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Turkish Federation of Breast Diseases Societies

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

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NCBC National Consortium of Breast Centers

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European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

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

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

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

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

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

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

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

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

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European Journal of Breast Health

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Case Report	1000	200	15	No tables	10 or total of 20 images
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Current Opinion	300	No abstract	5	No tables	No media

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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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Future of Breast Radiology

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ABSTRACT

The landscape of breast imaging has transformed significantly since mammography's introduction in the 1960s, accelerated by ultrasound and image-guided biopsies in the 1990s. The emergence of magnetic resonance imaging (MRI) in the 2000s added a valuable dimension to advanced imaging. Multimodality and multiparametric imaging have firmly established breast radiology's pivotal role in managing breast disorders. A shift from conventional to digital radiology emerged in the late 20th and early 21st centuries, enabling advanced techniques like digital breast tomosynthesis, contrast-enhanced mammography, and artificial intelligence (AI) integration. AI's impending integration into breast radiology may enhance diagnostics and workflows. It involves computer-aided diagnosis (CAD) algorithms, workflow support algorithms, and data processing algorithms. CAD systems, developed since the 1980s, optimize cancer detection rates by addressing false positives and negatives. Radiologists' roles will evolve into specialized clinicians collaborating with AI for efficient patient care and utilizing advanced techniques with multiparametric imaging and radiomics. Wearable technologies, non-contrast MRI, and innovative modalities like photoacoustic imaging show potential to enhance diagnostics. Imaging-guided therapy, notably cryotherapy, and theranostics, gains traction. Theranostics, integrating therapy and diagnostics, holds potential for precise treatment. Advanced imaging, AI, and novel therapies will revolutionize breast radiology, offering refined diagnostics and personalized treatments. Personalized screening, AI's role, and imaging-guided therapies will shape the future of breast radiology.

Keywords: Artificial intelligence; breast imaging; diagnostic techniques; screening; theranostics; radiology; interventional

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Key Points

- Advancing integration of artificial intelligence (AI): AI is becoming integral to breast radiology, streamlining workflows, smart dataprocessing, aiding detection and diagnosis, and optimizing decision-making processes.
- Personalized screening and diagnosis: Evolving from mammography, automated breast ultrasound, magnetic resonance imaging (MRI), and contrast-enhanced mammography offer personalized screening options with AI-driven enhancements for accuracy.
- Innovative imaging and therapies: Multiparametric MRI, virtual biopsy, and photoacoustic imaging provide advanced diagnostic insights. Imaging-guided therapies and theranostics promise targeted precision treatment, transforming breast radiology's future.

Following the inception of mammography (MG) for screening purposes in the early 1960s, the field of breast imaging has undergone a transformative progression. This evolution gathered significant momentum by incorporating ultrasound (US) and advanced image-guided biopsies into routine clinical practice during the 1990s. Subsequently, in the early 2000s, magnetic resonance imaging (MRI) emerged as a discriminating option for advanced imaging modalities. Furthermore, the shift from conventional to digital radiology occurred between the late twentieth and early twenty-first centuries. Concerns mainly revolved around the reduced resolution of digital images compared to conventional MG, which raised worries about potentially missing lesions like microcalcifications and the challenge of detailed breast tissue visualization. Nevertheless, due to the broader dynamic range of digital MG compared to screen-film MG, it displayed greater tolerance to exposure errors. Additionally, the digital format of images offered a significant advantage, allowing for the integration of advanced techniques. This, in turn, facilitated the incorporation of digital breast tomosynthesis imaging, contrast-enhanced MG, and artificial intelligence (AI) applications. Subsequently, in the early 2000s, MRI emerged as a discerning option for advanced imaging modalities. Through the assessment of multimodality and multiparametric imaging, breast radiology has indisputably established itself as an indispensable and irreplaceable component in the management of breast disorders.

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The essence of AI lies in its ability to develop algorithms that emulate human intelligence, while learning from data and making informed decisions. Given the digital nature of radiology, AI's integration appears inevitable (1). However, the gradual integration of AI into breast radiology sparks curiosity and concern about the potential impact on the profession. AI will inevitably play a significant role in the future of breast radiology. The questions remain: what specific role will AI hold within breast radiology practice? Would AI replace radiologists, and could AI's findings be relied upon exclusively?

The Integration of AI in Breast Radiology

Radiology departments of the future will operate alongside AI, which will serve as a support mechanism, streamlining processes, aiding decision-making, and improving regulation. The role of AI in breast radiology will manifest in three key ways: Computer-aided diagnosis (CAD) algorithms, workflow support algorithms, and data processing algorithms.

AI as a support tool in breast radiology dates back to the 1980s when computer support was initiated for mammographic film evaluation (2, 3). Early systems flagged suspicious areas for the ultimate decision of the radiologist. Image perception errors, human factors like fatigue, and overlapping structures all contributed to erroneous diagnoses that could be reduced with such support algorithms (4). However, due to the emergence of convolutional neural networks and deep learning (DL), these CAD systems have transformed, transitioning from basic, user-defined algorithms to autonomous learning algorithms. This capability allows DL models to potentially uncover features that are unidentifiable or imperceptible to the human eye. Practical, AI driven new generation CAD applications, including detection, triage, and diagnosis, hold promise in breast imaging. These AI based applications address issues like false positives and negatives in screening mammograms, optimizing patient recall rates, and improving cancer detection rates (1). The prevalence of false positive outcomes in screening MG can be high as 30% (5, 6). On the other hand, retrospective analyses reveal that up to 60% of interval cancers exhibit affirmative findings within prior mammograms (6, 7). Research indicates that the introduction of AI systems in screening mammograms has the potential to decrease interval cancers and increase cancer detection rates in routine screening mammograms (8-10). AI algorithms will prioritize examinations, mark suspicious lesions, and facilitate decision-making, allowing radiologists to use their time more efficiently. This AI-assisted workflow will reshape the role of radiologists, transforming them into specialized clinicians engaging more in multidisciplinary collaborations (11-14). Pending examinations will be prioritized based on their significance, and comparative reports involving comparison with prior studies and meticulously AI-generated clinical information will be ready for review (15, 16). Naturally, as these advances unfold, radiologists' characteristics will also evolve. General radiologists, who constitute the majority, will gradually be succeeded by specialized radiologists who possess expertise in their specific domains and adopt a personalized clinical approach when engaging with patients (15, 16). Radiology clinic reading rooms will function as central "hubs", fostering multidisciplinary collaboration, shaping patient-centered diagnoses, and informing clinicians about treatment options. Leveraging AI alongside intranet and internet connectivity, patient data from hosting and external hospitals will be aggregated and showcased during multidisciplinary meetings. Thus, radiology will gain value as clinically based and patient oriented.

