was no correlation between age and recurrence in both studies. Contrary to these studies, we found a statistically significant relationship between age and recurrence.

In recent years, the factors affecting recurrence following the treatment of IGM have been examined in retrospective studies (21-23). Demographics, the number of births, breastfeeding period, smoking, use of oral contraceptives, and the type of pharmaceutical course on the breast were evaluated, and different findings for recurrence were reported in these studies. Uysal et al. (21) found that pregnancy, breastfeeding, previous mastitis, and smoking were related to recurrence in a multicenter retrospective study. In addition, Yılmaz et al. (22) found high BMI, the number of births, breastfeeding period, luminal inflammation, fistula, and abscess to be closely related to recurrence, but smoking was not with a lower recurrence rate (8/63, 12.7%). Even though the treatment modalities were different, all patients received steroids in our study. The number of births, breastfeeding period, smoking, and oral contraceptives were not found to be related to recurrence in our study. Tan et al. (24) reported a recurrence rate of 17.7%. Moreover, different treatment modalities, including antibiotics, steroids, and surgery, were used in their study. Even though it was not significant, inflammatory findings and symptoms in the breast, and previous treatment with antibiotics, were reported to be more common in recurrent cases. Findings in the breast and previous treatment with antibiotics were not related to recurrence in our series.

Altunkeser et al. (25) conducted a retrospective evaluation of MRI findings to predict treatment success in IGM. While they did not find a significant relationship between MRI findings and treatment success, they observed that patients with involvement in the retroareolar region had lower treatment success rates. In our study, we found no significant relationship between the involvement of more than one quadrant in the breast, retroareolar involvement, and recurrence.

We suggest evaluating radiological responses in addition to clinical response when deciding if to discontinue treatment of patients with IGM receiving steroids as first-line treatment. Prolonging the steroid therapy until the achievement of CRR for the disease, or excision with care taken for breast preservationto preserve for radiologically detected residual disease could lower recurrence rates in IGM. Excision of radiologically marked disease may be a reasonable approach. Additionally, studies should be conducted to assess residual disease in patients with CCR using US, a more cost-effective imaging method compared to MRI.

Ethics Committee Approval: The study protocol was approved by Kartal Dr. Lütfi Kırdar Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020/514/177/43, date: 13.05.2020).

Informed Consent: Informed consent was taken from patients to collect and use data.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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Original Article

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Evaluation of the Influence of Geodimensional and Histological Parameters on the Need for Margin Widening in Breast Lesions Marked With Magnetic Seeds

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ABSTRACT

Objective: Breast cancer is an important topic worldwide, posing morbidity and mortality to women. Considerable efforts have been put in the early recognition of malignancy through different screening methods, such as mammography and ultrasound. The precise localization of infraclinical malignant lesions is key in surgical management and magnetic seeds gather particular interest for this purpose. As with other systems, a need for reintervention may be needed to obtain adequate surgical margins. This work evaluated the relation between the need for surgical reintervention in order to obtain negative margins and geodimensional and histological parameters. The main objective was the identification of parameters significantly associated with reintervention for margin widening.

Materials and Methods: A retrospective analysis of 198 patients from a single centre was performed. The association between pre-defined geodimensional and histological parameters and the need for margin widening in infraclinical lesions marked with magnetic seed was evaluated.

Results: Results showed that reintervention to widen margins was significantly higher in patients with ductal carcinoma *in situ* (DCIS) in the pre-operative biopsy when compared with invasive carcinoma ($p = 0.03$) in the bivariate analysis. No statistically significant differences were observed between the need for reintervention and lesion size ($p = 0.197$), breast quadrant location ($p = 0.626$) and distance of skin to lesion ($p = 0.356$).

Conclusion: This work suggests that a more invasive margin clearance in lesions with a pre-operative DCIS diagnosis might obviate the need for reintervention to obtain negative margins. On the other hand, it is not necessary to be surgically more invasive in larger lesions, deeply located or that are present in a certain quadrant, since there are no significant differences regarding the need for reintervention.

Keywords: Breast cancer; recurrence; risk factors; surgery

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Key Points

- Mammography and ultrasound play a crucial role in detecting non palpable breast lesions.
- Magnetic seeds enable adequate location for the surgeon, but still, positive resection margins occur to some extent.
- This work investigated the relationship between the need for surgical reintervention in positive margins and specific geodimensional and histological parameters in breast cancer patients.
- Patients diagnosed with ductal carcinoma *in situ* (DCIS) during preoperative biopsy had a significantly higher likelihood of requiring reintervention compared to invasive carcinoma.
- No statistically significant differences were observed regarding lesion size, breast quadrant location, or lesion depth.

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Introduction

Breast cancer is an important health concern worldwide. It is the second most common cancer after skin cancer, and the second leading cause of cancer-related deaths among women globally, with an estimated mortality of nearly 700 000 and 2.3 million new cases diagnosed in 2020 alone. Nearly half (45.4%) of these are diagnosed in Asia - where nearly 50% of worldwide fatalities occur - with Europe being responsible for 23.5% (1, 2). It is a complex and heterogeneous disease, with several risk factors associated with its development including age, gender, family history of breast cancer, hormonal factors, lifestyle factors, and exposure to ionizing radiation (3). Age is the most significant risk factor for breast cancer, with the majority of cases occurring in women aged 50 years and above. The incidence of breast cancer varies across different countries and regions with highest numbers in North America, Europe, and Australia, and lowest in Africa and Asia. The incidence of breast cancer has been increasing, likely due to changes in lifestyle factors such as obesity, physical inactivity, and delayed childbearing, along with some forms of hormone replacement therapy and alcohol consumption (4). Despite significant progress made in its diagnosis and treatment, breast cancer remains a major public health issue.

Screening is crucial in the management and overall burden of the disease, since early detected lesions usually carry good prognosis and can be dealt with less invasive methods delivering good cosmetic outcomes (5). One aspect related with early lesions is that they are often non palpable and therefore not clinically detected, reinforcing the role for imaging screening. Methods available for detecting non-palpable lesions include mammography, ultrasound, and magnetic resonance imaging (MRI) (6-8). Mammography is the most widely used for detecting breast cancer and has been shown to reduce breast cancer mortality by up to 30% (9). However, mammography has limitations, particularly in young women with dense breast tissue, where cancers may be missed or masked. Ultrasound is a useful adjunct to mammography in these cases or in those with suspicious findings on mammography (10). MRI is a highly sensitive imaging modality and is particularly useful in high-risk women and those with a personal or family history of breast cancer.

Once a lesion is detected on image-based screening, providing its precise localization is crucial for further management, especially when considering a surgical approach. One of the first methods used for such a purpose were harpoon-wires. Its use dates back to the 1980s, when the development of mammography and breast imaging led to an increase in the detection of small, non-palpable breast lesions (11). These harpoon-wires can be inserted as an office procedure, under local anaesthesia, to conveniently locate the non-palpable lesion and the patient can return home the same day. However, there are also some disadvantages to consider, namely associated pain and discomfort, migration outside the vicinity of the lesion, bleeding and bruising and tissue damage from the wire barbs. In this way, alternatives to their use have been proposed, such as radio-guided occult lesion localization (ROLL) and radioactive seed localization (RSL) with advantages and disadvantages that are outside the scope of this article (12-15).

Magnetic seeds are a recent aid in the pre-operative localization of non-palpable breast lesions. The technique involves the insertion of a small magnetic seed into the breast tissue adjacent to the lesion under ultrasound or mammographic guidance. The seed possesses strong magnetic properties that can be easily detectable using specialized equipment, allowing the accurate location of the lesion during surgery. It can be placed in the breast up to one month before surgery, thereby obviating the need for a breast radiologist on the day of surgery. This technique provides increased accuracy, reduced surgical time, and improved patient comfort (16).

As with other techniques, a positive margin after breast-conserving surgery – defined by the presence of tumour cells at the edge of the surgical specimen our tumour on ink – can also occur with the use of magnetic seeds (overall estimates can reach 15%) (16-19). If the margins are positive, further surgery is required to achieve clear margins (20).

The main objective of this work was to analyse the relationship between the need for margin enlargement of excised breast lesions marked with magnetic seeds and geodimensional and histological parameters, in order to anticipate scenarios where reintervention for clear margins is more likely.

Materials and Methods

Study Design and Variables

A total of 198 patients were analysed retrospectively during a 2-year period (2018-2020) in Centro Hospitalar Universitário de Santo António (CHUdSA), Portugal. These have been submitted to excision of breast lesions previously marked with a magnetic seed (Magseed®, Sysmex Europe GmbH) by a radiologist under imaging aid (ultrasound in the majority of cases). In order to locate the marked lesions intraoperatively, the surgeon used a Sentimag® device (Sysmex Europe GmbH), which is a probe that contains a sensitive magnetometer that detects the magnetic seed. It emits an audible signal with variable pitches (alongside a coherent numeric value on screen) based on the proximity to the seed with higher pitched tones referring to closer proximity.

Eligibility criteria were as follows: Age 18 or higher, elective surgical procedure, existence of pre-operative histology, and absence of mastectomy as the proposed surgical procedure.

A set of variables were collected, namely: size of the lesion (wider axis in cm measured by ultrasound), distance of skin to lesion (determined by the smallest distance in cm between the skin and the magnetic seed measured on mammography scan), quadrant location of the lesion (defined as five regions quadrants, namely superolateral, superomedial, inferomedial, inferolateral and periareolar, and determined as described on the pre-operative ultrasound) and pre-operative histology [determined by dedicated biopsy and defined as ductal carcinoma *in situ* (DCIS), invasive carcinoma of no special type (NST), invasive lobular carcinoma, medullary carcinoma and benign]. Moreover, several other parameters were retrieved from this sample, including magnetic seed placement method, malignant/benign histology, need for reintervention, existence of complications - both related with the magnetic seed and the surgical intervention - and need for margin widening, the latter constituting the testing variable of our main hypothesis. A descriptive diagram is presented in Figure 1.

The patients were followed up for a minimum period of 2 years. Data were collected through the electronic database of the hospital.

The work was conducted in accordance with the Declaration of Helsinki (1964) and was approved by the Local Ethics Committee (CHUdSA 1_21/04/2022, date: 21.04.2023).

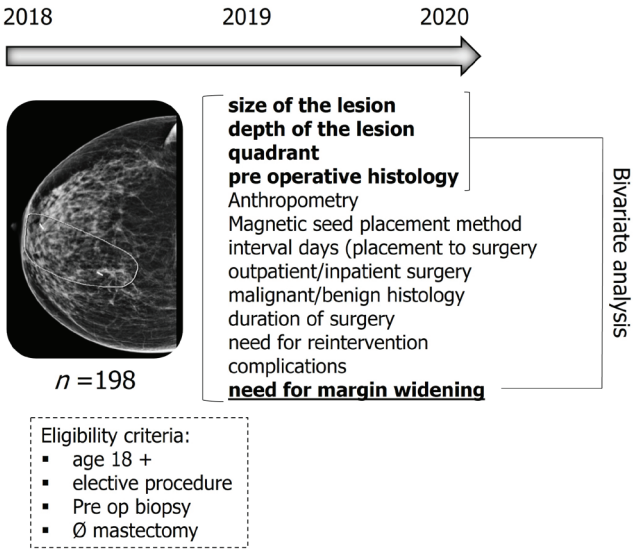

Figure 1. Study design and variables. A total of 198 patients were evaluated between 2018-2020. Among the several variables, those highlighted in bold were analysed in terms of their relevance in the need for margin widening

This paper was written with the aid of STROBE guidelines for observational original research studies (21).

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. Kolmogorov-Smirnov test was used to evaluate parametric and nonparametric distributions. Comparison of categorical data was performed with Chi-square tests. Comparison of quantitative variables was performed using parametric and non-parametric tests, accordingly. All reported *p* values are two-tailed, with a *p* value of 0.05 indicating statistical significance. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 27 (IBM Corp., Armonk, NY, USA) and are in accordance with international statistical reporting standards (22).

Results

A total of 198 cases were included in the study. Tables 1 and 2 summarise the variables analysed for this group of patients.

The patients had an average age of 60 years (59.34±12.969). The most common method for magnetic seed placement was ultrasound (68.2%) and a median time of 1 day was the interval between placement and the surgical procedure (1±3). Regarding location of the lesions, these were more prevalent in the superolateral quadrant (44.6%), followed respectively by superomedial quadrant (19.5%), inferomedial quadrant (13.8%), inferolateral (11.8%) and finally periareolar (10.3%). The average distance between the magnetic seed and the skin, measured on mammography scans was 24 mm (24.07±15.54). The majority of these patients were submitted to surgery in an inpatient setting (76.3%) with 23.7% being treated under outpatient surgery. The average time of surgery was 1h13m (73.71±40.32 min). The vast majority of excised lesions were malign (84.3%) with the remaining presenting a benign histology. The majority of these benign lesions were intraductal papilloma (45.8%) and fibrocystic lesions (33.3%). Representative mammography images of malignant lesions are presented in Figure 2.

Table 1. Categorical variables

		F	%
Magnetic seed placement method	Ultrasound	135	68.2
	Stereotaxis	46	23.2
	Ultrasound and stereotaxis	17	8.6
	(missing)	0	
Quadrant	Superolateral	87	44.6
	Superomedial	38	19.5
	Inferomedial	27	13.8
	Inferolateral	23	11.8
	Periareolar	20	10.3
	(missing)	3	
Inpatient/ outpatient	Inpatient	151	76.3
	Outpatient	47	23.7
	(missing)	0	
Malignant/ benign	Malignant	167	84.3
	Benign	31	15.7
	(missing)	0	
Reintervention	No	161	81.7
	Yes	36	18.3
	(missing)	1	
Magnetic seed related complications	Infection	1	0.5
	Ecchymosis	6	3.1
	None	189	96.4
	(missing)	2	
Margin widening	No	171	86.4
	Yes	27	13.6
	(missing)	0	
Biopsy	Ductal carcinoma *in situ*	42	21.4
	Invasive carcinoma NST	110	56.1
	Invasive lobular carcinoma	14	7.1
	Medullary carcinoma	1	0.5
	Benign	29	14.8
	(missing)	2	

NST: No special type

A need for reintervention by any cause, including need for margin widening, was generally low (18.3%). All the reinterventions occurred in non-cystic lesions. Among complications associated with the use of magnetic seed localization, the authors highlight ecchymosis (3.1%) and infection (0.5%). However, the vast majority of cases (96.4%) did not present any type of complication. A need for reintervention in order to attain negative margins was present in 13.6% of cases with the majority (86.4%) retrieving negative margins on the histological evaluation of the first specimen. Pre-operative histological analysis of malignant lesions showed that invasive carcinoma NST was the most prevalent (56.1%), followed by DCIS 21.4%, invasive lobular carcinoma (7.1%) and a residual number of cases of medullary

Table 2. Continuous variables

	Mean	Standard deviation	Median	Interquartile range	(missing)
Age (years)	59.34 (56.75–61.94)	12.97			3
Magnetic seed distance (mm)	24.07 (21.83–26.32)	15.54			0
Duration of surgery (min)	73.71 (67.00–80.42)	40.32			2
Lesion size (mm)			13	12	0
Interval days (placement to surgery)			1	3	0

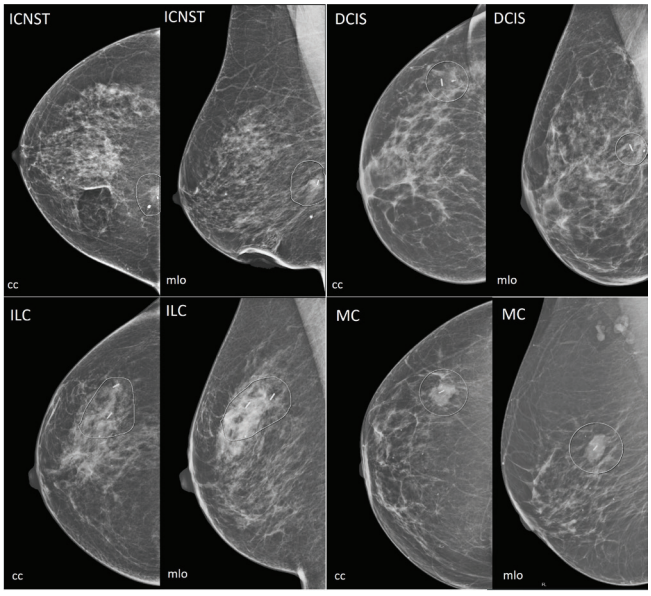

Figure 2. Representative mammograms of the different histological subtypes

ICNST: Invasive carcinoma of no special type; DCIS: Ductal carcinoma in situ; ILC: Invasive lobular carcinoma; MC: Medullary carcinoma; cc: Craniocaudal view; mlo: Mediolateral oblique view.

carcinoma (0.5%). Nine patients that were reoperated not due to margin widening: eight patients (89%) were resubmitted to surgery due to axillary node dissection and one (11%) was reoperated due to superficial wound infection.

A representative image of a magnetic seed after its placement in a breast lesion is shown in Figure 3.

The bivariate analysis of geodimensional and histological parameters is present on Table 3.

This encompassed the analysis of the patients which required reintervention due to a positive margin result in the index surgery with the following variables: size of the lesion measured by its longer axis on mammography scan; quadrant where the lesion was located as determined by the radiologist on ultrasound; distance of skin to lesion of the magnetic seed determined by the shortest linear distance between the seed and the skin measured on mammography scan; and finally pre-operative histology for the two most prevalent types, namely DCIS and invasive carcinoma NST.

On bivariate analysis, reintervention to widen margins was significantly more frequent when the patients had a pre-operative histological analysis of DCIS, as compared to those who had a histological

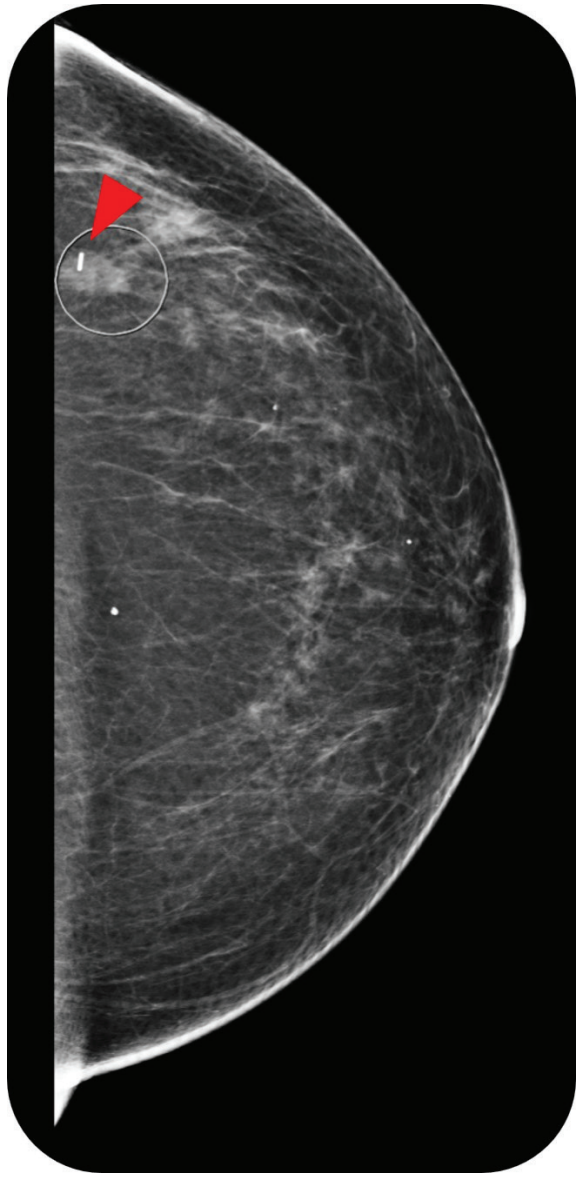

Figure 3. Mammography after placement of the magnetic seed (arrowhead)

diagnosis of invasive carcinoma NST (p = 0.03). Concerning the remaining three analysed groups, no statistically significant differences were observed between the need for reintervention and lesion size (p = 0.197), breast quadrant location (p = 0.626) and distance of skin to lesion defined by the distance between the magnetic seed and the skin (p = 0.356).