From Volume Screening to Personalized Screening

Screening in breast cancer, which began as a simple MG examination and has now evolved to a personalized screening approach. A better understanding of the significance of breast density has led to a change in screening strategies for women with dense fibroglandular tissue, driven by heightened awareness of its influence on false negatives and elevated breast cancer risk. Supplementary US screening is widely used for women with dense breast tissue. A recent large, randomized US screening study showed the impact of ultrasonography in detecting two additional cancers per 1000 women, in line with previous studies (17). However, US encounters significant limitations, including its real-time nature and user-dependent operation, leading to archiving and retrospective analysis challenges. Automated breast ultrasound system (ABUS) can be used for screening and diagnostically, providing a 3-dimensional volume view (18). Undoubtedly, AI algorithms to be developed in the future will enable better visualization of this 3D data, facilitate lesion detection with CAD solutions, and allow faster evaluation with decision support algorithms. Since ABUS can also help teleradiology, US scanning can be performed where radiologists are unavailable. Research continues on automated US imaging with a tomography mechanism by allowing the breast to sag with gravity in the prone position instead of the supine position (19). In this way, it will be possible to evaluate other parameters, such as speed of sound, which may show higher specificity in lesion differentiation (20).

Breast MRI is also valuable as a supplementary screening tool and is effective not only in high-risk women but also in women with average risk but increased breast density (21). Furthermore, a recent randomized controlled MRI screening study included women with extremely dense breast tissue from a national breast cancer screening program. These women were offered supplementary MRI screening every two years, resulting in a notable reduction in interval cancers and the detection of an additional 15 cancers per thousand screenings (22). However, breast MRI is expensive and hard to access as a large-volume screening method. Contrast-enhanced MG can be an excellent alternative to MRI and offers a cost-effective and convenient solution for screening high-risk women and those with dense breast tissue (23, 24). This approach has the potential to facilitate efficient and rapid large-scale female screening.

Wearable technologies, such as specialized bras equipped with US sensors, can potentially transform follow-up and screening approaches (25). Meanwhile, non-contrast MRI techniques are gaining traction, providing valuable information, particularly in screening without invasive contrast agents. Combining T2-weighted or STIR images with diffusion imaging can provide comparably high-sensitivity results to contrast-enhanced MR scanning (26, 27). Future advancements aim to enable rapid, non-contrast breast MRI scans, suitable even for women with contrast contraindications.

Innovations in Diagnostic Imaging

The cornerstone of breast MRI examination is dynamic contrast-enhanced imaging. MRI, highly sensitive in breast radiology, evaluates multiple parameters such as diffusion-weighted imaging, spectroscopy, and dynamic contrast enhancement (28-30). Through multiparametric MRI, neovascularization, tissue water diffusion, and molecular markers can be assessed enabling molecular-level imaging (31). Tumor characteristics like proliferation, angiogenesis, apoptosis, metabolism, and hypoxia can also be demonstrated (31). Dynamic contrast-enhanced MRI depicts contrast material kinetics, quantifying neovascularization via tumor perfusion. Excessive tumor cell

proliferation narrows intercellular space and hinders fluid movement, detected through diffusion imaging and vectorial movement with diffusion tensor imaging. These methods allow contrast-free breast cancer screening with improving image quality. Furthermore, using these different parameters, radiomic information, which enhances diagnostic accuracy, is obtained. MR spectroscopy (MRS) examines various molecules; choline, used in cell membranes, enables molecular mapping for virtual biopsy. Hyperpolarized MRS imaging detects rare molecules. While current MRI visualizes hydrogen atoms, other rare particles like carbon (C) and phosphorous (P) can be facilitated, and different parametric MRI outcomes can be achieved (32).

Photoacoustic or optoacoustic imaging is a hybrid imaging modality combining optical illumination and US (33). Angiogenesis and hypoxia are some of the main features of cancer, and the capability of optical imaging to detect various hemoglobin forms enhances its sensitivity in imaging (33, 34). The oxygenation capacity of blood vessels and treatment-induced changes in the blood vessels can be demonstrated (34). The functional aspect of optoacoustic US has the potential to address certain challenges related to morphological similarities in distinguishing between benign and malignant masses (35-37). In recent studies, the incorporation of optoacoustic US (OA/US) showed an increase in breast mass assessment specificity of 14.9%, and high positive predictive values for malignancy (35, 38). Other studies show that utilizing OA/US may assist radiologists in more effectively distinguishing between various breast cancer molecular subtypes (39).

Virtual biopsy, notably through multiparametric MR examination, has emerged as a pivotal differential diagnostic tool. Imaging genomics (radiomics) plays a vital role here. Radiomics integration involves aligning the molecular attributes of diverse genetic subgroups of breast cancer with their multiparametric imaging features. This approach links disease imaging phenotypes with their genotype, representing their genetic expression - a vigorously researched subject (40). Leveraging AI-enhanced segmentation, lesion features identified by radiologists and computers can be matched with genotypes. This process enables classification and predictive model creation, addressing clinical and biological queries (40, 41).

Since MRI is a frequently used technique for screening, diagnosis, and staging in breast radiology, difficulties are often encountered in diagnosing lesions detected only by MR examination. MRI-guided biopsy is required for these lesions, but MRI-guided biopsy is a technically challenging, time-consuming, and expensive technique. MRI-guided biopsy can be performed in a few centers worldwide. Contrast-enhanced MG, an excellent alternative to MRI, also provides biopsy (42). In this way, the lesions detected only with contrast-enhanced MRI can be diagnosed with contrast-enhanced MG-guided stereotaxic vacuum biopsy. This method can be widely used as a more practical alternative to MRI-guided biopsy.