Table 3. Bivariate analysis regarding the need for margin widening

Magnetic seed distance – Margin widening	$p = 0.356$	t
Quadrant – Margin widening	$p = 0.626$	$\varkappa^2$
Lesion size – Margin widening	$p = 0.197$	M-W
Biopsy – Margin widening	$p = 0.030$	$\varkappa^2$

t: t-test; $\varkappa^2$: Chi-square test; M-W: Mann-Whitney U test

Discussion nd Conclusion

Breast cancer is one of the most prevalent cancers in women worldwide, representing a relevant health problem with an estimated 2.3 million new cases diagnosed in 2020 (1). Early detection of breast lesions is important as it can lead to timely and adequate treatment, improving the chances of successful outcomes. Breast cancer screening methods have evolved over the years, and today, several techniques are available to detect early-stage lesions. Some of the most common screening methods include mammography, ultrasound, and MRI (6-8). In some cases, breast lesions may not be palpable, making their location crucial for surgical planning. Among the different techniques, recently developed magnetic seed localization may be used to aid in this matter. It has been shown to be effective in locating non-palpable breast lesions, with a high success rate and low complication rates (23). However, as in other methods of detection, magnetic seed localization has an associated percentage of positive margins, which can increase the risk of local recurrence, prompting the need for further surgery. Indeed, previous work by other authors have addressed this issue. The rates of positive margins reported among different techniques present some variability in terms of range but are overall comparable. The harpoon-wire has been shown to deliver 54–90% negative margins, RSL 74–96% and ROLL a rate of 67–87% negative margins (17-19). Concerning magnetic seed localization, work conducted by Powell et al. (16) reported an 85–86% negative margin rate after excision.

The main objective of this work was to evaluate the influence of geodimensional and histological parameters in the need for reintervention after tumorectomy under magnetic seed localization.

The authors analysed several parameters (detailed on Tables 1 and 2), namely pre-operative size of the lesion, quadrant where the lesion is located, the distance at which the lesion is located, and histology on pre-operative biopsy.

The results showed that there were a median 1-day time between magnetic seed placement and surgery. Indeed, in our institution, scheduling for magnetic seed placement is coordinated with the surgical procedure. After multidisciplinary group discussion, the patients are usually admitted in the morning for imaging evaluation and seed placement by the radiologist, being submitted to surgery during the same day. One of the main advantages associated with magnetic seed as compared to wire for example is the possibility to be implanted several days before the procedure without the associated discomfort and infection risk associated with the latter technique (23). Although our procedure is as abovementioned and the median of patients had the magnetic seed placed in the same day of surgery, some patients had its placement several days earlier benefiting from higher comfort at home in the days before surgery.

Regarding location, the lesions were mostly present in the superolateral quadrant (44.6%), followed respectively by superomedial quadrant (19.5%), inferomedial quadrant (13.8%), inferolateral quadrant (11.8%) and finally periareolar (10.3%). The superolateral is in fact the most common location for breast lesions (24), possibly due to the fact that lesions in this quadrant are more easily accessible and detectable during a physical examination or mammography. Lesions in other quadrants, such as superomedial or inferomedial, located close to the sternum and chest wall, may be more difficult to detect during physical examination or mammography being therefore less prevalent in the literature.

Most lesions were malignant (84.3%) with invasive carcinoma of no special type, being the most prevalent (56.1%), in accordance with the literature (16). DCIS was represented in 21.4% while invasive lobular carcinoma and medullary carcinoma represented minor percentages.

Our results are also in line with those reported in the literature regarding reintervention (overall result of 18.3% with a need for reintervention in order to attain negative margins in 13,6% in our cases). This indicates that although this technique is recent with a few hundred cases reported so far, it has a fast-learning curve providing success rates comparable to the other techniques more commonly used while alleviating some side effects such as discomfort, pain and elevated rate of site infection associated with others (25). An aggregated rate of complications of 3.5% is satisfactory, namely since the majority of those where local hematoma managed conservatively.

Focusing on the primary objective of this work, which was the evaluation of the influence of geodimensional and histological parameters on the need for margin re-excision, the authors found a statistically significant difference when comparing DCIS with invasive carcinoma on pre-surgery biopsy with a significantly higher need for reintervention in DCIS ($p = 0.03$). Indeed, similar findings have been described regarding in post-surgical specimens' margins of DCIS when compared to invasive breast carcinoma (16). DCIS is a non-obligate precursor non-contiguous lesion for invasive breast cancer that is confined to the milk ducts of the breast that has not invaded surrounding tissues (26). Such a histological difference from invasive breast carcinoma where cancer cells have broken the ductal barrier and progressed through the surrounding breast tissue, might confer altered mechanical properties to the tissue to be excised, despite the presence of the magnetic seed. Different mechanical properties of the tumour mass might facilitate an easier identification of its boundaries from the surrounding healthy tissues, allowing a more frequent attainment of negative margins. Indeed, since DCIS is confined to the ductal system it can be more difficult to visualize during surgery. Despite the usefulness of magnetic seed location in identifying a more precise location of the tumour, the probe will deliver an audible and visual signal over the tumour marker, not being able to clearly delimitate the tumour boundaries to the surgeon. This may explain to a certain extent the observed results. Also, a possible contributor is the fact that DCIS is tendentially more likely to be multifocal compared to invasive breast carcinoma. While invasive breast carcinoma can be multifocal as well, this is generally less common than in DCIS. The invasion of cancer cells into the surrounding tissue typically occurs from a primary tumour site and may spread to nearby lymph nodes or other areas, rather than developing multiple independent tumour sites within the breast **[27]**. In our institution, as in most, excised breast lesions

identified with a magnetic seed are further screened under X-ray to confirm seed inclusion in the lesion area. *In loco* imaging evaluation by a dedicated breast radiologist might obviate the need for reoperation if margin assessment was considered adequate. Still, this process is not as accurate as histopathological analysis and would require nearly permanent availability from radiologists.

Regarding the geodimensional parameters, no statistically significant differences in terms of pre-operative size of the lesion (p = 0.197), quadrant where the lesion is located (p = 0.626), and the distance from the skin at which the lesion is located (p = 0.356), as shown on Table 3.

Overall, this work suggests that the surgeon should consider a wider margin excision if a patient has a pre-operative biopsy of DCIS when compared to invasive carcinoma, in order to decrease the likelihood of reintervention to obtain negative margins. No difference in terms of surgical gesture is apparently needed for lesions with larger size, more deeply located or that are present in a certain quadrant.

This work has inherent limitations. It describes the experience of a single centre in a western European tertiary hospital, which represents a certain reality. Nonetheless, the methods used are established in the current state of the art and the results are expected to translate similar healthcare scenarios. A reduced number of positive margins after tumorectomy in our series 13.6%, is in accordance with data described in the literature. These numbers, although positive regarding treatment, provide reduced numbers for statistical analysis during the chosen timeframe. Furthermore, the analysis of which margin is significantly most represented as positive is also hindered by this fact. Future studies shall benefit from including more centres and enrolling more patients with the expectancy that these will render higher absolute patients' number for statistical analysis.

Breast cancer is a relevant health issue and early detection of breast lesions is crucial for successful treatment outcomes. Magnetic seed localization is an effective technique for locating non-palpable breast lesions, but it has an associated percentage of positive margins as in other similar systems. This work suggests that a preoperative histology of DCIS on biopsy should prompt a wider margin excision, thereby decreasing the need for reintervention to attain clear margins. No such concern is needed regarding size of the lesion, its quadrant location and distance of skin to lesion at which it is located.

Ethics Committee Approval: The work was conducted in accordance with the Declaration of Helsinki (1964) and was approved by the Local Ethics Committee (CHUdSA 1_21/04/2022, date: 21.04.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Omission of Radiotherapy in Women >60 Years Old After Breast Conserving Surgery for Breast Cancer is Non-Inferior in Terms of Local Recurrence: A Retrospective Cohort Study

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ABSTRACT

Objective: Local recurrence rate may show no significant differences between women aged 60 and older who receive breast-conserving surgery followed by radiotherapy and those in the same age group who undergo breast-conserving surgery without subsequent radiotherapy.

Materials and Methods: Retrospective cohort study from a single practice with median follow-up time 44 months (interquartile range: 16, 82), comparing women older than 60 years old at diagnosis of breast cancer, treated with breast conserving surgery and either receiving or not receiving radiation therapy postoperatively. The primary endpoint was local recurrence difference between the two groups.

Results: Local recurrence did not differ significantly between the two groups in terms of radiotherapy or not [odds ratio (OR) 0.96, 95% confidence interval (CI) 0.89–1.02, Fisher's exact test $p = 0.388$], nor between two age groups with cut-off at 65 years of age (OR: 0.99, 95% CI 0.92–1.07, Fisher's Exact test $p = 0.6$). Local recurrence also did not differ when subgroups of age (60–65 years and >66 years) were considered. All patients received 5 years of hormonal therapy.

Conclusion: Omission of radiotherapy in selected patients is not inferior to radiotherapy after breast conserving surgery in terms of preventing local recurrence.

Keywords: Breast conserving surgery; local recurrence; radiotherapy omission

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Key Points

- Local recurrence risk was not significantly different in radiation-receiving and radiation-omitting women older than 60 years at diagnosis.
- This lack of difference was detected among patients who underwent breast conserving surgery with positive estrogen receptor status and had received 5 years of endocrine therapy.
- Radiation therapy may be safely omitted in patients older than 60 years of age at diagnosis in terms of the risk of local recurrence.

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Introduction

Radiotherapy in breast cancer cases was commonplace across clinical guidelines in the past decades (1). Associated morbidity, together with poorer patient-reported quality of life needs to be taken into consideration when planning postoperative treatment with the advance of patient age at diagnosis (2). During the Coronavirus disease 2019 pandemic, the limitation of resources and the need for protection of oncological patients brought up the question of omitting radiation therapy in selected subgroups of patients with breast cancer. A literature review of the available studies (3) concluded that older adults with early-stage breast cancer and favourable prognostic factors should undergo tailored therapeutic strategies, including the omission of radiation therapy. Later studies have demonstrated the lack of benefit concerning local recurrence in patients older than 65 years (4-6). The purpose of this retrospective study was to evaluate whether the omission of radiotherapy after breast conserving surgery was non-inferior to outcomes in patients receiving radiotherapy in terms of local recurrence.

Materials and Methods

This was a retrospective cohort study to assess the impact of postoperative radiotherapy following breast conserving surgery on local recurrence. The records of a single practice were the source of data. Patients older than 60 years at the time of initial surgical consultation, candidate for breast conserving excision, hormonally dependent tumour biology and histologic grade up to III were assessed for inclusion. Patients with hormonally dependent tumours and histological grade up to III were considered low risk patients and thus included in the cohort. The age limit was chosen in accordance with recent publications (2, 5, 6). Breast conserving excision was defined as lumpectomy or partial mastectomy with clear margins combined with sentinel lymph node biopsy. A minimum of six months follow up was required to be assessed for local recurrence. Local recurrence was defined as any abnormal clinical or ultrasonographic finding at the site of initial excision undergoing biopsy (fine needle or open) and proving to be malignant. Patients with lymph node involvement confirmed either intra-operatively or post-operatively were not included. The radiation therapy protocol was whole breast irradiation with approximately 45–50.4 Gy (1.8–2 Gy/fraction, 25–28 fractions) with or without boost dose to the tumour bed (external radiotherapy of 10–16 Gy at 2 Gy/fraction). All included patients were eligible for a five-year hormonal treatment protocol. Systemic chemotherapy was administered only to patients with histologic grade III.

Written consent was not obtained since all patient records were anonymized. The study was approved by the Ethics Committee of the Department of Medicine of the Aristotle University of Thessaloniki (approval number: 6/2023, date: 07.11.2023).

Statistical Analysis

Descriptive statistics, dictated by normality assessment where appropriate, were used to summarise the raw data. Pairwise comparisons between the two groups were done with either Wilcoxon rank-sum test (non-normally distributed, continuous data) or chi-square test and Fisher's Exact test (categorical data). Significance level was set to 5%. Kaplan-Meier curves were used to investigate the time to local recurrence and the log-rank test was used to formally assess the difference in curves. Due to the nature of the initial database (single private practice records) a proportion of patients were followed up in tertiary centres after receiving radiotherapy and their data on local recurrence were not available. To account for this loss of patients we decided to run subgroup analysis including only patients followed up for more than 21 months after surgery (roughly up to the sixth follow-up visit) and compare the results with the initial estimation. Starting point was defined as the date of surgery to ensure all patients had similar initiation of follow-up.

Sample Size Calculation

Based on the natural history of the disease, specifically the local recurrence rate (7), and published data from large, randomized trials we can estimate that 125 observations should suffice to detect an effect (w = 0.25) with level of significance 5% and 80% power using Pearson's chi-squared test.

This study is reported in accordance with STROBE guidelines (8) for cohort studies.

Data were collected using an Access database (Microsoft Office 365©) and calculations were done with R Statistical Software (v4.2.3; R Core Team) (9–13) for Windows (Microsoft Corporation©) using the RStudio IDE (14).

Results

A hundred and twenty-nine patients were identified but only 127 were included in this analysis since the last two patients underwent breast-conserving surgery less than six months ago (Table 1). All patients were positive for estrogen and progesterone receptors. Median age was 67 years old [interquartile range (IQR) 63, 72], and did not differ significantly between the two groups (Wilcoxon rank-sum test p = 0.2). Similarly, median follow-up time (no radiotherapy median: 46 months, IQR: 18–73 and radiotherapy median: 44 months, IQR: 16–88 respectively, Wilcoxon rank-sum test p = 0.7), tumour size (no radiotherapy median: 1.50, IQR: 1.00–2.00 and radiotherapy median: 1.50, IQR: 1.05–2.00, Wilcoxon rank-sum test p = 0.2), histologic grade (Figure 1 and Table 1), sentinel lymph node status (100% negative in both groups), five-year hormonal therapy adherence (one non-adherent patient in the no radiotherapy group and none in the radiotherapy group) and Ki-67 status (no radiotherapy median: 14, IQR: 8–17 and radiotherapy median: 15, IQR: 15–30, Wilcoxon rank-sum test p = 0.093) were comparable between groups. Local recurrence rate was not statistically different between the groups [odds ratio (OR) 0.96, 95% confidence interval (CI) 0.89–1.02, Fisher's Exact test p = 0.388; see Figure 1]. All patients had negative resection

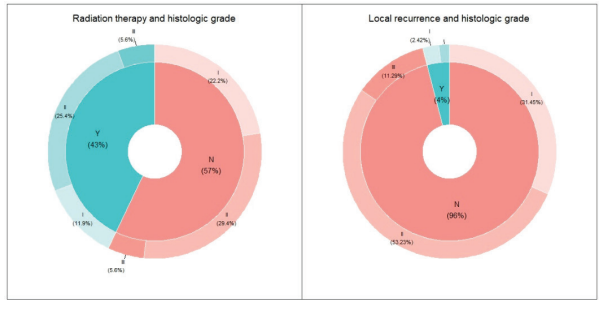

Figure 1. Donut-pie charts depicting the analogy of histological grade (I: grade I, II: grade II, III: grade III, along with relative frequencies) between the two radiation groups (Y: Receiving postoperative radiation, N: Not receiving postoperative radiation) on the left side, and the analogy of histological grade (I: grade I, II: grade II, III: grade III, along with relative frequencies) between those with local recurrence (Y) and those without (N) on the right side

margins. Seven patients in each group received systemic chemotherapy (Fisher's Exact test $p = 0.78$).

There were 55 patients in the radiotherapy group. Median total radiotherapy dose was 4082 (IQR: 4005–5000) and ten patients were treated with boost radiotherapy (29%), though there were many missing data on the boost protocol (n = 20). Interestingly, in the subgroup analysis of patients receiving radiotherapy, a difference in the radiotherapy dose was detected regarding the radiotherapy protocol (with or without boost doses). The initial dose was higher in the group in the boost protocol compared to the dose in the no boost protocol (Boost group: 4256 (4005, 5000), no Boost group: 4005 (2951, 4121), Wilcoxon rank-sum test $p = 0.022$).

Table 1. Sample baseline characteristics

Characteristic	Overall, n = 127[1]	No radiotherapy, n = 72[1]	Radiotherapy, n = 55[1]	p[2]
Age	67 (63, 72)	67 (63, 74)	65 (63, 70)	0.2
Tumour size	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)	1.50 (1.05, 2.00)	0.2
Histologic grade				0.4
I	43 (34%)	28 (39%)	15 (28%)	
II	69 (55%)	37 (51%)	32 (59%)	
III	14 (11%)	7 (9.7%)	7 (13%)	
Unknown	1	0	1	
Chemotherapy				0.78
No	113 (89%)	65 (90%)	48 (87%)	
Yes	14 (11%)	7 (10%)	7 (13%)	
Sentinel lymph node status				
Negative	127 (100%)	72 (100%)	55 (100%)	
Hormonal therapy				>0.9
No	1 (0.8%)	1 (1.4%)	0 (0%)	
Yes	126 (99%)	71 (99%)	55 (100%)	
Ki-67 status	15 (10, 24)	14 (8, 17)	15 (14, 30)	0.093
Unknown	80	42	38	
Radiotherapy				-
No	72 (57%)	-	-	
Yes	55 (43%)	-	-	
Radiotherapy dose (cGy)	4082 (4005, 5000)	-	4082 (4005, 5000)	
Unknown	19	72	19	
Boost radiotherapy protocol				>0.9
No	10 (29%)	-	10 (29%)	
Yes	25 (71%)	-	25 (71%)	
Unknown	92	72	20	
Local recurrence				0.4
No	120 (96%)	67 (94%)	53 (98%)	
Yes	5 (4.0%)	4 (5.6%)	1 (1.9%)	
Unknown	2	1	1	
Surgery date	1994-03-01 to 2023-02-22	1994-03-01 to 2023-03-28	1998-05-01 to 2023-02-22	0.3
Last follow-up	2003-06-01 to 2023-08-02	2003-06-01 to 2023-08-02	2010-05-01 to 2023-08-02	0.13
Follow-up (months)	44 (16, 82)	46 (18, 73)	44 (16, 88)	0.7
Follow-up (years)	4.0 (1.0, 7.0)	4.0 (1.8, 6.0)	4.0 (1.0, 7.0)	0.7

[1]Median (IQR); n (%); range

[2]Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's Exact test

The study population was also assessed based on age, with a cut-off at 65 years on surgery. There were no systematic differences detected on local recurrence rates (OR: 0.99, 95% CI 0.92–1.07, Fisher's Exact test p = 0.6, Table 2). Local recurrence did not differ among radiotherapy groups either in the 60–65 years old group, nor the >65 years old group (OR: 0.21, 95% CI 0.01–4.13, p = 0.49 for the 60–65 years group and OR: 0.79, 95% CI 0.08–8.4, p = 0.89 for the >65 years group). Median follow-up time was similarly distributed between groups (median 62 months, IQR 15–93 in the 60–65 years old group and median 38 months, IQR 16–74 in the 66–88 years old group, Wilcoxon rank-sum test p = 0.11). Patients' characteristics were not found to differ systematically between the two groups. Tumour size was not different between the two groups (median 1.50, IQR: 1.00–2.00 in both groups, Wilcoxon rank-sum test p = 0.9), neither was the relative frequencies of histologic grade (chi-squared test p = 0.5). Sentinel lymph node status was 100% negative in both groups and ki-67 status was similarly distributed (median: 14, IQR: 14–20 in the 60–65 years old group and median: 15, IQR: 8–25 in the 66–88 years old group, Wilcoxon rank-sum test p = 0.6). Adherence to hormonal therapy demonstrated no difference with one non-adherent patient in the 60–65 years old group and none in the 66–88 years old (Fisher's Exact test p = 0.4). The proportion of patients undergoing radiotherapy was similar between the two groups (OR: 0.81, 95% CI: 0.59–1.11, Fisher's Exact test p = 0.2) as was the proportion of patients receiving boost doses (OR: 0.79, 95% CI: 0.27–2.32, Fisher's Exact test p = 0.7). Radiotherapy doses were comparable between groups (median: 4160, IQR: 4005–5000 in the 60–65 years old group and median: 4240, IQR: 4005–4428 in the 66–88 years old group, Wilcoxon rank-sum test p = 0.3). Eight patients in the 60–65 years old group and six in the 66–88 years old group received systematic chemotherapy (Fisher's Exact test p = 0.39).

Table 2. Sample characteristics between age groups

Characteristic	60–65 years old n = 56[1]	66–88 years old n = 71[1]	p[2]
Tumour size	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)	0.9
Histologic grade			0.5
I	17 (31%)	26 (37%)	
II	30 (55%)	39 (55%)	
III	8 (15%)	6 (8.5%)	
Unknown	1	0	
Chemotherapy			0.39
No	48 (85.8%)	65 (91.6%)	
Yes	8 (14.2%)	6 (8.4%)	
Sentinel lymph node status			
Negative	56 (100%)	71 (100%)	
Hormonal therapy			0.4
No	1 (1.8%)	0 (0%)	
Yes	55 (98%)	71 (100%)	
Ki-67 status	14 (14, 20)	15 (8, 25)	0.6
Unknown	33	41	
Radiotherapy			0.2
No	28 (50%)	44 (62%)	
Yes	28 (50%)	27 (38%)	
Radiotherapy dose (cGy)	4160 (4005, 5000)	4240 (4005, 4428)	0.3
Unknown	35	52	
Boost radiotherapy protocol			0.7
No	4 (25%)	6 (32%)	
Yes	12 (75%)	13 (68%)	
Unknown	40	53	
Local recurrence			0.9
No	53 (96%)	67 (96%)	
Yes	2 (3.6%)	3 (4.3%)	
Unknown	1	1	
Surgery date	1994-03-01 to 2023-02-21	2000-11-01 to 2023-02-22	0.9
Last follow-up	2005-02-01 to 2023-08-02	2003-06-01 to 2023-08-02	0.2
Follow-up (months)	62 (15, 93)	38 (16, 74)	0.11
Follow-up (years)	5.0 (1.0, 8.2)	3.0 (1.0, 6.0)	0.076

[1]Median (IQR); n (%); range
[2]Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's Exact test

Kaplan-Meier curves were used to assess the time to local recurrence and compare the two radiotherapy groups. In this sample, median survival time could not be determined for either group since less than half of the patients were diagnosed with local recurrence until the end of observation. The log-rank test did not detect any systematic difference between the two survival curves (Figure 2). When comparing Kaplan-Meier curves in the two age groups, the absence of statistically significant difference between radiation groups remained (Figure 3).

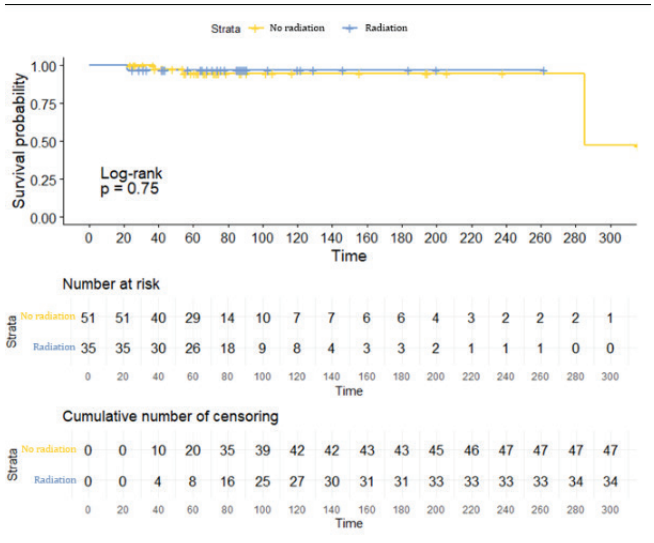

Figure 2. Kaplan-Meier curves for local recurrence between the two radiation groups, along with tables with number remaining at risk and cumulative censoring at each time interval. No statistically significant difference is detected, either from inspection of the curves or with the log-rank test

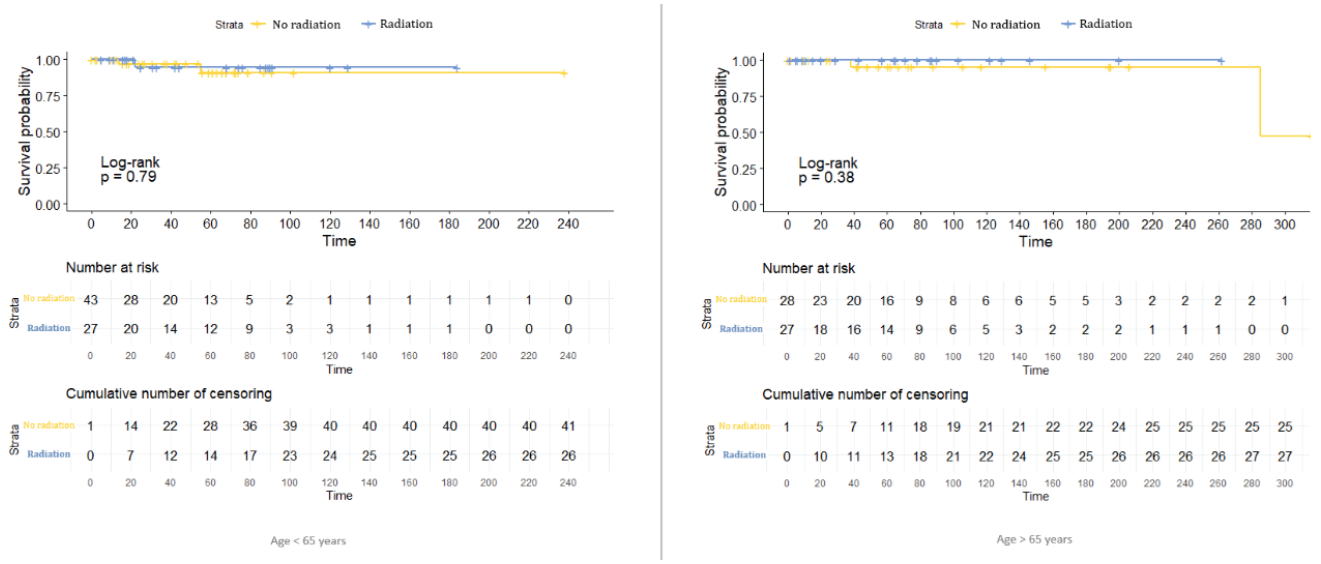

Figure 3. Kaplan-Meier curves for local recurrence between the two radiation groups, along with tables with number remaining at risk and cumulative censoring at each time interval and for each age group (left: age <65 years old, right: age >65 years old). No statistically significant difference is detected, either from inspection of the curves or with the log-rank test

Discussion and Conclusion

The main finding of this retrospective analysis was the lack of difference in survival rates for local recurrence between those receiving radiation therapy and those who did not in patients older than 60 years old, over a follow-up period of around 45 months.

In this cohort, patients with T1 or T2 breast tumours and node-negative status were found to have no significant difference in local recurrence survival time whether they had radiotherapy or not. Stueber et al. (15) conducted an analysis of 2384 patients from the BRENDA registry and concluded that patients aged older than 70 years old with low-risk early breast cancer (luminal A, T1 or T2 and node-negative) receiving GA-BCS were a suitable group to forego postoperative radiation as there was no significant benefit for either local recurrence or for tumour-associated death. In the same study, higher-risk (G3 or T3/T4 or node-positive or other than luminal A tumours) patients were found to have benefit and should undergo irradiation. Subsequent reports were in accordance with these findings (16).

Our cohort study included women aged 60 to 88 years old. Further cohort (5, 17) studies as well as RCTs (4) suggested that the age cut-off for radiation omission in low-risk breast cancer could be at 65 years of age at diagnosis. These concluded that the omission of radiation should be considered based on comorbidities considering that lack of apparent benefit in overall survival. In our subgroup analysis with a cut-off at 65 years of age, local recurrence rate did not differ significantly between those receiving radiation and those not in either group.

Our cohort consisted entirely of ER+ tumours undergoing endocrine therapy for five years. Previous studies (4, 18) found evidence of the protective role of endocrine therapy for local recurrence. Additionally, it has been a decade since the establishment of the similarity of reduction of local recurrence between radiotherapy and endocrine therapy (19). A common conclusion was that the decision for radiation omission in patients can be safely considered given that they will adhere to five-year endocrine therapy. This decision should take into consideration the patient's preference and potential markers of radiation sensitivity (20) since an analysis of cost-effectiveness comparing treatment options did not reveal systematic differences (21) to rely upon.

Radiation therapy has been a close adjunct to breast cancer treatment for many decades. There are several (22, 23) registry reports that advocate the benefits of radiation therapy in elderly patients with low-risk breast cancer undergoing either breast conserving surgery or mastectomy. However, even these studies that found statistically significant differences in tumour-specific survival, concluded that individual counselling in elder patients is the preferred decision-making process regarding radiation therapy. It is noteworthy that prospective, randomised trials of the same period (6) had already begun to suggest the omission of radiotherapy in selected patients without greater hazard for death or local recurrence.

One of the most notable systematic reviews on the subject is an extensive meta-analysis of individual patient data (1). This comprehensive analysis demonstrated a clear advantage after receiving radiotherapy, significantly reducing the risk of recurrence and moderately lowering the overall risk of death. Another recent systematic review and meta-analysis (24) specifically focused on elderly patients, evaluating both the omission of radiation therapy and endocrine therapy. Interestingly, the endpoint related to the omission of radiotherapy showed a significant impact on local recurrence but not on overall survival. Despite their data supporting the omission of radiotherapy, it should be noted that their literature search concluded before the publication of subsequent large cohorts and randomized controlled trials. This gap in the existing literature calls for a fresh synthesis that incorporates various study types as methodologically appropriate. To address this, a protocol has been registered in the Cochrane database. The aim is to assess the omission of radiation in postmenopausal women, with planned subgroup analyses based on age, receipt of adjuvant chemotherapy, and receipt of adjuvant hormonal treatment, providing a more up-to-date and comprehensive understanding of the topic.

Several ongoing studies aim to address the question of personalizing radiation therapy omission. The expansion of patient age (25, 26) and the incorporation of new genetic markers (25, 26), in conjunction with standard histopathological tumour evaluation, are being explored to identify patients who can safely omit radiotherapy. Additionally, research is underway to investigate the effect of human epidermal growth factor receptor 2 status (27) and explore the feasibility of

omitting radiation therapy in favour of partial irradiation instead of whole breast irradiation (28). The diversity in study protocols and modalities used for identifying at-risk patients underscores the ongoing necessity for more individualized treatments based on evidence-derived recommendations (29).

Study Limitations

The limitations of this study are the sample size and the rarity of the local recurrence. We believe that this is due to the fact that a proportion of the sample continued their follow-up in the referral centre where they underwent oncological consultation. This loss from follow-up resulted in high censoring and thus the inability to determine median survival times. The retrospective nature of the collected data cannot allow for generalization, but the aim of this study was to provide a motive for tailoring radiation therapy rather than provide broad recommendations. Several additional sources of bias should be taken into consideration when interpreting these results. These include that no confounding factors could be investigated due to the few local recurrences, the cohort may suffer sampling bias due to its source from a single practice and possibly, immortal time bias since the starting time is the surgery date and not the treatment completion day, which is the final radiotherapy session for the patients in the radiotherapy group.

In conclusion, our findings support the existing evidence on personalized omission of radiation therapy with primary focus on the patient's age, given they present with low-risk breast tumours and estrogen receptor positive status. A systematic review of the existing literature should determine whether more RCTs and registry analyses are needed to address this question.

Ethics Committee Approval: study was approved by the Ethics Committee of the Department of Medicine of the Aristotle University of Thessaloniki (approval number: 6/2023, date: 07.11.2023).

Informed Consent: Written consent was not obtained since all patient records were anonymized.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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Original Article

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Does F-18 FDG-PET/CT Have an Additional Impact on Axillary Approach in Early-Stage Breast Cancer?

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ABSTRACT

Objective: Breast cancer (BC) is a significant health concern and one of the most diagnosed cancers in women, both in Turkey and globally. Despite advances in the management of BC, axillary lymph node involvement remains a significant consideration for treatment planning, local recurrence, and prognosis. We aimed to evaluate the contribution of F-18 fluorodeoxyglucose-positron emission tomography/computed tomography (F-18 FDG-PET/CT) in detecting axillary lymph node metastasis compared to ultrasound (US).

Materials and Methods: Eighty patients who were diagnosed with stage I and II BC and underwent US and F-18 FDG-PET/CT scans before surgery were enrolled in this study. Those who did not undergo F-18 FDG-PET/CT imaging, patients with distant metastases at the time of diagnosis and patients with micrometastases in the axilla were excluded from the analysis. Imaging results of the status of axillary lymph nodes were verified with the final pathology report of axillary lymph nodes.

Results: The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of F-18 FDG-PET/CT for the detection of ipsilateral axillary lymph node metastases were 75%, 77.27%, 72.97%, 79.07%, and 76.25%. The corresponding values for US were 72.22%, 81.82%, 76.47%, 78.26%, and 77.50%, respectively. When US finding is negative or suspicious in axillary lymph node evaluation, the accuracy of F-18 FDG-PET/CT for the detection of ipsilateral axillary lymph node metastases were 65.38%, 83.33%, 70.83%, and 79.55%, respectively.

Conclusion: This study found that F-18 FDG-PET/CT does not provide an additional advantage over US in assessing the axilla in early-stage disease.

Keywords: Breast cancer; lymph node metastasis; axillary staging; positron emission tomography; ultrasound

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Key Points

- Metastatic involvement of axillary lymph node remains significant for treatment planning, local recurrence, and prognosis of breast cancer.
- F-18 FDG-PET/CT did not provide an additional advantage over US in assessing the axilla in early-stage disease.
- US examination by an experienced breast radiologist is sufficient for evaluating the axillary lymph nodes.

Introduction

Breast cancer (BC) is a significant health concern and one of the most diagnosed cancers, and the second leading cause of cancer-related deaths in women both in Turkey and globally. BC accounts for one out of every four female cancers (1). Despite advances in the management of BC, axillary lymph node involvement remains the most important prognostic factor, and has importance for treatment planning, local recurrence, and prognosis. Over the past two decades, the increased morbidity associated with axillary surgery has prompted extensive research efforts. This has resulted in a shift towards more personalized treatments, as exemplified by the American College of Surgeons Oncology Group Z0011 clinical trial (ACOSOG Z0011) (2) and ongoing trials aimed at eliminating the need for surgical axillary staging. Currently, no single ideal imaging method exists for accurately staging the axilla.

The AMAROS trial included patients with clinically negative axillary lymph nodes and T1 or T2 stage BC with micro- or macro-metastatic sentinel lymph node biopsy (SLNB). Axillary lymph node dissection (ALND) and axillary radiotherapy arms showed comparable results regarding local recurrence and survival outcomes (3).

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Prospective ongoing studies, such as SOUND (Sentinel node v Observation after axillary UltrasouND), INSEMA (Intergroup Sentinel Mamma study), and BOOG 2013-08 (Borstkanker Onderzoek Groep) are focused on evaluating the safety of omitting SLNB in breast conserving surgery (BCS) for patients with clinically negative axillary nodes. The SOUND trial is a prospective randomized multicenter study, and its objective is to compare the outcomes of SLNB versus observation (no axillary surgery) in patients with early BC, smaller than 2 cm, low-grade, biologically favorable tumors, and a negative preoperative axillary ultrasound (US) finding. In this clinical trial, where patients with small BC and negative axillary lymph nodes on US, omitting axillary surgery demonstrated non-inferiority in terms of disease-free survival compared to SLNB (4).

Considering these studies, the presence or absence of lymph node involvement in BC and its accurate determination at the time of diagnosis still cannot be reliably achieved. Although US is known to be the most reliable, easily accessible, and cost-effective modality for interpreting lymph node status, its sensitivity can be compromised due to its operator-dependent nature. F-18 fluorodeoxyglucose-positron emission tomography/computed tomography (F-18 FDG-PET/CT) is recommended for imaging in cases of locally advanced disease and primarily for detecting distant metastasis (5). It is also utilized in cases of uncertainty regarding axillary lymph node involvement (6). Our study aimed to evaluate the contribution of F-18 FDG-PET/CT in detecting axillary lymph node metastasis compared to US.

Materials and Methods

Study Design

This study retrospectively evaluated the imaging and pathology reports of 80 BC patients treated at Koç University Hospital, Breast Surgery Clinic, between June 2015 and March 2023. Stage I and II BC patients who had undergone initial diagnostic US and F-18 FDG-PET/CT scans were enrolled. This study was approved by the Koç University Institutional Review Board (2023.252.IRB1.081).

The staging of BC was done according to the 8th edition of the American Joint Committee on Cancer staging system (7). Data were collected from medical records, including operative notes, radiology, nuclear medicine, and pathology reports. Patients were initiated on treatment with neoadjuvant chemotherapy (NAC) or upfront surgery based on their clinical stage and immune phenotype. Clinical lymph node status by imaging was compared with the pathological assessments of surgically removed lymph nodes, either by SLNB or ALND. In patients who underwent NAC, in case of pathological complete response, the signs of response to therapy in the lymph node (LN) were reported, and those patients were assigned as LN positive.

US is the method of choice to evaluate the axillary lymph nodes. When there was suspicion of lymph node metastasis, fine needle aspiration biopsy (FNAB) was performed. Patients with micrometastatic LN were excluded from the study to minimize bias, as none of the imaging modalities used are intended to diagnose micrometastasis. Radiological evaluation of the axillary lymph nodes was compared with the final surgical pathology results (Figure 1). The US and F-18 FDG-PET/CT assessments were blinded to the findings of the other modality.

US Protocol

Preoperative axillary US was performed by a breast radiologist experienced in breast imaging using GE Logiq E10 and GE Logiq S8 machines (GE Healthcare, Milwaukee, Wisconsin, USA), which were equipped with high-frequency matrix linear transducers at a frequency range of 6 to 15 MHz. Bilateral axillary regions were scanned using an orthogonal direction along the axillary artery from the lower axilla to the junction of the axilla and upper arm, as well as the retro-pectoral area.

Suspicious axillary lymph nodes (ALNs) were identified based on the detection of one or more of the following US features: cortical thickness greater than 3.0 mm, focal cortical lobulation, irregular or round shape, markedly hypoechoic or heterogenous cortex, loss of fatty hilum and increased peripheral blood flow or abnormal cortical blood flow (nonhilar flow) on Doppler US.

For all identified suspicious ALNs during the preoperative axillary US, US-guided fine needle aspiration (FNA) or core-needle biopsy was recommended. The same breast radiologist performed the FNA procedure using a 22-gauge needle with a freehand technique. Each lymph node was aspirated at least twice. Immediately after aspiration, all FNA samples were evaluated at the bedside to obtain rapid cytological results. A fully automatic method was utilized, using 14 or 16-gauge needles for core-needle biopsies.

F-18 FDG-PET/CT Protocol

All patients refrained from eating for at least four hours before the PET study. The F-18 FDG-PET/CT scan was conducted 60 minutes after administering 0.8–1 mCi/kg of F-18 FDG if the blood glucose was <11 mmol/L, and the resulting images, spanning from the head to the proximal calf, were reconstructed using Q-clear time-of-flight and point-spread function data. No contrast agent containing iodine was used during the CT scan. The standardized uptake value (SUV) was determined by adjusting for the injected FDG dose and the patient's body weight. All F-18 FDG-PET/CT examinations were retrieved from the electronic archive system and assessed using a GE Healthcare AW workstation in Milwaukee, Wisconsin, USA. The F-18 FDG-PET/CT images were taken from the head to the proximal thighs. Before obtaining the PET images, a helical CT was performed with the person breathing shallowly, using a low-dose CT protocol to create an attenuation map. ALNs were evaluated visually and deemed positive when the F-18 FDG uptake level exceeded that of the adjacent ALN and the reference background. The ALN's morphological characteristics and dimensions were examined and documented. The PET signal revealed that ALN displaying basal physiological lymphatic uptake was classified as negative. The SUV_{max} was identified as the highest SUV value within the region of interest, delineated over the most intense area of F-18 FDG accumulation in the ALN for each patient.

Statistical Analysis

The obtained findings in the study were evaluated using the SPSS, version 26 (IBM Inc., Armonk, NY, USA). Descriptive statistical methods, such as mean, standard deviation, median, minimum, and maximum values are used for quantitative variables, while qualitative variables are presented using frequency and percentage. The normality of the data was assessed using the Shapiro-Wilk test and Box Plot graphs. Diagnostic screening tests (sensitivity, specificity, positive predictive value, negative predictive value, and accuracy), the McNemar test, and the Kappa agreement level were used to compare qualitative data. Receiver operator curve (ROC) curve area was used to evaluate the US and F-18 FDG-PET/CT results for predicting pathological outcomes. The results were evaluated at a 95% confidence interval, with a significance level of $p<0.05$.