Conducting MRI scans with the patient in the prone position while performing surgical and biopsy procedures in the supine position presents challenges in accurately localizing lesions identified by MRI. This incongruity in patient positioning hinders precise pre-surgical planning, lesion evaluation, and procedures like biopsy or marking (43, 44). However, real-time US examinations can merge supine MRI images with US images, allowing for accurate lesion localization and guidance during interventional procedures (45, 46). Consequently, fusion US-guided biopsy is an alternative to MR-guided biopsy (46). With the advancement of fusion biopsy techniques and their integration with non-contrast MRI methods, this challenge will be more effectively addressed in the future. Transforming prone imaging to the supine position also holds significance in preoperative planning and locating tumors before and after neoadjuvant chemotherapy, providing crucial guidance for surgical interventions.

Imaging Guided Therapy

Cryotherapy is a treatment method that can be applied with US guidance and has been recently researched to treat breast cancer. A pivotal study on this subject is the Ice3 study, in which 194 women over 60 were evaluated, and the tumor size ranged from 8-14.9 mm. In a mean follow-up of 3 years after treatment, ipsilateral tumor recurrence was 2.06% (47). Cryotherapy holds promise as a viable alternative treatment avenue, particularly for instances wherein surgical intervention is not feasible.

Theranostics is derived from therapy and diagnostics and can be defined as using diagnostic methods to provide targeted therapy. Modern breast cancer treatment is optimally individualized and targeted, and theranostics appears to be an excellent method to achieve this goal. In theranostics, the active therapeutic substance will be delivered to the target cell without affecting the surrounding healthy tissues, and the process will be monitored with imaging guidance. The basic procedure is to load the lethal dose to the contrast agent carriers, monitor the agent with imaging, and control the release of the therapeutic agent loaded to the contrast agent into the tumor with the help of imaging methods when it reaches the tumor tissue. For example, after loading the chemotherapeutic agent into microbubbles with US contrast, this contrast agent is injected into the patient, and the tumor is monitored under ultrasonography (48). After tracking the contrast material reaching the tumor, these carrier microbubbles are deflated with the help of US waves, and the drug is released within the tumor without damaging the surrounding tissue (48). Particles or nanoparticles suitable for imaging modality are used as therapeutic agent carriers. One of the most used particles for MRI are superparamagnetic iron oxide nanoparticles (49, 50). Carbon nanotubes are important carriers for MRI, and targeted molecules such as drugs, contrast agents, antibodies, cell membrane penetrants, and iron oxide nanoparticles can be loaded onto these nanotubes (50). Theranostics will play an important role in targeted precision therapy in the future.

Conclusion

In the future, breast radiology will be able to offer more patient-focused diagnosis and treatment approaches, thanks to the developing technological applications and AI's support to radiologists in every field, from workflow to image formation and CAD systems. Integrating imaging genomics will aid differential diagnosis, aligning genetics with multiparametric features via AI-enhanced solutions. Novel image-guided therapeutic solutions will provide alternative treatment approaches. The future holds enhanced integration of imaging, AI, and innovative therapies in breast radiology. From personalized screening to innovative theranostics, the trajectory of breast imaging is laden with promise, transforming the landscape of breast radiology, and ultimately improving patient outcomes. The future of breast radiology is not one of replacement, but of transformation as technology and human expertise converge to advance patient care to new heights.

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Original Article

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Short-Term Biomarker Modulation Study of Dasatinib for Estrogen Receptor–Negative Breast Cancer Chemoprevention

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ABSTRACT

Objective: Risk-reducing therapy with selective estrogen receptor (ER) modulators and aromatase inhibitors reduce breast cancer risk. However, the effects are limited to ER-positive breast cancer. Therefore, new agents with improved toxicity profiles that reduce the risk in ER-negative breast cancers are urgently needed. The aim of this prospective, short-term, prevention study was to evaluate the effect of dasatinib, an inhibitor of the tyrosine kinase Src, on biomarkers in normal (but increased risk) breast tissue and serum of women at high risk for a second, contralateral primary breast cancer.

Materials and Methods: Women with a history of unilateral stage I, II, or III ER-negative breast cancer, having no active disease, and who completed all adjuvant therapies were eligible. Patients underwent baseline fine-needle aspiration (FNA) of the contralateral breast and serum collection for biomarker analysis and were randomized to receive either no treatment (control) or dasatinib at 40 or 80 mg/day for three months. After three months, serum collection and breast FNA were repeated. Planned biomarker analysis consisted of changes in cytology and Ki-67 on breast FNA, and changes in serum levels of insulin-like growth factor 1 (IGF-1), IGF-binding protein 1, and IGF-binding protein 3. The primary objective was to evaluate changes in Ki-67 and secondary objective included changes in cytology in breast tissue and IGF-related serum biomarkers. Toxicity was also evaluated.

Results: Twenty-three patients started their assigned treatments. Compliance during the study was high, with 86.9% (20/23) of patients completing their assigned doses. Dasatinib was well tolerated and no drug-related grade 3 and 4 adverse events were observed. Since only one patient met the adequacy criteria for the paired FNA sample, we could not evaluate Ki-67 level or cytological changes. No significant change in serum biomarkers was observed among the three groups.

Conclusion: Dasatinib was well tolerated but did not induce any significant changes in serum biomarkers. The study could not fulfill its primary objective due to an inadequate number of paired FNA samples. Further, larger studies are needed to evaluate the effectiveness of Src inhibitors in breast cancer prevention.

Keywords: Chemoprevention; breast cancer risk; Src inhibitors

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Key Points

- Evaluation of agents that can reduce the risk of estrogen receptor-negative breast cancer development is urgently needed.
- Phase 3 breast cancer prevention trials require large numbers of patients and long follow-up durations and are costly.
- Short-term phase 1 and 2 biomarker modulation prevention trials offer a convenient method of studying potential preventative agents for ER-negative breast cancer.

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Introduction

Over the past 30 years, researchers have evaluated selective estrogen receptor (ER) modulators (SERMs) such as tamoxifen and raloxifene and aromatase inhibitors as breast cancer preventive agents in large, prospective phase 3 trials, which showed a reduction in breast cancer risk of 50-65% (1-8). In the United States, tamoxifen and raloxifene have been approved by the US Food and Drug Administration for reduction of breast cancer risk. However, these agents only reduce risk in ER-positive breast cancer. Currently, no agents are available and approved for the prevention of ER-negative breast cancer.

The Src family of kinases (cSrc, Lyn, Fyn, Yes, Lck, Blk, and Hck) is a group of non-receptor tyrosine kinases involved in the regulation of important cellular functions, such as cell proliferation, differentiation, apoptosis, migration, and metabolism (9, 10). Investigators found Src overexpression and activation in more than 80% of ductal carcinoma *in situ* lesions and that they were associated with HER2 expression in such lesions (11, 12). Additionally, Src phosphorylation at Y416 (indicating activation of the Src family of tyrosine kinases) was associated with ER negativity and tamoxifen resistance. The reverse relationship between Src and ER is consistent with previous reports that Src promotes estrogen-dependent ERα degradation in human breast cancers (13). Tamoxifen-resistant breast cancer cells have also exhibited Src activation, and treatment with the Src inhibitor saracatinib suppressed the invasion of tamoxifen-resistant cells (14). Furthermore, a recent study demonstrated that saracatinib administration improved tumor-free and overall survival in two mouse models of ER-negative, Src-activated mammary tumors by delaying the onset and progression of premalignant lesions (15). These results are suggestive of a critical function of Src in ER-negative breast cancer development. Therefore, inhibiting the Src pathway may be an effective strategy for breast cancer prevention.

Large-scale randomized prevention trials are costly, take a long time to produce results, and require large numbers of patients. Short-term, phase 1-2 biomarker modulation prevention trials are practical ways to study potential chemopreventive agents (16) that may show promise for future large-scale trials. Dasatinib, a potent oral tyrosine kinase inhibitor against the Src family kinases, BCR-ABL, platelet-derived growth factor receptor, c-KIT, and ephrin receptor kinases, has displayed anti-proliferative activity against solid tumors and is approved for use in patients with chronic myelogenous leukemia (17) and Philadelphia chromosome-positive acute lymphoblastic leukemia (18).

Several biomarkers associated with breast cancer could be evaluated as potential candidates for short-term phase I and phase II breast cancer prevention trials. The insulin-like growth factor (IGF) signaling pathway plays a vital role in regulating cell proliferation and apoptosis. It is known that IGF-1 and its binding proteins are associated with an increased risk of breast cancer (19). Ki-67, a proliferation index of neoplasm, is well-known as a prognostic and predictive marker for cancer assessment in patients (20). Additionally, cytomorphology has been evaluated as a potential biomarker for breast cancer risk and has been demonstrated to be useful in the context of short-term prevention studies.

In this short-term biomarker modulation prevention study, the aim was to establish the effect of treatment with dasatinib in women who are at increased risk for a second, contralateral, primary breast cancer by evaluating the modulation of a panel of potential biomarkers including IGF-1, IGF-binding protein (IGFBP)-1, IGFBP-3, and Ki-67, as well as cytological findings in normal, but high risk breast tissue and serum samples. Our goal was to understand the pathway involved in ER-negative breast cancer development and progression to inform future studies with agents targeting the Src pathway, ultimately leading to the development of prospective phase 3 studies aimed at ER-negative breast cancer prevention. The toxicity of dasatinib was also assessed in this phase 2 pilot study.

Materials and Methods

Patient Eligibility

Patients diagnosed with ER-negative invasive breast cancer at The University of Texas MD Anderson Center were offered participation in this prospective study. Eligibility criteria included: histologically confirmed stage I, II, or III ER-negative (defined as <10% of tumor cells positively stained for ER expression by immunohistochemistry) breast cancer; completion of all adjuvant therapy, including surgery, chemotherapy, and radiation therapy, if indicated; and an intact contralateral breast. The study was reviewed and approved by the University of Texas MD Anderson Institutional Review Board, and all subjects provided written informed consent.

Study Design

After providing informed consent, eligible patients underwent baseline blood sampling and random, periareolar fine-needle aspiration (FNA) of the contralateral unaffected breast for biomarker evaluation. Patients were randomized in a 1:2:1 fashion to no treatment (control) or treatment with dasatinib at 40 or 80 mg/day for three months (arms A, B, and C, respectively). Patients returned to the clinic at one month for evaluation and received a follow-up telephone call at two months for toxicity assessment. At the end of three months, patients underwent a second blood sampling and repeat FNA and toxicity assessment. Participants were evaluated if they received at least 75% of their assigned treatments.

FNA Samples and Cytological Evaluation

FNA and slide preparations were performed as described previously (21). Briefly, patients underwent FNA of the intact opposite breast. In all patients, eight FNA passes were performed: four at the 3 o'clock position and four at the 9 o'clock position. Following injection of 2 mL of 1% lidocaine, the aspiration needle was moved in multiple directions to ensure sampling of most of the breast tissue, with emphasis on areas of dense breast tissue, where proliferative glandular tissue may often be present. All of the FNA samples were pooled in 5 mL of CytoLyt solution (Hologic Inc. Marlborough, MA, USA).

Cytological samples were prepared using the ThinPrep technique (Cytyc Corporation, Marlborough, MA, USA). One slide per patient was subjected to Papanicolaou staining for cytological diagnosis; the remaining slides were saved in a tissue bank for biomarker studies as per the study protocol. Sample adequacy was defined as having more than 10 epithelial cells on the slide, and sample cellularity was scored based on the number of epithelial cell groups/clusters on the slide as follows: group 1+, one to three groups; group 2+, four to six groups; and group 3+, more than six groups. All slides were assessed by a single expert breast cytopathologist (N.S). Cytological diagnoses were based on previously published criteria (22). The cytological categories used were non-proliferative epithelium (normal), hyperplasia without atypia (benign), atypical hyperplasia, and malignant lesion.