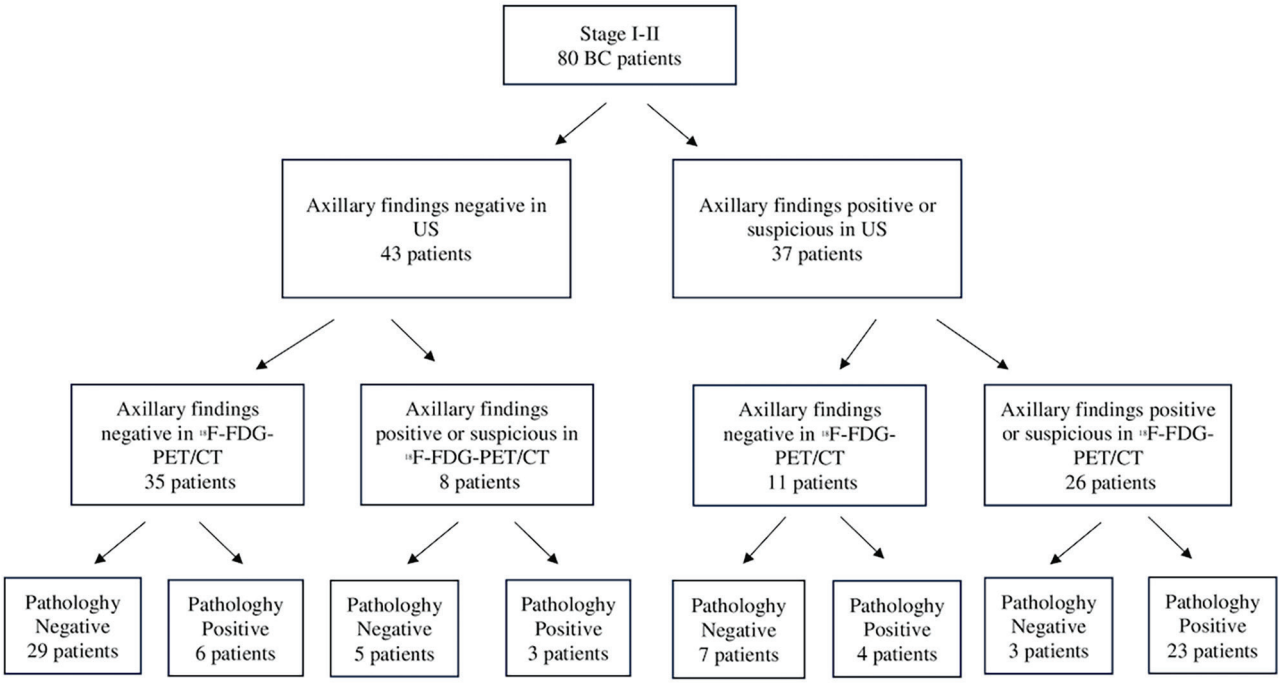

Figure 1. Study chart

F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound; BC: Breast cancer

Sensitivity is defined as the ability of the test to correctly identify individuals with the condition among true positive cases. Specificity is defined as the ability of the test to correctly identify individuals without the condition among true negative cases.

Positive predictive value (PPV) is defined as the conditional probability of the individual having the condition when the test result is positive (indicating the presence of the disease) while the negative predictive value (NPV) is defined as the probability of the individual being free of the condition when the test result is negative (indicating the absence of the disease).

The κ (Kappa) value is used to assess the level of agreement beyond chance between two raters or methods. The interpretation of κ values helps determine the strength of agreement, ranging from poor to very good.

Results

One male and 79 females, a total of 80 patients, were enrolled in this study. The mean ± standard deviation age was 55.38±14.05 years, and the median was 55 (range: 27–86). The clinical T-stage distribution was as follows: cT1, 42 (51.3%) patients; cT2, 38 (47.5%) patients; and cT3, 1 (1.3%) patient. The clinical N stage distribution was as follows: cN0, 53 (66.3%) patients and cN1 27 (33.8%) patients. The clinical stage distribution was as follows: 1A, 33 (40.9%) patients; 2A, 26 (32.5%) patients; and 2B, 21 (26.2%) patients. Among them, 65 (81.3%) patients were diagnosed with histopathological proven ductal carcinoma, 10 (12.5%) with lobular carcinoma or mixed histology, 2 (2.5%) with mucinous carcinoma, 2 (2.5%) with micropapillary carcinoma, and 1 (1.3%) with tubular carcinoma. Twenty-three (28.8%) patients received NAC before surgery, while 57 (71.2%) patients underwent upfront surgery. In the subtype analysis, 59 (73.6%) patients were HR+/HER2-, 14 (17.5%) patients were HR-/HER2+, and 7 (8.8%) patients were HR-/HER2-. Of 80 patients, 30 underwent SLNB followed by ALND, while SLNB was performed on the remaining 50. The results were analyzed based on these procedures.

According to preoperative US, axillary lymph node involvement was negative in 53.8% (n=43) of patients, suspicious in 31.3% (n=25) of patients, and positive in 15% (n=12) of patients. Preoperative F-18 FDG-PET/CT revealed negative axillary lymph node involvement in 57.5% (n=46) of patients, suspicious involvement in 12.5% (n=10) of patients, and positive involvement in 30% (n=24) of patients. On US examination, there was one metastatic lymph node in 30% (n=24) of the patients, 2 in 13.8% (n=11) of the patients, and 3 in 2.5% (n=2) of the patients. In the F-18 FDG-PET/CT examination, there was one metastatic lymph node in 25% (n=20) of the patients, 2 in 15% (n=12) of the patients, 3 in 1.3% (n=1) of the patients, and 4 in 1.3% (n=1) of the patients (Table 1). FNAB was performed on 25 (31.25%) out of 80 patients, revealing carcinoma metastasis in 18 (22.5%) cases and yielding negative results in 7 (8.75%) cases. The remaining 55 (68.75%) patients did not undergo FNAB.

Axillary evaluation by US was true-negative (TN) in 34 (45.0 %) patients, true-positive (TP) in 27 (33.8%) patients, false-negative (FN) in 9 (11.3%), and false-positive (FP) in 10 (12.5%) patients. Kappa correlation level between US and axillary lymph node pathology results was 52.1% and found to be statistically significant (Kappa coefficient: 0.521; p = 0.001 (Table 2).

Axillary evaluation by F-18 FDG-PET/CT was TN in 36 (45%) patients, TP in 26 (32.5%) patients, FN in 10 (12.5%) patients, and FP in 8 (10%) patients. Kappa correlation level between F-18 FDG-PET/CT and axillary lymph node pathology results was 54.3% and found to be statistically significant (Kappa coefficient: 0.543; p = 0.001) (Table 2).

Axillary evaluation by US and F-FDG-PET/CT both were TN in 29 (47.5%) patients, TP in 23 (37.7%) patients, FN in 6 (9.8%) patients

Table 1. Distribution of descriptive characteristics

Age	Mean ± SD	55.38±14.05
	Median (Min-Max)	55 (27–86)
Histopathological type	Invasive ductal carcinoma	65 (81.3)
	Invasive lobular carcinoma/ mixt	10 (12.5)
	Mucinous carcinoma	2 (2.5)
	Micropapillary carcinoma	2 (2.5)
	Tubular carcinoma	1 (1.3)
Subtype	Luminal A (ki-67<20%)	37 (46.3)
	Luminal B (ki-67>20%)	22 (27.5)
	HER2 +	14 (17.5)
	Triple negative	7 (8.8)
Neoadjuvant chemotherapy	None	57 (71.3)
	Given	23 (28.8)
Clinical T stage	T1	41 (51.3)
	T2	38 (47.5)
	T3	1 (1.3)
Clinical N stage	N0	53 (66.3)
	N1	27 (33.8)
Stage	IA	33 (41.3)
	IIA	26 (32.5)
	IIB	21 (26.3)
Evaluation of axilla in US	Negative	43 (53.8)
	Suspicious	25 (31.3)
	Positive	12 (15.0)
Metastatic lymph node number in US	None	43 (53.8)
	1	24 (30.0)
	2	11 (13.8)
	3	2 (2.5)
Evaluation of axilla in F-18 FDG-PET/CT	Negative	46 (57.5)
	Suspicious	10 (12.5)
	Positive	24 (30.0)
Metastatic lymph node number in F-18 FDG-PET/CT	None	46 (57.5)
	1	20 (25.0)
	2	12 (15.0)
	3	1 (1.3)
	4	1 (1.3)
Axillary lymph node pathology	Negative	44 (55.0)
	Positive	36 (45.0)

*F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound; T: Tumor; N: Nodal; HER2: Human epidermal growth factor receptor 2; SD: Standard deviation; Min-Max: Minimum-Maximum

and FP in 3 (4.9%) patients. Kappa correlation level between US and F-18 FDG-PET/CT and both axillary lymph node pathology results was 70.3% and found to be statistically significant (Kappa coefficient: 0.703; p = 0.001) (Table 2).

The sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG-PET/CT for detecting ipsilateral axillary lymph node metastases were 75%, 77.27%, 72.97%, 79.07%, and 76.25%. The corresponding values for the US were 72.22%, 81.82%, 76.47%, 78.26%, and 77.50%, respectively. When US finding was negative or suspicious in axillary lymph node evaluation, the accuracy of F-18 FDG-PET/CT for the detection of ipsilateral axillary lymph node metastases were 65.38%, 83.33%, 70.83%, and 79.55%, respectively. In predicting axillary lymph node metastasis, the area under the ROC curve for F-18 FDG-PET/CT was 0.77 (77%), with a standard error of 5.5%. This finding was statistically significant (p = 0.001), indicating that the ROC curve for F-18 FDG-PET/CT is a reliable predictor of axillary lymph node metastasis. Also, in predicting axillary lymph node metastasis, the area under the ROC curve for the US test was 0.761 (76.1%), with a standard error of 5.6%. This finding was again statistically significant (p = 0.001), indicating that the ROC curve for the US test was a reliable predictor of axillary lymph node metastasis. When comparing these areas pairwise, no statistically significant difference was found between the predictive abilities of USG and ^{18}F-FDG-PET/CT tests in predicting axillary lymph node pathology (p = 0.871). When US is negative or suspicious in axillary lymph node evaluation, the area under the ROC curve for F-18 FDG-PET/CT was 0.744 (74.4%), with a standard error of 6.5%.

Discussion and Conclusion

In BC treatment, axillary staging continues to be important in determining the treatment approach. The nodal staging process typically involves various imaging studies, such as US and magnetic resonance imaging (MRI).

US is widely used as a prevalent imaging modality in assessing the axillary region in BC. It offers the advantages of being non-intrusive, economically efficient, and without ionizing radiation exposure. US facilitates comprehensive characterization of axillary lymph nodes, encompassing their dimensions, configuration, and structure. Additionally, it can identify noteworthy attributes, such as aberrant lymph node morphology, augmented cortex thickness, diminishment of adipose hilum, and heightened vascularity, potentially suggestive of metastatic engagement. Conversely, F-18 FDG-PET/CT synergistically amalgamates functional insights from PET with anatomical data garnered from CT. The combination of F-18 FDG-PET/CT furnishes insights into the metabolic vitality of tissues, offering utility in identifying metastatic pathology. The modality is proficient in identifying regions characterized by heightened glucose metabolism, a trait often linked to highly active neoplastic cells. F-18 FDG-PET/CT exhibits superiority over traditional staging modalities, such as physical examination and conventional imaging, when detecting metastatic afflictions within the axillary region. Nevertheless, it is imperative to acknowledge that the use of F-18 FDG-PET/CT could be constrained in its capacity to identify micrometastasis within the axillary lymph nodes. The potential inadequacy of F-18 FDG-PET/CT in detecting axillary lymph node metastases arises when dealing with either a limited count of lymph nodes or nodes of diminutive dimensions. In the investigation conducted by Segaert et al. (8), it was observed that F-18 FDG-PET/CT exhibited diminished sensitivity in accurately assessing axillary involvement in surgically treatable BCs characterized by a limited tumor burden within the breast. ^{18}F-FDG-PET/CT alone is not recommended as the primary imaging method for routine staging of axillary lymph nodes in BC patients. This is due to its limited sensitivity in detecting axillary metastases, which has been observed to range from 37% to 85% (9, 10).

Table 2. The level of agreement between US, F-18 FDG-PET/CT, both US and F-18 FDG-PET/CT and axillary lymph node pathology results

	True positive	True negative	False negative	False positive	Kappa	*p*
US	27 (33.8)	34 (42.5)	9 (11.3)	10 (12.5)	**52.1**	**1.000**
F-18 FDG-PET/CT	26 (32.5)	36 (45.0)	10 (12.5)	8 (10.0)	**54.3**	**0.815**
US/F-18 FDG-PET/CT both	23 (37.7)	29 (47.5)	6 (9.8)	3 (4.9)	**70.3**	**0.648**

Mc Nemar test; *F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound

Table 3. ROC analysis and diagnostic scans of US, F-18 FDG-PET/CT, and F-18 FDG-PET/CT findings when US negative or suspicious

	Diagnostic scan					ROC curve		*p*
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	Area	95% confidence ınterval	
F-18 FDG-PET/CT	75.00	77.27	72.97	79.07	76.25	0.770	0.662–0.879	0.001
US	72.22	81.82	76.47	78.26	77.50	0.761	0.652–0.871	0.001
F-18 FDG-PET/CT (US negative or susp.)	65.38	83.33	70.83	79.55	76.47	0.744	0.616–0.871	0.001

*F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound; ROC: Receiver operator curve

FNAB is a crucial procedure for the assessment of axillary lymph nodes in BC patients. It is used for preoperative staging and effectively detects metastatic involvement in axillary lymph nodes. Its high sensitivity, accuracy, and minimally invasive nature make it a valuable tool for initial axillary staging and decision-making regarding further surgical interventions. The meta-analysis of 35 studies conducted by Houssami and Turner (11) showed the sensitivity and specificity of US alone at 61.4% (51.2–79.4%) and 82% (76.9–89%), respectively, and US with FNAB at 79.6% (74.1–84.2%) and 98.3% (97.2–99%), respectively. The PPV and NPV of US with FNAB was 100% and 67.4% (60–76.2), respectively.

The sentinel lymph node (SLN), often the initial node within the lymphatic basin to receive drainage from a specific anatomical territory, assumes immunological responsibility for the associated area. SLNs have a comparatively modest false negative rate of 5 to 10% and a heightened sensitivity rate ranging from 90 to 95% in identifying malignancy within the lymph node basin (12). SLNB, utilizing either dye contrast material or preferably radioisotopes, has gained widespread acceptance as the preferred invasive method for assessing lymph nodes.

Despite studies reporting high sensitivity and specificity rates in detecting axillary lymph node involvement using F-18 FDG-PET/CT, this technique is not accurate enough to replace the currently accepted methods for axillary staging. The limited spatial resolution of F-18 FDG-PET/CT may result in false-negative results, particularly for microscopic metastases that cannot be reliably detected (5, 6).

A study including 90 patients was conducted by Riegger et al. (13) and also compared F-18 FDG-PET/CT and US as non-invasive imaging techniques for detecting axillary lymph node metastases, using US as the reference standard. The sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG-PET/CT for detecting axillary lymph node metastases were 54%, 89%, 77%, 74%, and 75%, respectively. For US, it was 38%, 78%, 54%, 65%, and 62%, respectively. F-18 FDG-PET/CT was significantly more accurate than US for detecting axillary lymph node metastases (p = 0.019). The findings indicated that while F-18 FDG-PET/CT appeared more accurate than US, it demonstrated a sensitivity like that of US in detecting axillary lymph node metastases. Consequently, it was not recommended as a substitute for SLNB. However, F-18 FDG-PET/CT did prove effective in identifying unexpected loco-regional extra-axillary lymph node metastases that were not previously detected. Another study by Aukema et al. (14) also supported the utility of F-18 FDG-PET/CT as an additional imaging tool for assessing extra-axillary lymph node metastases, significantly impacting patient management. These findings highlight the potential advantage of F-18 FDG-PET/CT in evaluating regional lymph nodes, particularly in specific locations such as the internal mammary and supraclavicular lymph nodes. Another recent study by Aktaş et al. (15) also compared the sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG-PET/CT, US, and MRI in 336 patients. The results of US for detecting ALN metastases were 83%, 62%, 59.2%, 54.8%, and 79.1%, respectively. For MRI, these values were 86.1%, 75%, 68.5%, 51.6%, and 85.3%, respectively, and for F-18 FDG-PET/CT, they were 78%, 53%, 56.2%, 51.4%, and 72.5%, respectively. Kappa correlation levels between ALN positivity and US, MRI, and F-18 FDG-PET/CT results were 67.3%, 77.5%, and 60.5%, respectively.

Our study found similarities among all findings (sensitivity, specificity, PPV, NPV, and accuracy) of US and F-18 FDG-PET/CT. Our statistical analysis demonstrated that F-18 FDG-PET/CT did not contribute additionally when axillary lymph node status in US was

negative or suspicious (Table 3). US and F-18 FDG-PET/CT both increased the specificity (83.33%) compared to US (81.82%) alone but had no advantage in sensitivity (65.38%, 72.22%, respectively). When US and F-18 FDG-PET/CT evaluated the axillary lymph nodes both, we demonstrated that false negativity decreased from 11.3% to 9.8% compared to US alone. The accuracy of the modalities did not surpass one another. We observed that when lymph nodes are categorized as negative or suspicious by US, F-18 FDG-PET/CT scans had no added value on lymph node staging (Table 3).

Both US and F-18 FDG-PET/CT have utility in assessing the axillary region in individuals afflicted with BC. US, a widely employed imaging method, facilitates comprehensive elucidation of axillary lymph nodes. In contrast, F-18 FDG-PET/CT yields functional insights into tissue metabolic activity and has demonstrated its superiority over conventional staging techniques in detecting metastatic pathology. Nonetheless, F-18 FDG-PET/CT may exhibit limitations when detecting minuscule axillary lymph node metastases. The selection of the suitable imaging approach hinges on many considerations, encompassing the clinical context, resource availability, and unique patient attributes.

Fibroblast Activation Proliferation Inhibitor (FAPI) PET in BC has gained significant attention due to its potential in detecting primary and metastatic lesions. FAPI targets fibroblast activation protein (FAP), which is overexpressed in cancer-associated fibroblasts of several tumor entities, including BC (16). Studies have shown that FAPI PET/CT is superior to FDG PET/CT in detecting primary and metastatic lesions in various cancers, including BC, with higher tracer uptake (17). However, it is important to note that FAPI PET/CT may also have limitations, such as high physiological uptake in normal breast tissue, which can obscure primary tumors (18). In the context of FAPI PET, while it is gradually gaining acceptance, there is currently a lack of studies demonstrating its ability to reveal axillary metastasis.

F-18 fluoroestradiol (F-18 FES) PET/CT has emerged as a valuable tool in the staging and management of estrogen receptor (ER)-positive BC. Studies have shown that F-18 FES PET/CT is sensitive in monitoring regional estrogen binding in advanced and metastatic ER-positive BC, and its uptake quantitation correlates well with ER expression measured by immunohistochemistry (19). This demonstrates the potential of F-18 FES PET/CT in influencing staging and management decisions for ER-positive BCpatients. Furthermore, the comparison of diagnostic accuracy between F-18 FES and F-18 FDG-PET/CT for BC recurrence in patients with a history of ER-positive primary BC has been investigated. This comparison provided insights into the potential of F-18 FES PET/CT as an alternative or complementary imaging modality in specific clinical scenarios (20). While F-18 FDG-PET/CT remains an important imaging modality in BC staging, the emerging evidence suggests that F-18 FES PET/CT may offer specific advantages in certain clinical contexts. However, no published study has shown that it could play a decisive role in the axilla.

The retrospective design of this study is a limitation, as well as the limited number of patients; the F-18 FDG-PET/CT is not routinely recommended in the guidelines for early-stage cancer. On the other hand, the radiologist's expertise is a well-known factor affecting the accuracy of an US evaluation. If this study had been done in a group of patients evaluated by a non-breast specialist, an F-18 FDG-PET/CT scan might have been found superior to US. Subsequent investigation is warranted to ascertain the optimal utilization of these imaging modalities for axillary evaluation in BC patients.

When looking at the 5-year follow-up results published in SOUND trial, where axillary observation was noted in patients and disease-free survival was found to be non-inferior to those with SLN procedures (98%, 97.7% respectively, p: 0.024), it emphasizes once again the importance of accurate and comprehensive preoperative US assessment of the axilla (4).

In conclusion, this study has demonstrated that US performed by an experienced breast radiologist is sufficient for evaluating axillary lymph nodes accurately. F-18 FDG-PET/CT did not provide an additional advantage over US in assessing the axilla in early-stage disease.