Serum Biomarkers

Blood samples were processed into serum fractions. The serum was frozen at -80°C for analysis of IGF-1, IGFBP-1, and IGFBP-3. IGF-1, IGFBP-1, and IGFBP-3 levels were measured using enzyme-linked immunosorbent assay kits from R&D Systems (Minneapolis, MN, USA) according to the manufacturer's instructions. Baseline and 3-month serum samples were analyzed at the same time.

Statistical Analysis

The primary endpoint was evaluation of Ki-67 changes in pre-treatment and post-treatment FNA samples. We assumed that the change of Ki-67 after the treatment would be positively associated with the dose level. Ki-67 was measured as a continuous variable and assessed by a one-way ANOVA followed by Dunnett's multiple comparison test comparing the change of Ki-67 of each of the two treated groups with control. Secondary endpoints included changes in cytology in high-risk breast tissue and IGF-related serum biomarkers in pre- and post-treatment samples. Enrollment of 66 patients was planned so that attrition would leave at least 60 patients for evaluation with 1:2:1 randomization to the three arms. Patients were evaluated if they had paired pre-and post-treatment serum and/or FNA samples for biomarker analysis. The standard deviation (SD) was about 10% for a single Ki-67 measurement at pre- or post-treatment. The SD of Ki-67 modulation is also 10% based on the conservative assumption that the correlation coefficient of the Ki-67 level before and after treatment is 0.5. As a result, a Ki-67 change of 10% is indicted by an effect size of 1. Assuming an effect size of 1 and a significance level of 0.05, a one-way design with sample sizes of 15 and 30 in the two treatment groups and 15 in the control group can yield an any-pair power of 0.87. The any-pair power is the probability of detecting a significant difference between any treatment groups and the control group. The effect size is the standardized mean difference between a treatment group and the control group, defined as the ratio of detectable difference between the two groups and the common SD within the groups. The difference in the levels of IGF-related serum biomarkers before and after treatment with dasatinib for each patient was summarized and compared between the three study arms using a Kruskal-Wallis test. The McNemar test was used to investigate if there was any difference in cytology before and after treatment.

Results

Patient Characteristics

Twenty-six patients were enrolled in this prospective study, 24 of whom were eligible and randomized. However, 23 patients started their assigned treatments because one patient withdrew consent after randomization within one week and never started treatment.

Characteristics of the 23 patients are shown in Table 1. Their median (range) age was 60.3 (30.7–74.4) years, and all were women. The patients underwent baseline FNA and had blood drawn before starting treatment.

Compliance during the study was high, with 20 patients (87%) completing their assigned treatment. Three patients discontinued dasatinib use early because they withdrew consent (within 2 weeks, 1 month, and 2.5 months, respectively) for reasons unrelated to toxicity. Eighteen patients underwent post-treatment FNA. Two of these patients completed at least 75% of the assigned treatment but did not return for FNA and blood draws. Therefore, they were included in the toxicity assessment but not biomarker assessment.

Toxicity

Toxicity data are reported for all 20 patients who completed study. Dasatinib was well tolerated by the patients as shown in Table 2. We observed no grade 3 or 4 drug-related adverse events. Grade 1–2 adverse effects included fatigue, headache, pruritus, nausea, and other gastrointestinal disorders. In the 40 mg/day arm, one patient experienced a grade 2 fracture that was unrelated to the study treatment. In the 80 mg/day arm, one patient experienced a grade 2 infection that was not related to the study treatment.

Changes in FNA samples

Eighteen patients underwent pre-treatment and post-treatment FNA. The cytological findings are summarized in Table 3. Based on the FNA sample adequacy definition, 14 of 20 patients had non-proliferative benign cellular findings prior to treatment, whereas 7 of 18 had non-proliferative findings after treatment. When we examined the

Table 1. Patient characteristics

	n (%)			
Characteristic	**All randomized patients (n = 23)**	**Arm A: No treatment (n = 5)**	**Arm B: Dasatinib 40 mg/day (n = 12)**	**Arm C; Dasatinib 80 mg/day (n = 6)**
Median (range) age, years	60.3 (30.7–74.4)	53.7 (40.6–63.2)	62.4 (46.1–74.4)	50.8 (30.7–69.6)
Race				
Asian	1 (4)	0	0	1 (17)
Black	4 (17)	2 (40)	1 (8)	1 (17)
Hispanic	4 (17)	1 (20)	2 (17)	1 (17)
White	14 (61)	2 (40)	9 (75)	3 (50)
ER status				
Negative	21 (91)	5 (100)	12 (100)	4 (67)
Low weak	2 (9)	0	0	2 (33)
PR status				
Negative	21 (91)	5 (100)	11 (92)	5 (83)
Positive	2 (9)	0	1 (8)	1 (17)
HER2 status				
Negative	17 (74)	2 (40)	9 (75)	6 (100)
Positive	6 (26)	3 (60)	3 (25)	0
Disease stage				
I	5 (22)	0	4 (33)	1 (17)
II	14 (61)	3 (60)	7 (58)	4 (67)
III	4 (17)	2 (40)	1 (8)	1 (17)

ER: estrogen receptor; PR: progesterone receptor

adequacy of paired pre-treatment and post-treatment FNA samples, we found that only one patient had adequate samples, so we could not assess Ki-67 level or cytological changes. Seventeen of the 18 patients received previous chemotherapy, which may have contributed to the low FNA cellularity yield.

Changes in Serum Biomarker Levels

Of the 20 patients who completed their assigned treatment, 17 underwent both baseline and 3-month measurement of IGF-1, IGFBP-1, and IGFBP-3 in serum: 4 in arm A, 8 in arm B, and 5 in arm C. The differences in serum biomarker levels before and after treatment are shown in Figure 1. We observed no significant differences in the changes in the level of any of these markers in the three arms.

Table 2. Adverse events following treatment with Dasatinib versus no treatment

Adverse event	Two Dasatinib treatment arms			
	Arm B: 40 mg/day (n = 10)		Arm C: 80 mg/day (n = 5)	
	Grade 1 (n)	Grade 2 (n)	Grade 1 (n)	Grade 2 (n)
Alopecia	1	0	1	0
Arthralgia	1	0	0	0
Increased aspartate aminotransferase level	1	0	0	0
Back pain	0	0	1	0
Cough	1	0	1	0
Diarrhea	1	0	1	0
Dizziness	1	0	1	0
Dysgeusia	1	0	0	0
Fatigue	3	0	1	0
Fever	0	0	1	0
Fracture	0	1	0	0
Gastritis	0	0	1	0
Other gastrointestinal disorders	3	0	0	0
Headache	4	0	0	0
Hot flashes	1	0	0	0
Infections and infestations	0	0	0	1
Musculoskeletal and connective tissue disorder	1	0	0	0
Nausea	2	0	2	0
Pain	1	0	0	0
Pain in extremity	0	0	1	0
Peripheral sensory neuropathy	0	0	1	0
Pruritus	2	0	1	0
Rash acneiform	0	0	1	0
Rash maculopapular	1	0	0	0
Renal and urinary disorders	0	0	1	0

Discussion and Conclusion

In this prospective biomarker modulation, breast cancer prevention study of three months of dasatinib-based treatment, we observed no significant differences in serum biomarker levels before and after treatment. Given the very small number of adequate paired samples we could not perform cytological or Ki-67 analysis. Having received previous chemotherapy may have contributed to low cellularity.

Src family kinases are postulated to have roles in insulin and IGF signaling pathways (23, 24). The IGF signaling pathway contains a dynamic network of proteins, including ligands (insulin, IGF-1, and IGF-2), their related receptors (IGF-1R and IGF-2R), and several IGFBPs, that participate in the regulation of human cancer development (25). Many studies have demonstrated a strong positive correlation between circulating IGF-1 levels and breast cancer risk, particularly in premenopausal women (26-30). In light of its mitogenic and anti-apoptotic activity, authors have closely linked IGF-1 with breast cancer progression (31). In this study, no significant differences in serum IGF-1 levels before and after treatment were detected, although the study numbers were small and the duration of treatment was limited to three months.

At least six known IGFBPs bind to IGF-1 and IGF-2 and may regulate their activity. In particular, IGFBP-1, which binds to only a small fraction of circulating IGFs, is thought to be crucial for controlling IGF-1 bioactivity at the cellular level (32). Low LGFBP-1 levels have been linked with increased risk of breast cancer (33). Researchers have studied the IGFBP-1 and IGFBP-3 biomarkers in several chemoprevention trials with different agents, including SERMs and aromatase inhibitors (34-37). We previously reported a significant increase in IGFBP-1 levels in women who received anastrozole-based therapy for six months (37). Likewise, in another study, we observed a significant increase in IGFBP-1 levels in women who received celecoxib-based therapy for six months (38). In this study, we did not see any significant differences in serum IGFBP-1 levels before and after treatment with dasatinib.

Other investigators have reported conflicting data regarding the association between the serum concentration of IGFBP-3, IGF's primary binding protein, and the risk of breast cancer. In some studies, high levels of circulating IGFBP-3 have been linked with decreased risk of breast cancer in premenopausal women (33, 39). In contrast, Renehan et al. (29) found that high concentrations of IGFBP-3 were associated with increased risk of premenopausal breast cancer. Moreover, IGFBP-3 mRNA expression in breast cancer tissue has been associated with poor prognostic factors (hormone receptor negativity, aneuploidy, and high S-phase fractions) (40, 41). Finally, in postmenopausal women with ER-positive breast cancers, Goodwin et al. (42) found that a high level of circulating IGFBP-3 was associated with distant metastasis and recurrence. In this study, we did not see any significant differences in serum IGFBP-3 levels before and after treatment with dasatinib.

Cytomorphology is a potential surrogate endpoint in breast cancer prevention trials. However, several chemoprevention trials failed to detect any changes in cytology after treatment with

Table 3. FNA cytological findings for pretreatment and posttreatment samples

	Cytology			
Cases evaluated	**Acellular**	**Non-proliferative (group 1)**	**Non-proliferative (group 2)**	**Non-proliferative (group 3)**
Pretreatment (n = 20)	6	13	1	0
Post-treatment (n = 18)	11	4	2	1

Sample adequacy was defined as having more than 10 epithelial cells on the slide, and sample cellularity was scored based on the number of epithelial cell groups/clusters on the slide as follows: group 1+, one to three groups; group 2+, four to six groups; and group 3+, more than six groups

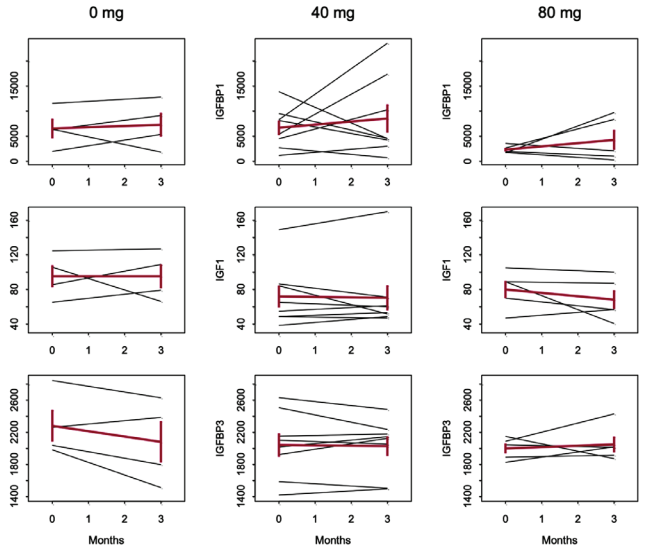

Figure 1. Changes in serum biomarker levels in the three study arms. The red horizontal lines represent the mean levels of each biomarker at each time point. The red vertical lines represent standard deviation. None of the changes differed significantly among the three arms

different agents for prevention (37, 38, 43-45). In this study, given the very small number of adequate paired FNA samples, we could not perform cytological or immunohistochemical marker analysis.