Ethics Committee Approval: This study was approved by the Koc University Institutional Review Board (2023.252.IRB1.081, date: 10.03.2023).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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Original Article

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Efficacy of the Radiofrequency Identification Technique in Breast Cancer Patients: A Single Institution Retrospective Study

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ABSTRACT

Objective: Breast conserving surgery is an excellent option in the treatment of breast cancer. To achieve a good result with this modality, a surgeon needs to identify and excise the tumor with adequate margins. The radiofrequency identification (RFID) technique is a wireless localization technique used for intraoperative breast lesion identification. We assessed the efficacy and outcomes of the RFID technique in breast cancer patients at our institution.

Materials and Methods: This is a single institution, retrospective study (BSMH 22-02X-MWH) of 73 patients. We analyzed the medical records of women with biopsy-proven breast cancer from June 2020 to August 2022; participants received surgical care at Mercy Health West Hospital. Data collected included demographics, clinicopathological characteristics, and surgical procedure. The primary objective was to determine the safety and efficacy of RFID. The secondary objective was to assess the impact of obesity and breast density on the RFID outcomes.

Results: A total of 73 female patients met the eligibility criteria with stage I (59%) and grade 1 (51%) breast cancer with mean age of at diagnosis of 66.8 years and mean body mass index of 31.4 kg/m^2. Patients had invasive ductal carcinoma (61%), hormonal positive (56%), and human epidermal growth factor receptor 2 negative (68%) disease. All RFID tags were placed under image guidance with 100% accuracy of placement with no evidence of migration or procedure revision. Ninety percent of patients had free surgical margins and only seven patients needed margin re-excision with successful removal of the lesion and the tag.

Conclusion: RFID localization technique is a safe, effective and reliable procedure that results in favorable patient outcomes and quality of life.

Keywords: Breast cancer; breast conserving surgery; RFID technique; localization techniques

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Key Points

- Safety and efficacy of RFID technique in treatment of breast cancer.
- Feasibility of breast conservative surgery using RFID technique.
- Decreasing unnecessary excision of breast tissue.

Introduction

Breast cancer is the most frequently diagnosed cancer in females and accounts for the second highest number of cancer-related deaths in women (1). In 2021, The American Cancer Society estimated that 30% of the anticipated cancer incidence among women would be breast malignancy (2). Surgical treatment of breast cancer is either mastectomy or breast-conserving surgery (BCS) and it has been shown that there are no significant differences in the outcome (3, 4). Due to the expansion in radiological techniques and breast cancer screening, one-third of breast cancers are not palpable during physical examination (5). Pinpoint localization of the breast mass is one of the most important factors that determines the success of BCS (3). Numerous studies have demonstrated the advantages and disadvantages of different methods of breast mass localization. The wire-guided localization (WL) technique was the only preferable technique for non-palpable breast masses; however, this method has some complications such as infection, wire transection, migration, patient discomfort, and interference with surgical approach (6-8). A novel technique has been developed to overcome some of the potential complications.

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In 2017, The radiofrequency identification (RFID) technique was given approval by the US Food and Drug Administration (FDA). Simply, a radiofrequency tag is placed under radiographic image guidance one week preoperatively, allowing the tag to set in place and determine the optimal surgical approach. The primary objective of our study was to determine the safety and efficacy of RFID. The secondary objective was to determine the impact of obesity and breast density on RFID outcomes.

Materials and Methods

Study Design

This study was an IRB-approved (BSMH 22-02X-MWH) retrospective chart review of clinical and histopathological data from female patients ≥18 years of age, with biopsy-proven stage 0-IV breast cancer who underwent BCS using LOCalizer RFID and were seen at Mercy Health West Hospital between June 2020 and August 2022. Patients with incomplete clinical data and those treated at other institutions were excluded.

Data Collection

Data were obtained from the BSMH EPIC system and uploaded into a secured database. Any missing data was populated using manual review of each patient's electronic medical record. Data were collected on demographic characteristics, biomarker profiles including estrogen receptor (ER), prolactin receptor (PR), and human epidermal growth factor receptor 2 (HER2) positivity of the tumor, therapy modalities (surgery and radiotherapy), disease recurrence, and survival outcomes.

Statistical Analysis

Demographic and clinical characteristics, and treatment modalities were summarized using descriptive statistics. All data analyses were performed using IBM SPSS statistics, version 28 (IBM Corp., Armonk, NY, USA). Operative time and re-excision rate were assessed by independent t-test. Significance was assumed when $p<0.05$.

Surgical Technique

Preoperative: All cases with positive mammographic findings and biopsy-proven breast cancer underwent the RFID tag placement following The National Comprehensive Cancer Network guidelines. One week pre-operatively, the radiologist placed the RFID tag under image guidance using a local anesthetic. The RFID tag dimensions are 11-mm long and 2 mm in diameter (Figure 1). Each tag includes a distinctive identification number (Figure 2) and a polypropylene cap to protect against migration. Placing the tag involves making a 2-mm incision in the skin before inserting the applicator.

Intraoperative: Using a handheld reader, the LOCalizer™ RFID (Hologic, Inc., Marlborough, MA, USA) (Figure 3), the surgeon can identify the tag with safe and accurate lesion removal with adequate margin. Intraoperative radiograph of the specimen was done to confirm removal of the tag, biopsy clip, and the lesion (Figure 4).

Results

A total of 73 patients with biopsy-proven breast cancer stage 0–IV were included. Patient demographic and clinical characteristics are summarized in Table 1. Patients were predominantly white (80%) and postmenopausal (67%) with a median age of 66 years (range 30–91) and mean body mass index (BMI) of 31.4 kg/m^2 (median 30.26 kg/m^2; range 20–49) at diagnosis. The right breast was the predominant

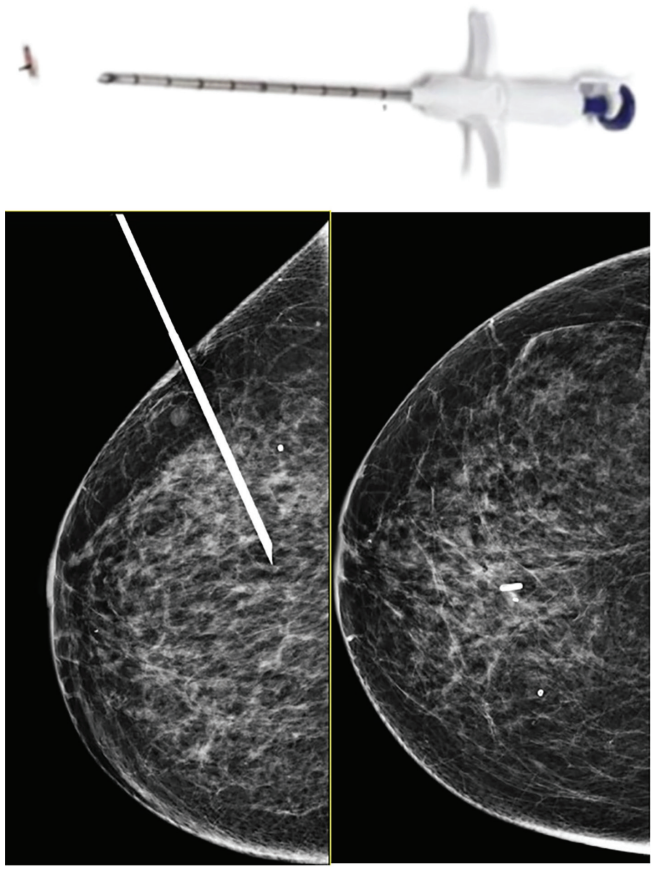

Figure 1. Tag applicator with mammography showing its placement

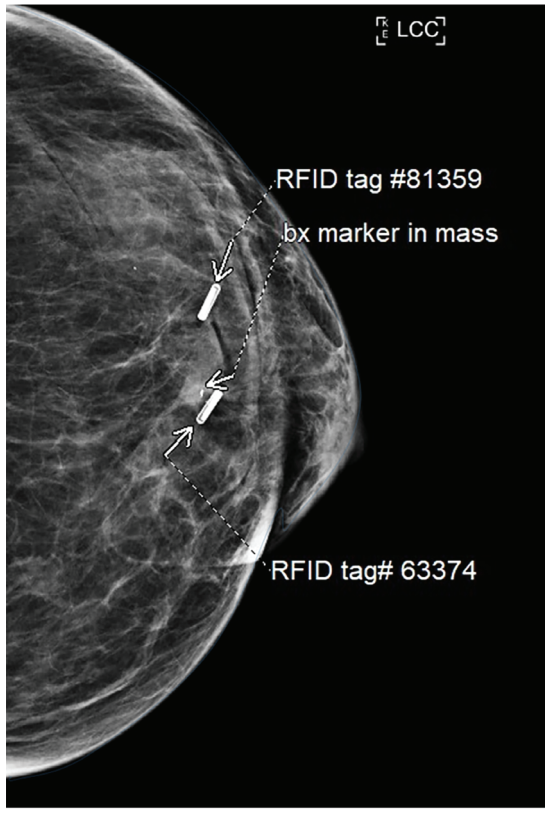

Figure 2. Mammography of the breast tissue showing the RFID tags with its identification numbers

RFID: Radiofrequency identification

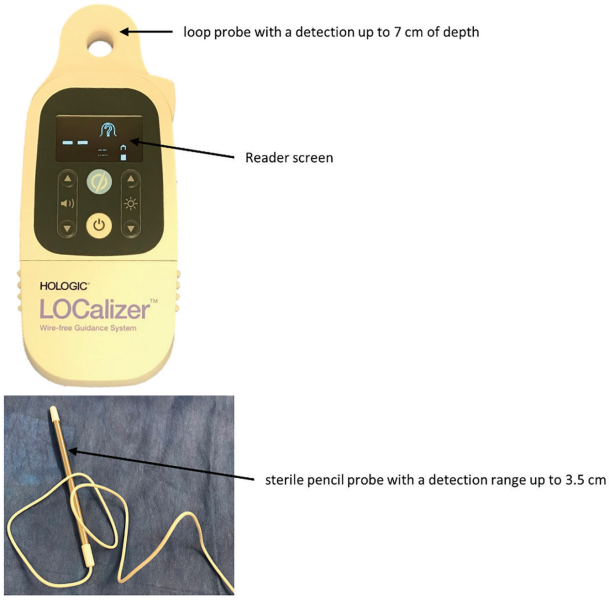

Figure 3. Handheld RFID hologic localizer (reader and detection probe)

RFID: Radiofrequency identification

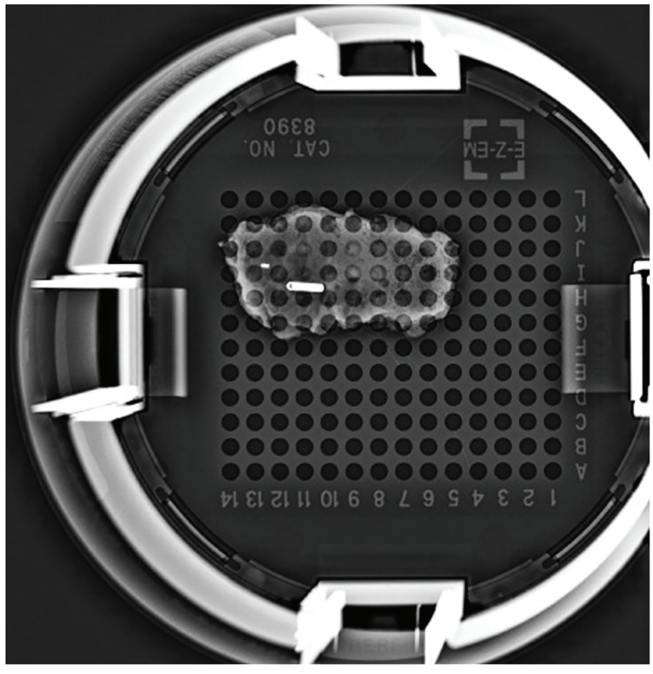

Figure 4. Intraoperative X-ray radiograph showing successful retrieval of the mass and the tags

cancer site in our cohort (59%). The mean size of the mass was 12.3 mm (range 2–58 mm). The majority of the excisions were for invasive ductal carcinoma (44%) which was stage I (59%), grade 1 (51%) and ten were node positive (14%). Biomarker evaluation revealed that 86% of patients were ER positive, 5% of patients were positive for HER-2, and 7% had triple negative breast cancer. Only six patients (8%) received neoadjuvant chemotherapy, three (50%) of them had pathological complete response. The mean operative time was 58.8±28.7 minutes. Postoperative pathology discussion revealed that 10% of patients required margin re-excision with no patient required completion mastectomy Table 2. The independent t-test found that

Table 1. Patients demographics and clinical characteristics

Variable		Total (n = 73)
Median (range) age at diagnosis, years		66.8 (30–91)
Gender	Female	73 (100%)
Menopausal status	Postmenopausal	67 (92%)
	Premenopausal	6 (8%)
BMI, kg/m²	≥30	38 (52%)
	<30	35 (48%)
Ethnicity	White	58 (80%)
	African American	14 (19%)
	Asian	1 (1%)
Laterality	Right	43 (59%)
	Left	30 (41%)
Stage (clinical)	Stage 0	23 (32%)
	Stage I	43 (59%)
	Stage II	2 (3%)
	Stage III	4 (5%)
	Stage IV	1 (1%)
Histological subtypes	DCIS	21 (29%)
	IDC	44 (61%)
	ILC	3 (4%)
	LCIS	1 (1%)
	Mucinous	2 (3%)
	Papillary	1 (1%)
	Metaplastic	1 (1%)
Grade	1	37 (51%)
	2	22 (30%)
	3	14 (19%)
Tumor size	≥2 cm	9 (12%)
	<2 cm	64 (88%)
Biomarker status	Positive	63 (86%)
Estrogen receptor	Negative	10 (14%)
	Positive	43 (59%)
	Negative	9 (12%)
Progesterone receptor	Unknown	21 (29%)
	Positive	4 (5%)
	Negative	48 (68%)
HER-2	Unknown	21 (29%)
Nodal involvement	Yes	10 (14%)
	No	63 (86%)
Breast density	B: Scattered areas of fibro-glandular density	27 (37%)
	C: Heterogeneously dense	43 (59%)
	D: Extremely dense	3 (4%)
Mean ± SD operative time, minutes		58.8±28.7

SD: Standard deviation; BMI: Body mass index; HER2: Human epidermal growth factor receptor 2; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; LCIS: Lobular carcinoma *in situ*

there was no significant difference in the technique outcomes between patient with high BMI (≥30 kg/m^2) and lower BMI (<30 kg/m^2) (p = 0.5). Furthermore, there was no significant difference in the outcomes in different types of breast density (p = 0.2). However, patients with higher BMI and heterogeneously dense breast had some postoperative adverse events, such as hematoma and seroma (8%).

Discussion and Conclusion

Several studies have established that BCS has the same survival outcomes compared to simple and modified radical mastectomy, as well as improved cosmetic outcomes (9-11). A positive surgical margin is the presence of any invasive or *in-situ* tumor on the surgical specimen, as defined by the surgical practice guidelines. Therefore, the most crucial step in BCS is obtaining a negative margin that will decrease the recurrence rate and contribute to successful cancer treatment (12-14). In order to obtain a successful BCS, you must determine the mass boundaries with adequate margins around it. Consequently, multiple methods of localization have emerged to accomplish the clear margin. The WL technique was the gold standard since its description in the 1970s. However, its limitations as highlighted earlier opened the space to develop alternative wireless localization techniques (15). The first attempt was radioactive seed localization (RSL) but its limitations were found in the extra requirements for handling the radioactive materials and arrangement of the combination of surgical and radiological appointments (16). A randomized prospective evaluation of RSL and WL determined that there were no significant differences as regard the re-excision of positive margin (26% vs 57%) and the operative excision (5.4 vs 6.1 minutes) (17). In 2016, the FDA approved another technique, Magseed, which was based on recognition of a ferromagnetic seed using the Sentimag, a handheld magnetometer. When compared to the WL in a single institution, randomized controlled trial, the Magseed had the advantage in terms of overall patient satisfaction (p<0.001) and surgical usability score (70.2±8.9 vs. 58.1±9.1, p<0.001). However, this technique has its limitation such as other ferromagnetic materials should be totally cleared from the operative field while using the magnetometer because it might interfere with seed localization (18-20). The RFID technique has been reported to be superior to the other techniques, such as wire localization, radioactive seeds, and cryo-assisted localization due to its wireless advance, absence of radioactive material, and feasibility of surgery scheduling (6, 19). Our findings are compatible with other studies investigating RFID technique outcomes. A recent study done by Lowes et al. (21) demonstrated that the re-excision rate was 8.7% with successful placement of the tags in all cases. Recently, two wireless methods have been developed for identification of breast masses but are still under investigation. SAVI SCOUT® radar localization has the limitation of its interaction with electrocautery, which can disturb the signal or deactivate the reflector. The magnetic marker implantation (Magseed) requires special instruments during the procedure that do not interfere with the marker detection (22-25). In contrast, the RFID technique is more reliable and does not have these limitations. Although, as determined by McGugin et al. (26), the operative time was higher in patients with ductal carcinoma *in situ* (DCIS), our study demonstrated that there was no significance difference in the operative time between invasive cancer and DCIS (p = 0.4) (Figure 5). A recent study by Christenhusz et al. (27), found that the breast density interfered with tag placement, especially type C and D densities. However, in our study, there was 100% successful tag placement and localization with no evidence of migration, regardless of the breast density and patient BMI.

Table 2. Margin re-excision for different histological types

Variable	Category	Number of patients (%) n = 73
Margin re-excision (n=7)	DIC	2 (2.7%)
	IDC	2 (2.7%)
	ILC	1 (1.4%)
	LCIS	1 (1.4%)
	Metaplastic carcinoma	1 (1.4%)

DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; LCIS: Lobular carcinoma *in situ*

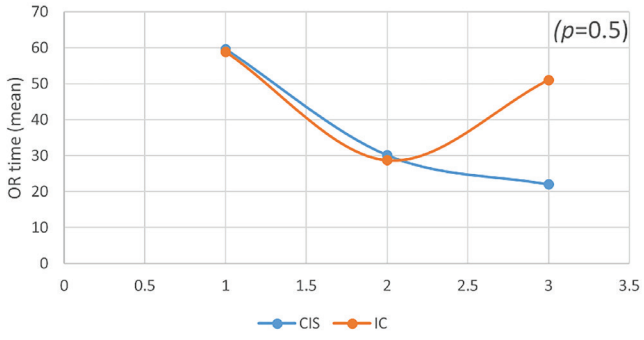

Figure 5. Plot graph of the odds ratio time for the Invasive and *in-situ* carcinoma

Study Limitations

Potential limitations of our study include being a retrospective study, having a small sample size, and being a single institution study.

To summarize, preoperative localization of breast lesion is an important factor in successful breast conserving surgery. In this study the RFID technique was shown to have favorable efficacy and safety margin rates among alternative localization techniques.

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Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Bon Secours Mercy Health (BSMH 22-02X-MWH, date: 07.04.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Potential Usefulness a Coronal View using an Automated Breast Ultrasound System in Detecting Breast Lesions

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ABSTRACT

Objective: An automated breast ultrasound system (ABUS) combined with screening mammography has increased cancer detection rates; however, supplemental ABUS use has increased recall rates. In this study, we aimed to identify an accurate and efficient method of ABUS interpretation and evaluate the potential usefulness of its coronal view versus the conventional transverse view.

Materials and Methods: This retrospective observer study included comprised 114 ABUS cases (40 normal, 35 benign, 39 malignant). Ten physicians from multiple institutions interpreted the anonymized coronal and transverse views independently. The observers scored their confidence in the lesion detection for each case using a continuous scale and recorded reading times for each coronal and transverse view interpretation. Free-response receiver operating characteristic analysis was employed to compare detection accuracies between views; a paired t-test was used to compare the average reading times.

Results: Detection accuracy did not differ significantly between the coronal and transverse views (figure of merit=0.740 and 0.745, respectively; p = 0.72). However, the average reading time for the coronal view was significantly shorter than that for the transverse view (149.7 *vs.* 200.3 seconds per case, p = 0.003).

Conclusion: The coronal view obtained with the ABUS was useful for interpretation and associated with significantly shorter reading times compared with the conventional transverse view while maintaining breast lesion detection accuracy.

Keywords: Automated breast ultrasound; breast cancer screening; breast ultrasonography; retrospective observational study

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Key Points

- The coronal view obtained from an automated breast ultrasound system was useful for results interpretation.
- This coronal view in the automated breast ultrasound system was associated with significantly shorter reading times compared with the conventional transverse view while maintaining breast lesion detection accuracy.
- Interpretation accuracy may be increased by interpreting a mass with retraction in the coronal view and focusing on hypoechoic non-mass lesions and lesions located behind the nipples in the transverse view.

Introduction

Mammography is the standard imaging method for breast cancer screening and allows for the early detection of breast cancers, resulting in reduced breast cancer mortality (1). However, the sensitivity of mammography depends on breast density, as tumor visibility is significantly reduced in dense breasts. The overall sensitivity of mammography is 72% (2). However, it is only 30–50% in women with dense breasts, either heterogeneously dense or with extremely dense parenchyma (2, 3). Approximately 55.4% of women aged <50 years and 29.3% of women aged >50 years have dense breasts with parenchymal density >50% (4).

An automated breast ultrasound system (ABUS) (5) was initially proposed as a screening modality, and adjunct use of the ABUS with mammography has increased cancer detection rates, especially in women with dense breasts (as defined by the American College of Radiology's Breast Imaging Reporting and Data System) (6, 7). The SomoInsight study, a trial reported by Brem et al. (7), revealed the detection of an additional 1.9 cancers per 1,000 women

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with dense breasts when an ABUS was combined with screening mammography.

The ABUS was developed to overcome the limitations of operator dependency, poor standardization, and reproducibility of handheld ultrasound (HHUS), with identical diagnostic accuracy to that of HHUS (8-10). Furthermore, ABUS showed similar efficacy for cancer detection with less benign findings compared with HHUS, suggesting that ABUS can potentially decrease the incidence of false positives (11). Use of an ABUS allows for the uncoupling of acquisition and interpretation, with the advantage of double-reading, objective comparison with previous examinations, and re-evaluation of stored images, even after the acquisition. Chou et al. (12) reported that an ABUS provided reproducible images for the proper orientation and documentation of lesions, which is useful for follow-up studies.

Another innovative feature of the ABUS is the coronal view, which is unavailable with HHUS. The ABUS acquires an entire series of consecutive transverse images and reconstructs three-dimensional datasets of the entire breast volume, which can be reformatted into three views, including sagittal and coronal views. The ABUS allows the analysis of lesions in all three views, and the coronal view provides additional information for breast lesion detection and diagnosis (8,10,13-19). These studies mainly reported that the value of the coronal view was related to a comprehensive view of the breast anatomy, which provides information that can assist in breast cancer surgery and the visibility of the retraction phenomenon, which is an important characteristic of breast cancer. In the coronal view, the important information required for surgical planning is visualized with regard to the lesion location in relation to the nipple, as well as the segmental organization of the ductal system and surrounding tissue. The retraction phenomenon, which is visible in the coronal view, may help in the detection and differentiation between benign and malignant breast lesions.

However, supplemental ABUS screening also increases recall rates, leading to biopsy, with decreased positive predictive values (7, 20). In addition, ABUS requires interpretation of the whole breast, which is another challenge because this possibly increases the burden on the reader. Thus, we aimed to identify an accurate and efficient method of interpreting ABUS findings. We assessed the potential usefulness of the coronal view for improving the detection accuracy of breast lesions and reading times compared with that of the conventional transverse view.

Materials and Methods

Study Design and Ethics

In this retrospective, multicase, observer study, we used cancer-enriched datasets of ABUS images at a single institution. This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Hokuto Hospital (approval number: 1034; date: October 23, 2018). The informed consent requirement was waived owing to the use of anonymized datasets.

Cases and Datasets

Our dataset comprised 114 ABUS cases with both coronal and transverse views obtained at our institution between October 2015 and September 2018. The cases were randomly and blindly selected by a radiological technologist. Two physicians who were not involved in this study reviewed the scan datasets to ensure suitability for analysis. The exclusion criteria were as follows: 1) a diagnosis of cancer by stereo-guided biopsy; 2) the presence of more than two malignant lesions; 3) the presence of more than five lesions; 4) the presence of a mass measuring ≥3 cm, and 5) a history of breast biopsy or surgery.

Image Acquisition

The Invenia™ ABUS (GE Healthcare, Chicago, IL, USA) was operated by one of five experienced radio technologists. Each breast was imaged with an automated 15.4 cm, 6–14 MHz, linear-array transducer. Three scans were performed for each breast (anteroposterior, lateral, and medial), although however, small breasts were imaged using two scans. Additional scans were performed as necessary for complete breast coverage.

Image Interpretation

The 114 scan datasets were assessed by 10 physicians from multiple institutions (5 Japanese and 5 Thai observers): 1 radiologist (with no experience using the ABUS), 1 internist (with 33 months of ABUS experience), and 8 breast surgeons (with ABUS experience ranging from 0–54 months). All observers completed the Invenia™ ABUS Mastery Program (Physician's Training) before study participation.

The scan datasets were anonymized and presented to the observers in the same order between June and October 2019. The observers interpreted the coronal and transverse views independently and while blinded to personal information or the results of the other view. Initially, the 114 ABUS scan datasets was interpreted in the coronal view and after a 4-week refresh period, they images were interpreted in the transverse view, thus ensuring that the observers had access to only the coronal or transverse view at any given time. A "coronal comparison" panel was displayed for coronal view reading (Figure 1) and a "transverse comparison" panel for transverse view reading (Figure 2).

The observers assessed each case for the presence or absence of abnormalities and were asked to complete a form to indicate the lesion locations and to report their confidence level on the presence of lesions. Confidence was assessed using a continuous rating scale from 0 to 1, with 0 corresponding to "definitely no lesion" and 1 to "definitely a lesion." This study focused on the detection of lesions rather than the discrimination between benign and malignant lesions. The assessments for lesions at different locations were excluded as false positives. The reading times for all observers for each of the coronal and transverse view interpretations were also recorded. The total reading time per day was limited to one hour to avoid the influence of fatigue.

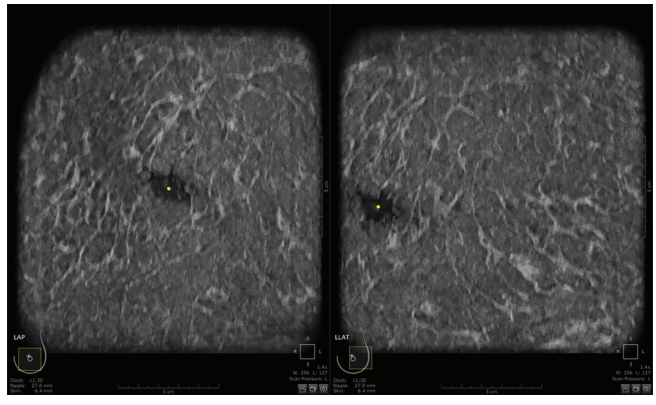

Figure 1. Coronal panel for coronal view reading. The left breast (anteroposterior, lateral) is shown. The yellow dots on the coronal view indicate the nipple positions

Statistical Analysis

Differences in the detection accuracy between the coronal and transverse views were statistically compared using the free-response receiver operating characteristic (FROC) analysis method for continuously distributed test results. The average reading time of each dataset was analyzed for each view and compared using a paired t-test. All statistical analyses were performed using JAFROC software version 4.2 (21). A $p<0.05$ was considered statistically significant.

Results

The selected scan datasets included 114 cases [healthy, n = 40 (5.1%); benign, n = 35 (30.7%); malignant, n = 39 (34.2%)] with 105 lesions (66 benign and 39 malignant lesions) from 83 women (mean age, 54±9 years) (Table 1).

In total, 2, 3, and 4 scans were performed in 83 (72.8%), 28 (24.6%), and 3 (2.6%) breasts, respectively.

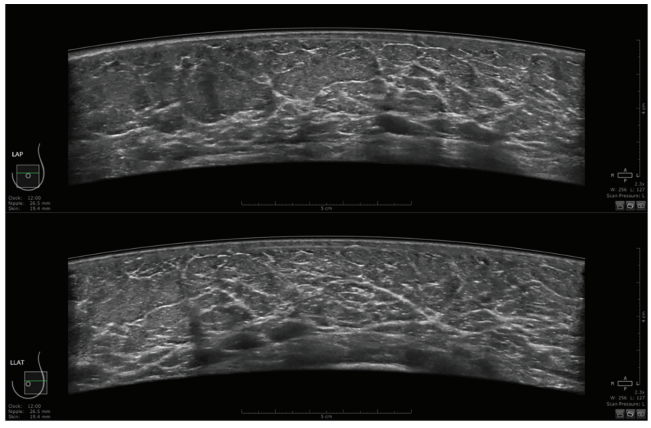

Figure 2. Transverse panel for transverse view reading. The left breast (anteroposterior, lateral) is shown

Table 1. Description of study sample (n = 114 breasts of 83 women)

Characteristic	Value
Age (years)	53.9 (40–69)
Age group	
40–49 years	42 (36.8)
50–59 years	36 (31.6)
60–69 years	36 (31.6)
Number of lesions per case	
0	40 (35.1)
1	53 (46.5)
2	14 (12.3)
3	5 (4.4)
4	1 (0.9)
5	1 (0.9)

Data are presented as the mean [range] or as numbers and percentages (%); percentages are rounded off

In addition, 82 mass lesions [78.1%; mean size, 10.6 mm; median (range), 9.0 mm (2.3–25.8 mm)] and 23 hypoechoic non-mass lesions [21.9%; mean size, 26.3 mm; median (range), 21.2 mm (5.5–65.3 mm)] were identified. Ultrasound-guided vacuum-assisted needle biopsy (VAB) (EnCor™, 10G, Becton, Dickinson and Company, Franklin Lakes, NJ, USA) was performed in 45 of the 114 cases, of which 6 and 39 cases had benign and malignant lesions, respectively. The pathological characteristics are shown in Table 2. The benign group included 6 VAB-confirmed cases and 29 non-VAB cases that showed no changes after >2 years of follow-up.

The figure of merit for the coronal view was slightly lower than that for the transverse view, although the difference was not statistically significant (0.740 vs. 0.745, respectively; p = 0.72) (Figure 3). Sensitivity, specificity, accuracy, and positive and negative predictive values for both coronal and transverse view are listed in Table 3. The average number of false negative benign and malignant lesions was 16.7 and 6.1 for the coronal view and 14.4 and 5.4 for the transverse view (Table 4), respectively. We defined a false negative as a rating of

Table 2. Pathological characteristics of breast lesions (n = 105 lesions in 74 breasts)

Pathological characteristic	Value
Benign	66 (62.9)
Intraductal papilloma	3 (2.9)
Fibrocystic change	2 (1.9)
Fibroadenoma	1 (1.0)
No change after >2 years follow-up	60 (57.1)
Malignant	39 (37.1)
Scirrhous carcinoma	12 (11.4)
Papillotubular carcinoma	9 (8.6)
Solid-tubular carcinoma	8 (7.6)
DCIS	6 (5.7)
Invasive lobular carcinoma	2 (1.9)
Mucinous carcinoma	1 (1.0)
Apocrine carcinoma	1 (1.0)

Data are presented as numbers and percentages (%); percentages are rounded off; DCIS: Ductal carcinoma *in situ*

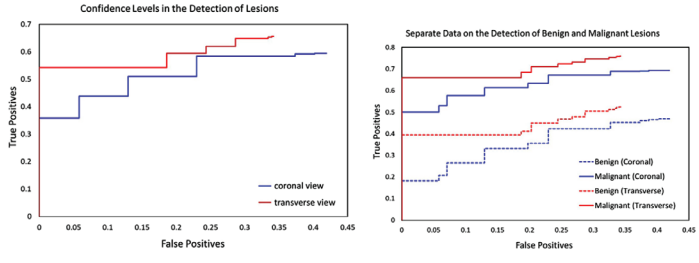

Figure 3. A) The free-response receiver operating characteristic curve revealed no significant difference in the average confidence levels in the detection of lesions between the coronal and transverse views (figure of merit=0.740 *vs.* 0.745, respectively; p = 0.718) across all observers. B) Separate data on the detection of both benign and malignant lesions showing the lower detection of benign by both coronal and transverse views

<50 on a continuous scale. The average reading time was significantly shorter for the coronal than transverse views (149.7 vs. 200.3 seconds per case, $p = 0.003$).

The characteristics of the malignant cases that most observers could not detect, and which at least six observers scored 0 on the scale, are summarized in Tables 5 and 6.

Five malignant cases were identified in which most observers could not detect the lesions in the coronal view although they were able to detect them in the transverse view. Two examples are shown in Figures 4 and 5. Moreover, two malignant cases were identified in which most observers could not detect the lesions in the transverse view although they could detect them in the coronal view (Figures 6 and 7). Table 5 summarizes the characteristics of hypoechoic non-mass lesions in four cases that were difficult to detect in the coronal view. The characteristics of a hypoechoic non-mass lesion differ from that of the surrounding parenchyma and do not conform to the definition of a "mass".

Discussion and Conclusion

We observed that the coronal view obtained using and ABUS was associated with a shorter reading time while maintaining detection

Table 3. Sensitivity, specificity, accuracy, and positive and negative predictive values for the coronal and transverse views

	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	Average
Coronal											
Sensitivity	58.1	5.27	66.2	79.7	67.6	83.8	70.3	74.3	74.3	64.9	69.2
Specificity	92.5	97.5	82.5	27.5	100	22.5	95.0	57.5	55.0	75.0	70.5
Accuracy	70.2	68.4	71.9	61.4	79.0	62.3	79.0	68.4	67.5	68.4	69.7
PPV	93.5	97.5	87.5	67.1	100	66.7	96.3	76.4	75.3	82.8	84.3
NPV	54.4	52.7	56.9	42.3	62.5	42.9	63.3	54.8	53.7	53.6	53.7
Transverse											
Sensitivity	79.7	39.2	66.2	73.0	71.6	91.9	70.3	79.7	82.4	78.4	73.2
Specificity	82.5	100	100	30.0	100	35.0	95.0	72.5	72.5	62.5	75.0
Accuracy	80.7	60.5	78.1	57.9	81.6	71.9	79.0	77.2	79.0	72.8	73.9
PPV	89.4	100	100	65.9	100	72.3	96.3	84.3	84.7	79.5	87.2
NPV	68.8	47.1	61.5	37.5	65.6	70.0	63.3	65.9	69.1	61.0	61.0

Data are presented as percentages (%). Percentages are rounded off; PPV: Positive predictive value; NPV: Negative predictive value

Table 4. Number of false negative benign and malignant lesions

	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	Average
Benign											
Coronal	24	24	19	11	17	8	19	14	12	19	16.7
Transverse	14	28	20	17	11	6	17	10	9	12	14.4
Malignant											
Coronal	7	11	6	4	7	4	3	5	7	7	6.1
Transverse	1	17	5	3	10	0	5	5	4	4	5.4

Data are presented as numbers, averages are rounded off

Table 5. Characteristics of the malignant cases that were difficult to detect in coronal view

	Pathology	Size (mm)	Findings
#1	Papillotubular carcinoma	14.0	Mass behind the nipple
#2	DCIS	17.6	Hypoechoic non-mass lesion behind the nipple
#3	DCIS	46.6	Hypoechoic non-mass lesion
#4	DCIS	65.3	Hypoechoic non-mass lesion
#5	Invasive lobular carcinoma	16.7	Hypoechoic non-mass lesion

DCIS: Ductal carcinoma *in situ*

Table 6. Characteristics of the malignant cases that were difficult to detect in transverse view

	Pathology	Size (mm)	Findings
#1	Papillotubular carcinoma	8.0	Mass with retraction
#2	Papillotubular carcinoma	10.1	Mass with retraction

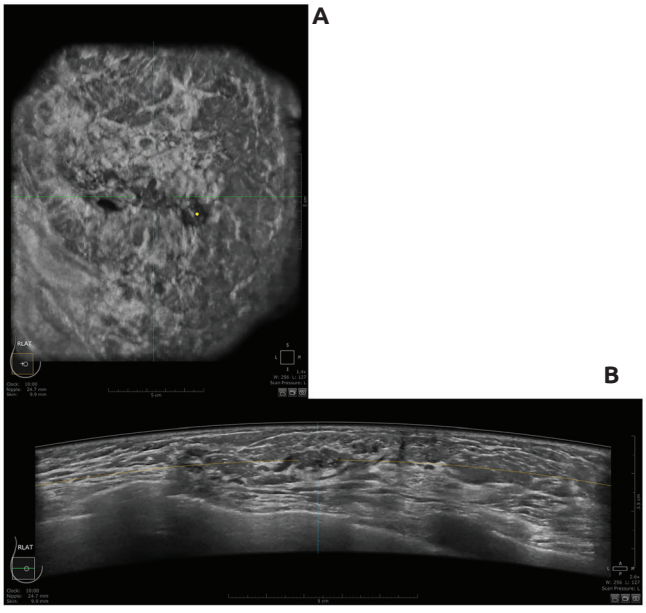

Figure 4. Images of a 50-year-old woman with ductal carcinoma *in situ* in the upper outer quadrant of the right breast. The lesion is visible at the center of the cross. A) The hypoechoic non-mass lesion could be difficult to detect in the coronal view, probably because it resembles subcutaneous fat entering the mammary gland. B) The transverse view in the lateral images shows the hypoechoic non-mass lesion

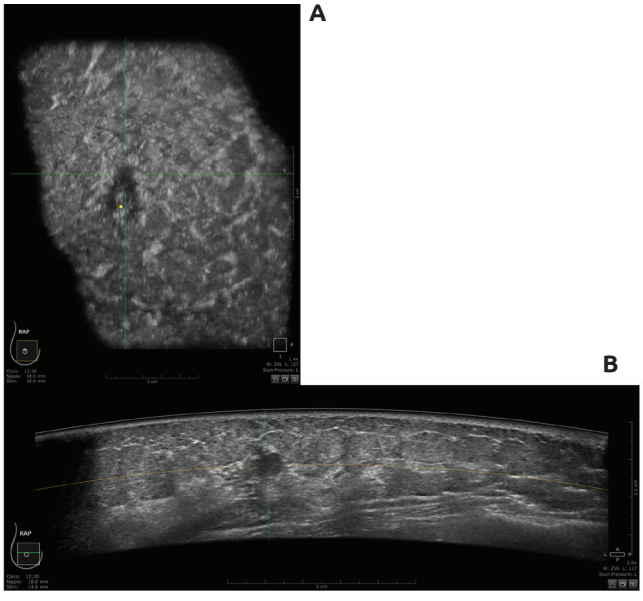

Figure 5. Images of a 55-year-old woman with a 14-mm papillotubular carcinoma located behind the nipple in the right breast. The lesion is visible at the center of the cross. A) The lesion behind the nipple is difficult to detect in the coronal view. B) The transverse view in the anteroposterior image shows the hypoechoic mass

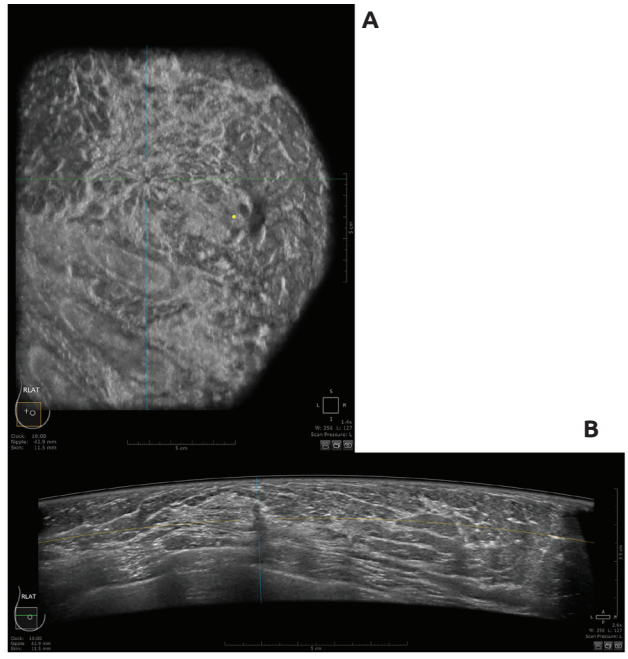

Figure 6. Images of a 50-year-old woman with an 8-mm papillotubular carcinoma in the upper outer quadrant of the right breast. The lesion is visible at the center of the cross. A) The coronal view in the lateral images shows a small mass with retraction. B) A small mass with shadowing could be difficult to detect because it appears as shadowing from dense fibroglandular tissue in the transverse view

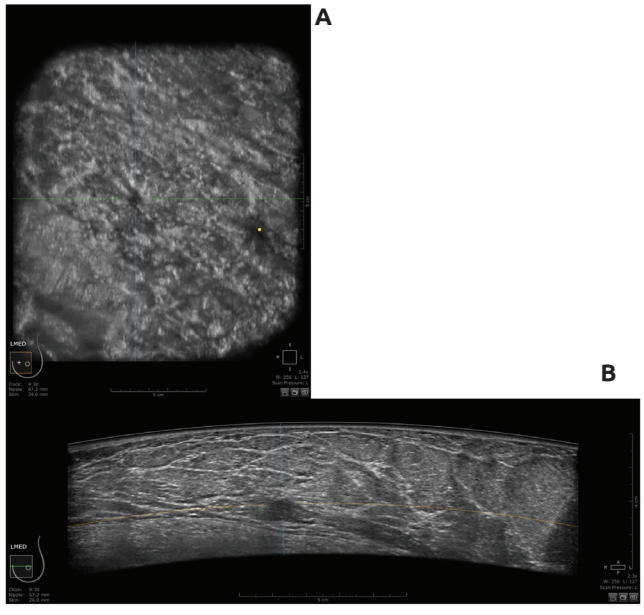

Figure 7. Images of a 58-year-old woman with a 10-mm papillotubular carcinoma in the upper inner quadrant of the left breast. The lesion is visible at the center of the cross. A) The lesion is easier to detect by identifying retraction in the coronal view. B) The lesion is indistinct in the transverse view because it is a deep mass

accuracy for breast lesions when compared with the conventional transverse view. Understanding the pitfalls in the interpretation of each view may improve the evaluation quality.