Our study has several limitations and results should only be taken as a starting point for further research. The first limitation is the small study size. However, prospective enrollment in prevention trials requiring analysis of paired breast tissue samples is challenging. Furthermore, it is possible that more tissue can be obtained when breast biopsies are done, but this procedure is likely to be less acceptable for patients compared with FNA. The cost of running biomarker modulation studies using core biopsies would also be higher. The other limitation is that the levels of cytological markers in FNA samples may have been altered as a consequence of previous chemotherapy.

In conclusion, the IGF signaling pathway is known to play a significant role in breast cancer development and progression, based on both epidemiological and molecular studies. Studies targeting this pathway for breast cancer therapy and the development of potential therapeutic agents for breast cancer are ongoing. The research findings concerning Src inhibitors to date highlight the need for further research to better understand the molecular mechanisms by which this signaling pathway drives breast cancer progression. The present study is the first clinical trial designed to determine whether treatment with dasatinib would modulate biomarkers of ER-negative breast cancer development. To date, effective predictive biomarkers for Src inhibition in the clinic have yet to be identified. Detecting phosphorylation of downstream signaling molecules, leading to the initiation of intracellular signaling cascades, such as insulin receptor substrate proteins, may be useful for potential biomarker identification. As a result, further, larger studies are needed to determine the effectiveness of Src inhibitors, ideally new generation agents that are less toxic, for breast cancer prevention.

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Ethics Committee Approval: The study was reviewed and approved by the University of Texas MD Anderson Institutional Review Board 1 on 1/18/2013.

Informed Consent: Written informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.K.A.; Design: B.K.A.; Data Collection and/ or Processing: F.N.A.M., D.D.L., A.M.G., J.E.L.; Analysis and/or Interpretation: D.D.L.; Literature Search: F.N.A.M.; Writing: F.N.A.M., A.M.G., J.E.L., N.K.I., V.V., D.J.B., J.K.L., K.K., D.Y., N.S., B.K.A.

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Original Article

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Does a 40% Cut-off Point for Ki-67 Expression Have a Role in Identifying the Development of Distant Metastasis Within 2 Years in Locally Advanced Triple Negative Breast Cancer Patients?

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ABSTRACT

Objective: Triple negative breast cancer (TNBC) has a higher proportion of patients with distant recurrence or metastasis. Ki-67 has been suggested as an essential factor in cancer grading and prognostic evaluation, although there is still a debate regarding the Ki-67 cut-off value in TNBC. The aim of this study was to determine the role of Ki-67 expression using a 40% cut-off point as a risk factor for developing distant metastasis within two years in patients with TNBC.

Materials and Methods: This analytical observational study was conducted with a case-control design from January 2021-2022. Subjects were divided into two groups (metastasis within two years or more than two years after diagnosis). Bivariate analysis was conducted using chi-square test and odds ratio (OR) was also analyzed.

Results: A total of 66 subjects were included. In patients with metastasized TNBC and a Ki-67 expression of ≥40%, 29 patients (55.8%) had metastasis occurring in ≤2 years and 23 patients (44.2%) had metastasis occurring in >2 years; in patients with metastasized TNBC and a Ki-67 expression of <40%, 4 patients (28.6%) had metastasis occurring in ≤2 years and 10 patients (71.4%) had metastasis occurring in >2 years. Chi-square analysis (p = 0.071) indicated no significant association between patients with Ki-67 expression of ≥40% and <40% with metastasis within 2 years [OR 3.152 (confidence interval: 95% 0.875–11.362)].

Conclusion: Ki-67 protein expression of over 40% in patients with locally-advanced TNBC does not indicate a greater risk of distant metastasis in the first two years after diagnosis.

Keywords: Triple negative breast cancer; breast cancer; Ki-67; metastasis

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Key Point

- Based on our study's analysis result, it could be concluded that Ki-67 protein expression of over 40% in patients with locally-advanced triple-negative breast cancer does not provide a risk of distant metastasis in under 2 years. There were still inconsistencies between Ki-67 expression and the impact on survival in patients with breast cancer due to the ongoing debate regarding the inaccurate assay's precision, the difference in methods in measuring Ki-67 and different cut-off values in differentiating tumors with high and low concentrations of Ki-67 expression.

Introduction

Triple negative breast cancer (TNBC) is defined as a tumor that does not express the three prognostic and predictive biomarkers typically used for routine clinical management, which are estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor type 2. TNBC is more commonly found in younger patients across varied ethnicities and races. Patients with TNBC typically have a larger tumor, with a higher grade and more rapid growth. TNBC is also associated with a greater likelihood of distant recurrence or metastasis compared to local recurrence. TNBC with metastasis usually involves visceral organs, such as the lung and brain and is less likely to involve bones, in contrast to tumors with positive ER. Thus,

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TNBC is regarded as a more aggressive tumor with a worse prognosis compared to other subtypes (1).

Patients with TNBC are also more likely to develop typical distant and local recurrence sequelae, within 1–3 years of initial diagnosis. Tseng et al. (2) showed that the median overall survival (OS) duration in TNBC patients with lung metastases was 16.6 years but only 4.3 years in cases with brain metastases. The median time to death in patients with TNBC is shorter compared to other subtypes. Furthermore, in addition to a more likely distant recurrence, patients with TNBC are also more likely to develop an earlier recurrence. The mean time to distant metastases in a cohort of patients diagnosed with TNBC in a single institution in Toronto was 2.6 years, compared to 5 years in other subtypes (3). The risk of relapse and mortality in patients with TNBC is the highest within the first 3–5 years of diagnosis. All deaths in TNBC occurred more rapidly and within a period of 10 years after diagnosis. In comparison, deaths due to other breast cancer subtypes occur up to 18 years after diagnosis (1).

Protein Ki-67 is an antigen that occurs in two protein isoforms with a molecular weight of 345 and 395 kDA; it was first identified by Scholzen and Gerdes (4) in the early 1980s. Ki-67 is strictly associated with proliferation and studies have suggested that Ki-67 is an essential factor in cancer grading and prognostic evaluation. Xiong et al. (5) showed that the Ki-67 index is associated with the prognosis of patients with advanced-stage cancer. A study by Wang et al. (6) in 2016 reported that TNBC patients with lower Ki-67 expression (<40%) had a better 3-year disease-free period compared to those with Ki-67 expression of >40% (90.8% compared to 78.4%, with a log-rank *p*-value of 0.001).