In this study, most observers could not detect hypoechoic non-mass lesions and lesions located behind the nipple in the coronal view. Hypoechoic non-mass lesions are difficult to detect in the coronal view because they resemble subcutaneous fat entering the mammary gland. Detecting lesions located behind the nipple in the coronal view was also difficult because of overlap between the lesion and the nipple. Meanwhile, even if the lesion is indistinct in the transverse view because it is a small or deep mass, it might be easier to detect by identifying retractions in the coronal view. Collectively, these findings support the interpretation of ABUS images; hypoechoic non-mass lesions and lesions located behind the nipple should be carefully investigated in the transverse view, and a small or deep mass that is difficult to detect in the transverse view could be detected by carefully identifying retraction in the coronal view.

Kim et al. (22) reported that the ABUS has a lower capability for detecting non-mass versus mass-type lesions, with a detection rate of 98% for mass-type and 77% for non-mass lesions. The current study revealed that hypoechoic non-mass lesions are difficult to detect in the coronal view, and the transverse view should be examined in order to detect these lesions are detected.

Our results showed that a lesion located behind the nipple is a cause of false negatives because the lesion overlaps with the nipple. Although lesions located behind the nipple should be carefully sought for in the transverse view, shadowing artifacts behind the nipple may also cause misinterpretation in the transverse view. Several studies have reported the misinterpretation of ABUS findings owing to artifacts (23, 24). Our study included a false negative case in which a micromass with shadowing appeared to be shadowing from dense fibroglandular tissue in the transverse view. However, this could be interpreted as a mass with retraction in the coronal view.

The retraction phenomenon has high sensitivity (70–89%) and specificity (96–100%) for cancer detection (15, 17, 18) and is a diagnostic imaging sign of cancer (13). Our study also showed that retraction was easy to detect in the coronal view. Zheng et al. (18) reported that retraction in the coronal view is the strongest independent predictor of malignant masses and has a high diagnostic value in the differentiation between benign and malignant breast masses.

Figure 3B shows that the detection of benign lesions was lower than that of malignant lesions while Table 4 shows that the false negative malignant lesions were fewer than the benign lesions using both the coronal and transverse views, consistent with the findings of Güldogan et al. (11) showing that ABUS detected fewer benign lesions than HHUS while having a similar performance to HHUS for cancer detection. This indicates that ABUS has the potential to decrease the incidence of false positives while maintaining the detection of malignant lesions.

The interpretation time when using ABUS, which is associated with an increased burden on readers, has been reported in some studies (24, 25). Chae et al. (25) analyzed the average interpretation times for the coronal and transverse views and found a markedly longer mean interpretation time for the transverse view (3.83±1.71 minutes vs. 5.57±2.21 minutes). Similar results were obtained in the current study. The detection time was faster in the coronal view conceivably because of the small number of slices from the superficial skin level to the thoracic wall. We examined the differences in interpretation time based on observer experience levels. The interpretation time for the readers with 0 months of experience and others was 101.2 and 161.8 seconds for the coronal view and 197.2 and 201.0 seconds for the transverse view, respectively. With the coronal view, the result indicated that the reading time was shorter for those with 0 months of experience, possibly because the sensitivity of the coronal view was lower for those readers. The sensitivity, specificity, accuracy, and positive and negative predictive values for readers with 0 months of experience and others were 55.4%, 95.0%, 69.3%, 95.5%, 53.6% and 72.6%, 64.4%, 69.7%, 81.5%, 53.7%, respectively.

The detection accuracy in our study might have been low for two reasons. First, two observers had no experience with the ABUS prior to the study, and the pre-study training might have been insufficient. Second, 28 out of 105 lesions were <5 mm, which were more difficult to detect.

Study Limitations

This study has some limitations, including the retrospective design and small sample size of cancer-enriched datasets, which were selected at our discretion and may have caused selection bias. Moreover, the proportions of case types were not representative of the general population. However, although the selection bias affected the FROC results, it did not impact the comparisons between the coronal and transverse views. The ABUS images were interpreted using either coronal or transverse views alone, which differs from an actual screening setting. Greater familiarity with the transverse versus coronal view might lead to bias. Therefore, the results of this study cannot be applied to general breast cancer screening and must be interpreted with caution. In Japan, breast surgeons often interpret ultrasound images for screening and so the percentage of breast surgeons among the observers who participated in this study was high. Finally, we did not compare the results between specialties or countries.

In conclusion, the coronal view obtained when using ABUS was useful for interpretation and associated with significantly shorter reading times than those of the conventional transverse view, while maintaining breast lesion detection accuracy. In addition, considering the characteristics of each view, interpretation accuracy may be increased by interpreting the mass with retraction in the coronal view and focusing on hypoechoic non-mass lesions and lesions located behind the nipples in the transverse view. An accurate use of each view will improve the diagnostic performance of the ABUS in breast cancer screening. In this study, only the detection of lesions was verified. In the future, we plan to verify the discrimination between benign and malignant lesions. Furthermore, we hope that computer-aided detection and artificial intelligence will provide support for interpretation, leading to greater uptake and widespread of the ABUS.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Hokuto Hospital (approval number: 1034; date: October 23, 2018).

Informed Consent: The informed consent requirement was waived owing to the use of anonymized datasets.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Novel Idea

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Construction of Low-Cost Simulators for Training in Minimally Invasive Breast Procedures

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ABSTRACT

Objective: The aim of this work was to describe a technique for building low-cost simulators for training in minimally invasive breast procedures guided by ultrasound (US) and stereotactic mammography (MMG), focusing mainly on training medical professionals studying related areas.

Materials and Methods: Low-cost phantoms were developed using organic structures that mimic breast tissue, such as chicken breast and eggplant, and materials that simulate breast lesions. A step-by-step description of the preparation and use of these simulators was made, enabling the reproducibility of the technique by the physicians in training themselves.

Results: The low-cost phantoms showed a high degree of echogenic and radiological similarity with human breast tissue, allowing adequate training in minimally invasive procedures.

Conclusion: It was possible to build low-cost phantoms that allow training in US- and stereotactic MMG-guided minimally invasive breast procedures.

Keywords: Breast biopsy; tissue model; imaging phantom; training; low cost

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Key Points

- Ultrasound Phantom: Chicken breast with skin and bone was chosen to simulate breast tissue, as both have very similar ultrasound properties. Inside a chicken breast, targets were randomly inserted, varying in depth and distance between them.
- Mammographic Phantom: To build the phantom that will simulate the breast tissue in the mammography, we used: eggplants and calcium carbonate tablets to simulate calcifications/microcalcifications.
- Cost Analysis: To make the low-cost ultrasound phantom, the approximate cost was $3.45.

Introduction

Breast cancer is the type of malignant tumor that most affects women in both Brazil and worldwide, after excluding non-melanoma skin cancer. In 2022, 73,610 new cases of breast cancer were diagnosed in Brazil, which corresponds to 30.1% of all cases of cancer in the female population, of which almost 18,000 resulted in death (1).

Screening should be performed in asymptomatic women with the aim of detecting the disease early (increasing the chances of cure), improving the prognosis of the disease, and reducing morbidity and mortality. In Brazil, the National Cancer Institute recommends biannual screening mammography in women aged 50 to 69 years (2). After obtaining the images, the findings are described according to the Breast Imaging Reporting and Data System (BIRADS) classification, a nomenclature created by the American College of Radiology, with the aim of standardizing the examination report. Medical practice guidelines recommend biopsy for cases of lesions classified as BIRADS 4 and 5. Currently, needle biopsy examination is the gold standard for the diagnosis of breast cancer (3, 4), allowing for the most appropriate treatment planning for each case.

The collection of pathological material should preferably be done by needle biopsies, rather than surgical biopsies, as needle biopsies are less invasive and offer less risks to the patient. Needle biopsy techniques include fine needle aspiration biopsy, core needle biopsy (CNB) and vacuum-assisted biopsy (VAB), all of which may be guided by ultrasonography and mammography. Thus, employing needle biopsies enable the elucidation of suspected breast lesions, avoiding unnecessary surgery and aiding in the treatment planning of positive cases (5).

In order to perform a needle biopsy, whether guided by ultrasound (US) or mammography, the professional needs to position the needle inside the lesion of interest in order to obtain a representative sample. The precise spatial orientation is essential for a satisfactory specimen, avoiding delays in diagnosis and iatrogenic events (6). Therefore,

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professional training to perform breast procedures is important to improve the effectiveness of the technique, reduce professional anxiety and reduce errors and improve diagnosis and ultimately patient outcomes.

Currently, training for breast procedures can be done using phantoms, which are structures used to imitate the properties of human tissue, built with specific substances that simulate the acoustic or radiological properties of the tissue to be studied. Phantoms date from the beginning of the 20th century, but it was in the 1960s that new substitute tissues – more reliable and with a greater degree of sophistication – began to emerge (7). Currently, phantoms are manufactured using a wide variety of available raw materials and sophisticated production processes. They are important, both for carrying out scientific studies and for assessing the operating condition of devices in Medicine and Clinical Engineering. Phantoms can also be used to train health professionals in clinical applications that involve the use of US and mammography, such as when performing breast biopsies (8).

In the case of breast phantoms, inclusions are inserted to represent cysts and solid masses that simulate tumors or other abnormalities. Several studies have shown that training of professionals in breast phantoms before performing human biopsies has been very effective in increasing self-confidence when performing the procedure on real patients and significantly reducing medical errors during the process (8-13).

However, the biggest limitation of these commercialized models is their high cost, currently around 170 U.S. dollars (14), an amount that may be unfeasible for some institutions to acquire the material for students. Despite being realistic and practical models, their high cost and difficult access make this training impractical for many professionals, especially those who are at the beginning of their training. Thus, there is a need to make training more accessible to doctors in training, so that they may be able to perform a procedure with greater skill, accuracy, confidence, and safety for the patient.

Therefore, the aim of the present study was to detail the construction technique of simulators using easily accessible and low-cost materials for training in breast procedures, whether freehand or guided by US or mammography. This technique offers many advantages, such as easy accessibility of the materials, the low cost of production, similarity with the echographic and radiographic properties of the model and of the breast tissue, and reproducibility (6). Hence, it can be widely applied for the training of professionals in the field of radiology and breast imaging, in addition to other professionals involved in breast health care, especially residents. The objective was to describe a technique for building low-cost simulators for training in minimally invasive breast procedures guided by US or mammography.

Materials and Methods

Ultrasound Phantom

To build a phantom that simulates breast tissue in US, the following items were used:

- Chicken breast with skin and bone
- Stuffed olives
- Surgical gloves
- #11 Scalpel
- Water

Chicken breast with skin and bone was chosen to simulate breast tissue, as both have very similar US properties (6). Inside a chicken breast, targets were randomly inserted, varying in depth and distance. To mimic "cysts", fingers of latex or similar gloves were filled with water and tied at the end, forming small water bladders. "Solid nodules" were simulated using pitted olives stuffed with red bell pepper, thus allowing the green portion or the red portion to be defined as the target (Figure 1). Using a #11 scalpel blade, openings were made in the form of small tunnels where the targets were gently introduced (Figure 2).

After "stuffing" the chicken breast, it was placed inside a latex glove, in order to form an ovoid. (NOTE: You can also use PVC film ("clingfilm") for this purpose, wrapping the whole chicken with plastic). The fingers and cuff of the glove were tied to make the phantom easier to handle.

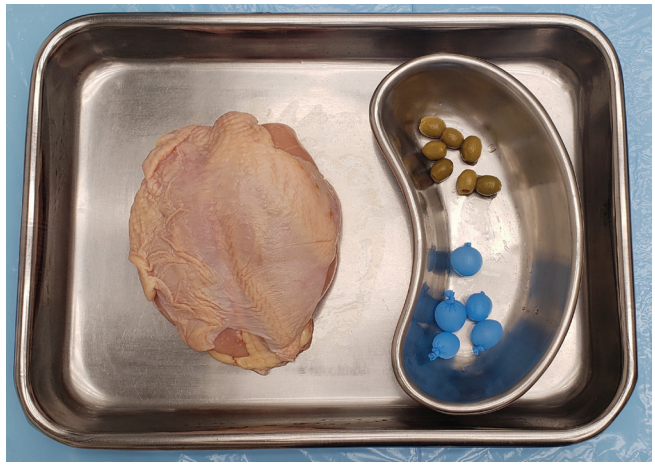

Figure 1. Chicken with skin and bone, stuffed olives, and small water bladders

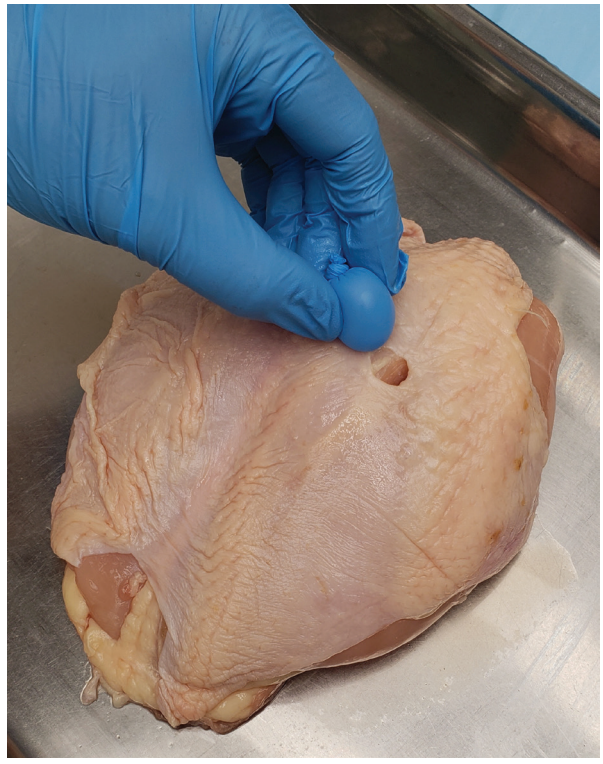

Figure 2. Insertion of small water bladders to simulate cysts and stuffed olives to simulate nodules

This US phantom allows the training of:

(1) Preoperative localization with metallic guide wire;

(2) Fine needle aspiration of cysts;

(3) Fine needle aspiration of nodes/lymph nodes;

(4) CNB of nodes/lymph nodes;

(5) VAB;

(6) And clipping of non-palpable lesions.

Mammographic Phantom

To build a phantom that will simulate breast tissue in the mammography, the following items were used:

• Eggplants (aubergine);

• Calcium carbonate tablets to simulate calcifications/fine calcifications

NOTE: In addition to these materials, 2 mL of barium sulfate (Bariogel) were used to simulate a nodule for mammography. However, this may be an optional step, as in some places outside the hospital environment, this material may be difficult to access. Not using barium sulfate does not compromise the functionality of the phantom.

Similarly, to chicken breast in breast US, the composition of the eggplant also resembles breast tissue in radiographic images on mammography (10). Therefore, it was chosen to be used in the manufacture of the mammographic phantom.

To simulate calcifications and fine calcifications, crushed calcium carbonate tablets were introduced in the eggplant, and to simulate a nodule, barium gel was used. Three targets were set, arranged along the length of a raw eggplant:

• Bigger calcium particles

• Smaller calcium particles

• Barium gel

After building the phantoms, simulation of invasive breast procedures was performed using training material from the mastology outpatient clinic (Figure 3).

Aims

a) For the target "gross calcifications", a perforation was performed in the eggplant with a 12-gauge core needle, which was subsequently widened with the cap of the hypodermic needle, and the coarsely crushed calcium tablet was introduced, with the aid of a paper funnel.

b) For the "fine calcifications" target, the same previous steps were performed using the finely ground calcium tablet.

NOTE: The 12-gauge core needle and the hypodermic needle can be replaced by some other material that helps in the introduction of calcium carbonate into the eggplant, rendering them non-essential materials for the preparation of the phantom.

c) For the "nodule" target, 2 mL of barium sulfate gel was injected with a syringe (Figure 4).

This mammographic phantom allows the training of:

(1) Preoperative location;

(2) CNB;

(3) Vacuum biopsy;

(4) And clipping of lesions guided by mammography/stereotaxis, both in an alphanumeric window and on a dedicated table.

Following preparation of the phantoms and employment of the material for training procedures, they must be stored in plastic bags

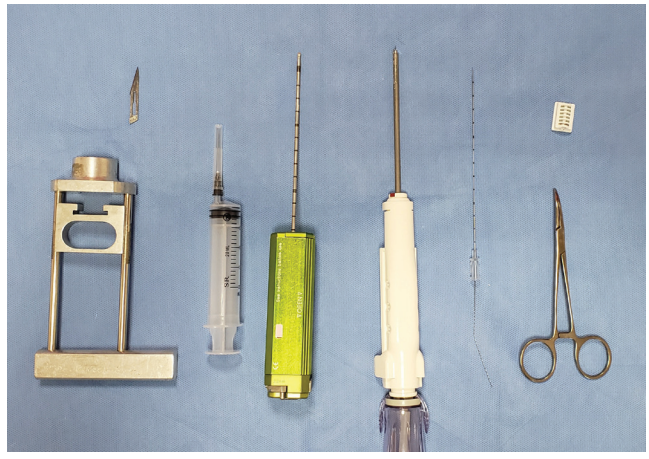

Figure 3. From left to right: cytoaspirator; #11 scalpel blade; syringe with hypodermic needle; core needle gun; vacuum biopsy device; metallic wire for preoperative localization; Hemostat, and above, a hemostatic clip

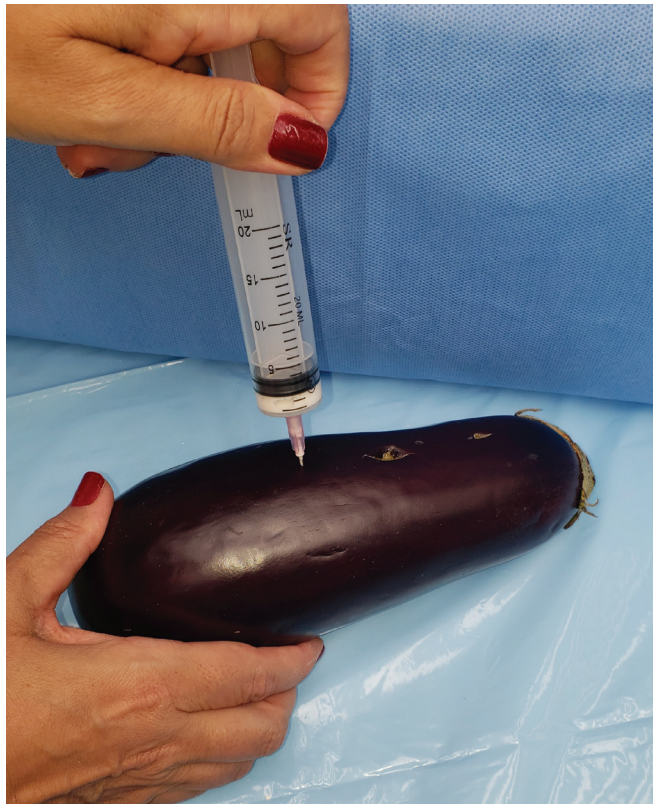

Figure 4. Introduction of 2 mL of barium sulfate (Bariogel®) into the eggplant, to simulate the nodule on the mammogram

and refrigerated (eggplant) or frozen (chicken) to be reused later. Each low-cost phantom can be reused about three times.

Cost Analysis

To make the low-cost US phantom, the approximate cost is shown in Table 1. Similarly, for the manufacture of the low-cost phantom for mammography, the approximate value is shown in Table 2.

Thus, for the manufacture of both phantoms, the approximate cost was $5.55.

NOTE: The cost of both phantoms (US and mammography) did not include the material used for the procedures (biopsy needles and needling wire)

This study was complies with the STARD Statement Checklist and following the Declaration of Helsinki.

Results

After making the breast phantoms, tests of some minimally invasive breast procedures were performed at the Diagnostic Unit of the Breast Imaging Ambulatory of the Gynecology Department, Federal University of São Paulo. Utilizing the institution's US and mammography equipment, it was possible to observe close similarities between the low-cost phantoms and real breast tissue.

For these tests on US and mammography devices, the following materials were used:

- Conductive gel for US
- LT 200 hemostatic clip
- Metallic wire for location of impalpable lesion (needling wire)
- Core-type biopsy needle
- Vacuum biopsy needle
- Core biopsy device (gun)
- Hemostat

Table 1. Estimated price for making the ultrasound breast phantom for training

Materials	Approximate cost (in U.S. dollars)*
Chicken breast with skin and bone	$3
Stuffed olives	20 c (6 olives)
Surgical gloves	10 c
#11 Scalpel blade	10 c
Plastic bag	5 c
Total	**$3.45**

* Values quoted on 03/14/2023 – City of São Paulo, Brazil.

Table 2. Estimated price for making the breast phantom for training in mammography

Materials	Approximate cost (in U.S. dollars)*
Eggplant	$2
Calcium carbonate tablets	10c (2 tablets)
Total	**$2.10**

* Values quoted on 03/14/2023 – City of São Paulo, Brazil.

Ultrasound

Contact gel was used to perform the US-guided procedures. It was possible to perform the following techniques: preoperative localization, fine needle aspiration of cysts, fine needle aspiration of nodules/lymph nodes, CNB of nodules/lymph nodes, vacuum biopsy, and clipping of non-palpable lesions (Figures 5 to 8).

Mammography

The constructed phantom has three different foci: calcifications, fine calcifications, and nodule (Figure 9). The X-ray of the eggplant phantom on the mammography equipment shows the simulated "lesions", allowing training in the following techniques: CNB,

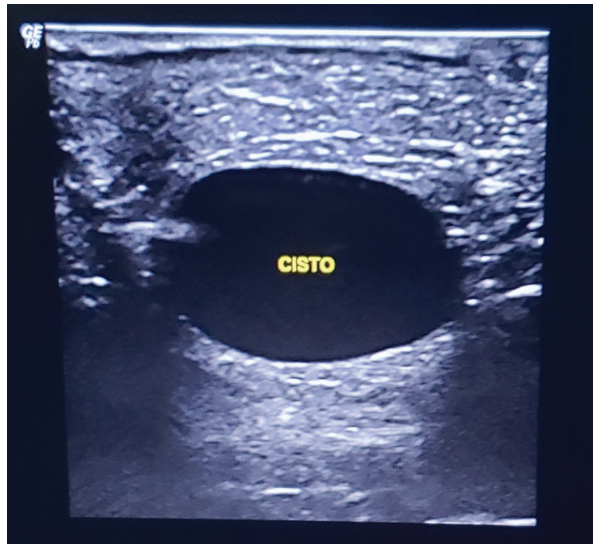

Figure 5. Appearance of the water bladder at US, very similar to a cyst

US: Ultrasound

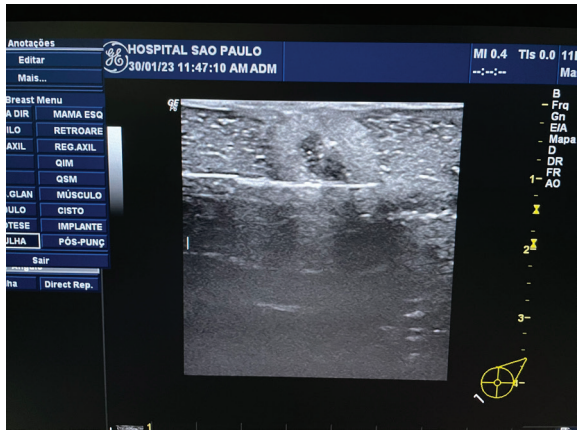

Figure 6. Tip of the core needle following piercing of the solid nodule (olive)

preoperative location, vacuum biopsy and mammography-guided lesion clipping/stereotaxis, both in alphanumeric window and in stereotactic table.

Discussion and Conclusion

Percutaneous techniques guided by US and mammography are basic procedures in radiological practice when imaging the breast. However, many residents graduate without a minimum of technical experience (12).

Several studies have shown that training on synthetic simulators increases the self-confidence of the training professional and reduces medical errors during the procedure (8-13). An ideal phantom should combine cost-benefit, availability, and similarity to the target organ/tissue (13). In terms of the synthetic breast simulators sold on the market, the biggest obstacles are their high cost and difficult access, making it difficult to practice the technique of minimally invasive breast procedures.

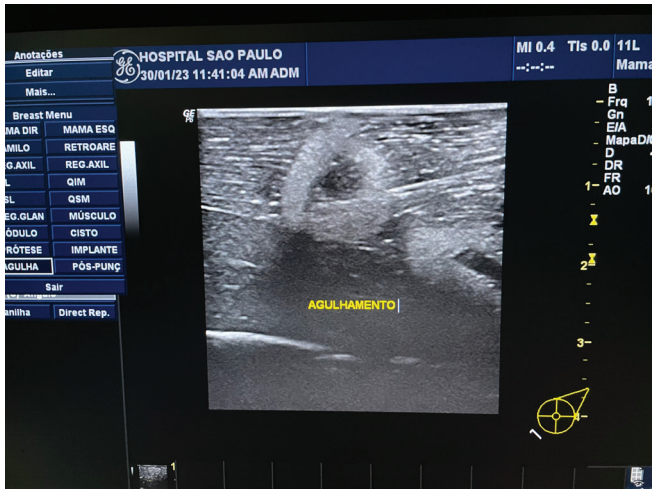

Figure 7. Detail of the metallic wire crossing the target lesion

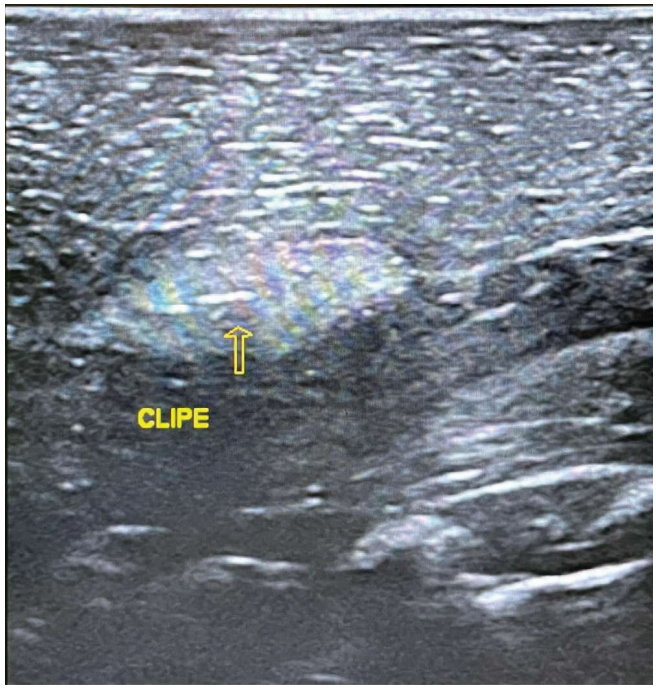

Figure 8. Location of the clip inside the olive on US

US: Ultrasound

Therefore, we describe the technique for the construction of low-cost phantoms, similar to breast tissue, and using easily accessible materials, in order to enable their easy replication. With these phantoms, it is possible to carry out the training in the main procedures in breast imaging, with an effectiveness similar to the procedure performed in patients.

The total cost for manufacturing both the phantoms described was around USD $5.55, or about 97% cheaper than the synthetic phantom available on the market (14).

Comparatively, the images obtained by the ultrasonic and mammographic phantoms resemble those of a real breast. On US, the simple cyst simulated by the phantom appears anechoic, well circumscribed, with thin walls, with liquid inside and posterior reinforcement, just like a simple cyst in a real breast (Figures 10 and 11). The "simple nodule" in the phantom, represented by the stuffed olive, appears circumscribed, with an oval shape and well-defined margins. It is possible to differentiate the olive from the filling by echogenicity, with the olive being more hyperechogenic and the filling being more hypoechogenic. In this way, it is possible to biopsy different portions of the "nodule". Similarly, to the phantom, the solid breast nodule may also appear with circumscribed margins and an oval shape (Figures 12 and 13). The echogenicity and shape of an actual nodule can vary according to the nodule composition.

On mammography, calcifications are always radiopaque. In the mammographic phantom, the "calcifications" displayed in a very similar aspect, sometimes coarse (depending on the size of the ground particles) as in a real breast (Figure 14).

The phantom "nodule" also appears hyperdense, like a suspected lesion, due to the insertion of barium sulfate. Note the similarity with the image of a nodule in a real breast (Figure 15).

We believe that these low-cost phantoms can be used for training professionals in the field of mastology, as the characteristics of the selected materials are extremely similar to real breast tissue and breast lesions.

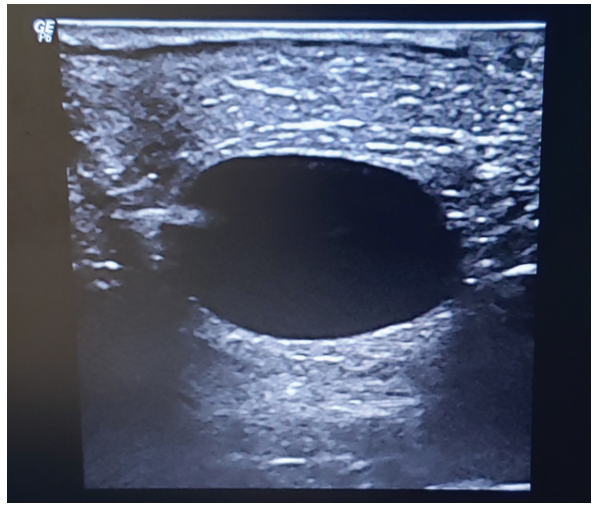

Figure 9. Mammographic image of eggplant with simulated lesions: calcification, fine calcification and nodule

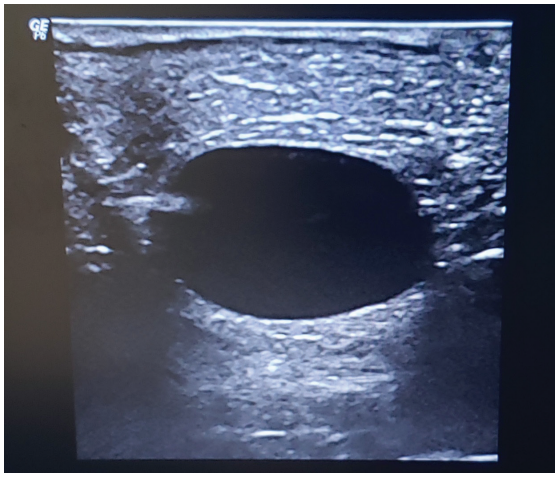

Figure 10. Simple cyst seen on US in the Phantom

US: Ultrasound

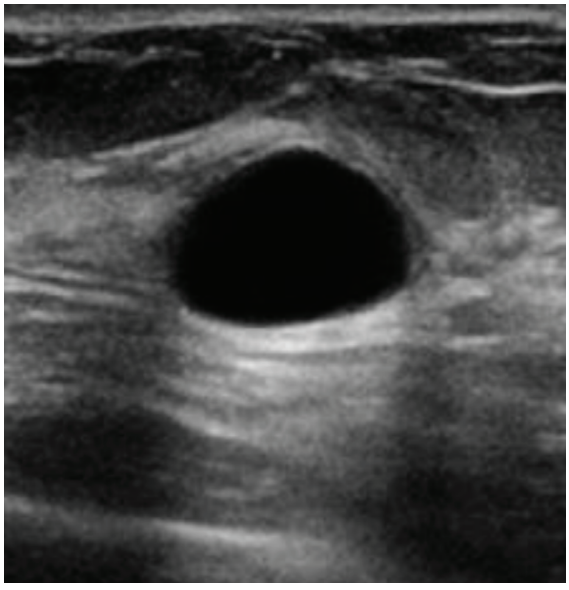

Figure 11. Simple cyst seen on US in the breast

US: Ultrasound

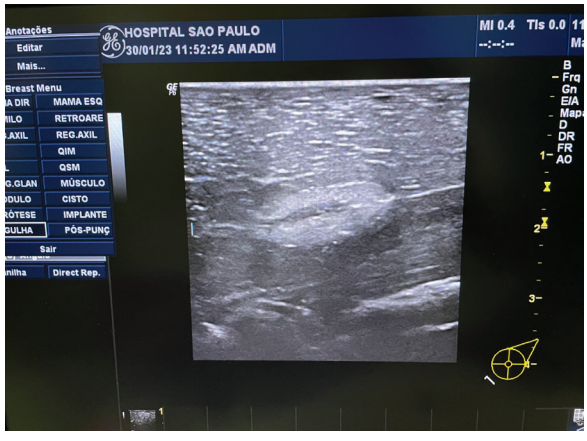

Figure 12. Solid nodule identified on US in the Phantom – note the similarity between the phantom image and on the real breast (Figure 14)

US: Ultrasound

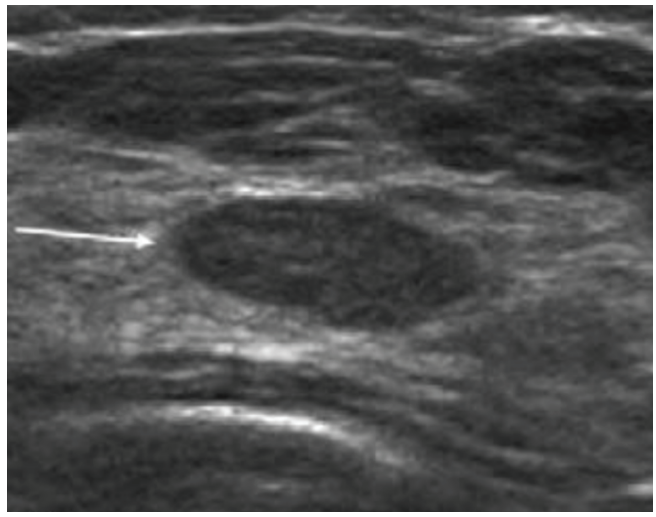

Figure 13. Solid nodule identified on US in the real breast

US: Ultrasound

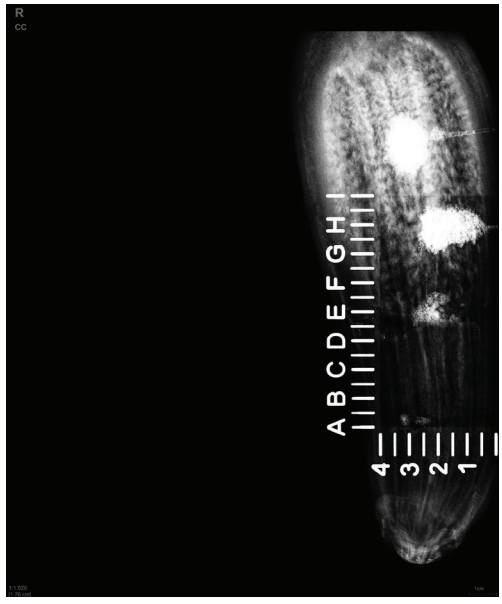

Figure 14. Calcifications seen on mammography in the Phantom

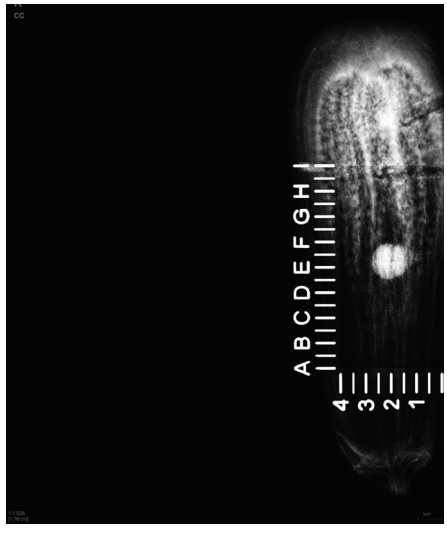

Figure 15. Nodule seen on mammography in the Phantom

The developed simulators used simple and easily accessible materials for manufacture, having an excellent cost-benefit ratio. Furthermore, they show great echographic and radiographic similarity with the real breast and associated lesions. Thus, these low-cost phantoms can be used to train professionals in the performance of invasive procedures in the field of breast imaging, enabling them to acquire self-confidence, experience, and mastery of the technique before performing *in vivo* procedures.

Ethics Committee Approval: This study was reported according to the STARD Statement Checklist and following the Declaration of Helsinki.

Informed Consent: Not necessary.

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

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Letter to the Editor

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Exploring the Relationship Between Tamoxifen and Hereditary Angioedema

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Dear Editor,

Hereditary angioedema (HAE) is a condition characterized by recurrent episodes of mucocutaneous edema, associated with abnormal levels or/and function of serum C1 inhibitor (C1-INH) (HAE type I or II, respectively) or with a normal complement study (1).

In at least two-thirds of women affected by this disorder, there is a distinct sensitivity to both endogenous and exogenous estrogens, and generally the frequency and severity of angioedema episodes increase in parallel with the rise in serum estrogen levels (1, 2). Some of the mechanisms involved in this process are the reduction in serum levels of C1-INH, coupled with the modulation of factor XII (FXII) gene transcription and of the kallikrein/bradykinin cascade, with induction of bradykinin receptors' expression and amplification of its action (2). Therefore, the general consensus between experts is the recommendation to avoid estrogen therapy in patients with HAE (2).

While the incidence of breast cancer in women with HAE mirrors that of the general population, caution is warranted when considering the use of estrogen modulators such as tamoxifen in these patients. This caution arises from the potential agonistic activity on estrogen receptors in specific tissues, which could exacerbate angioedema symptoms and, in severe cases, result in fatal outcomes. Physicians who frequently prescribe such medications should be mindful of these considerations in their decision-making processes (3).

We present a breast cancer patient whose angioedema episodes were exacerbated as a consequence of hormone therapy with tamoxifen.

A 54-year-old woman was referred to an allergy/immunology appointment due to recurrent episodes of facial and laryngeal angioedema exhibiting bradykininergic features. She reported previous history of angioedema, partially responsive to antihistamines/corticosteroids, whose initial manifestation occurred during adolescence, coinciding with the introduction of a combined contraceptive pill, subsequently controlled after replacement with a progestin pill. However, episodes currently recurred following initiation of hormone therapy with tamoxifen in the context of breast cancer diagnosis. She had no family history of angioedema.

In a prior assessment, C1-INH deficiency had already been excluded, and presently two consecutive quantitative and functional studies of this protein revealed no abnormalities-serum level of C1-INH = 24.6–37.5 mg/dL, with normal function. Given the clinical suspicion of HAE with normal complement, a genetic study was requested, identifying a mutation in the FXII gene - variant c.983C>A p. (Thr328Lys) in heterozygosity-and confirming the diagnosis.

In light of the symptomatic worsening observed after the initiation of tamoxifen, this agent was considered responsible. In collaboration with Oncology, this drug was replaced by anastrozole, an aromatase inhibitor, with subsequent complete symptomatic control, which reinforced our observations.

Tamoxifen, a selective estrogen receptor modulator, is widely used in breast cancer (3). To date, there are rare cases described in the literature, in which this drug was considered a factor in exacerbating HAE, namely due to its action as a partial agonist in certain estrogen receptors (2, 4, 5). Our observations not only reinforce these previous reports but also underscore the importance of increased awareness among physicians regarding this potential side effect of hormone therapy in women diagnosed with both HAE and breast cancer.

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