The consistent relationship between high Ki-67 index and poor outcomes in patients with breast cancer is conclusive, despite the uncertain precision of laboratory results, the difference in methods of measuring Ki-67 and different cut-off values in differentiating tumors with a high and low concentration of Ki-67 expression (7). The higher Ki-67 expression in TNBC is considered to play a role in the development of a more rapid metastasis, although there is still a debate regarding the standardization of the cut-off value for Ki-67 expression in TNBC. Considering the high risk of early distant metastasis in TNBC patients, the aim was to conduct a study comparing patients with TNBC and distant metastases either before or after two years of diagnosis and Ki-67 indexes either above or below a 40% cut-off.

Materials and Methods

This analytical observational study was conducted with a case-control design. This study was conducted in the Department of Oncology Surgery, Faculty of Medicine, University of Udayana in the Prof. Dr. I Gusti Ngoerah Gde Ngoerah Hospital, Denpasar, Bali for a duration of one year, from January 2021 to January 2022.

This study included all patients diagnosed with local-advanced TNBC and recorded in the medical records. The sample was divided into two groups, the case and control groups. The case group included locally-advanced TNBC patients with distant metastasis occurring less than two years after diagnosis, while the control group included locally-advanced TNBC patients with distant metastasis occurring over two years after diagnosis. TNBC patients under 18 years old, patients with incomplete clinical and histopathology medical records, patients who were not monitored for disease progression and patients diagnosed during pregnancy were excluded. Both groups received therapy (chemotherapy and/or radiotherapy) based on each patient's indications. Total consecutive sampling was conducted; therefore, patients who met the inclusion and exclusion criteria during the study period were considered as study samples until the minimum sample was met. This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Udayana (no: 2021.02.1.1086, date: 09.09.2021).

Ki-67 expression was counted in patient tumor samples, which were freshly obtained by incisional biopsy. Tumor samples were fixed using 10% formal saline in under 30 minutes and were delivered straight into the pathology department. Calculation of Ki-67 expression was done by counting total number of Ki-67-positive tumor cells in each field from immunohistochemistry (IHC) hotspot areas divided by the total number of tumor cells. This Ki-67 expressions was presented as percentages.

The independent variable in this study was the Ki-67 expression in the tumor sample. Ki-67 expression was startified into Ki-67 expression ≥40% as a positive risk factor and Ki-67 expression <40% as a negative risk factor. The instrument for measuring this variable was the IHC examination conducted by staff of the histopathology department. Time measurement of under or over 2 years of distant metastasis was started after a locally-advanced TNBC diagnosis based on the IHC examination from distant metastatic tissue samples was made. The control variables in this study were age, menopausal status, staging, histopathology features, tumor grading, tumor-infiltrating-lymphocytes (TIL), and lymphovascular invasion (LVI). The study's procedure is shown in Figure 1.

Statistical Analysis

Data analysis in this study consisted of univariate analysis (descriptive statistics) and bivariate analysis. Descriptive analysis aims to describe the study subjects' characteristics. The categorical variable is presented as the frequency of total (percentage), while numerical data are presented as mean and standard deviation. Bivariate analysis is conducted by making a cross-tabulation 2x2 (row x column) and measuring the effect size in odds ratio (OR). The used hypothesis

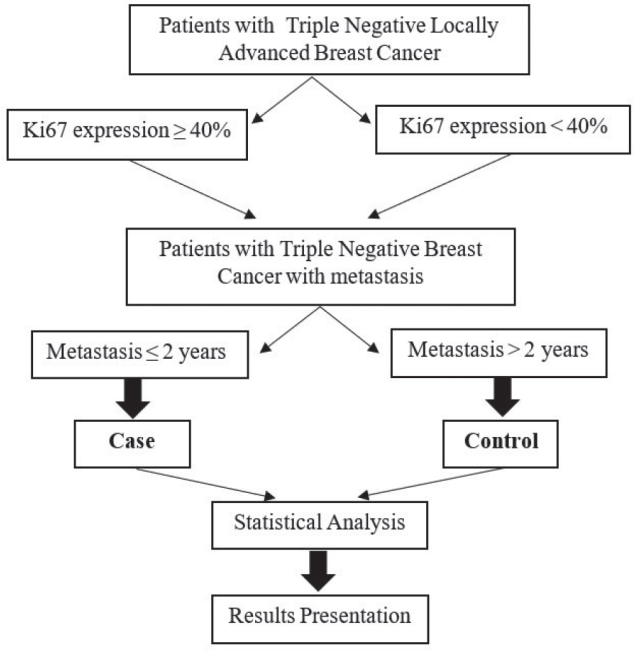

Figure 1. Procedural steps of the study

test was chi-square, in which a $p<0.05$ was considered statistically significant. All data analysis in this study was performed using the statistical program SPSS, version 25.0 (IBM Inc., Armonk, NY, USA).

Results

A total of 66 locally-advanced TNBC patients with metastasis who met the inclusion and exclusion criteria were included in this study. The subjects were divided into two groups: locally-advanced TNBC patients with distant metastasis occurring in less than 2 years from diagnosis (n = 33); and locally-advanced TNBC patients with distant metastasis occurring later than 2 years after diagnosis (n = 33). The variables of interest were age, menopausal status, histopathology type, staging, tumor grading, TIL and LVI. All these variables were comparable between the two groups (Table 1).

Then the association between Ki-67 using the 40% cut-off and metastasis of TNBC patients with a cut-off of 2 years after diagnosis was analyzed with a cross-tab using a 2x2 table with a chi-square test and a significance level of <0.05. Based on Table 2, in patients with metastasized TNBC and a Ki-67 expression of ≥40%, there were 29 patients (55.8%) with metastasis occurring in ≤2 years and 23 patients (44.2%) with metastasis occurring in >2 years. In patients with metastasized TNBC and a Ki-67 expression of <40%, there were 4 patients (28.6%) with metastasis occurring in ≤2 years and 10 patients (71.4%) with metastasis occurring >2 years. The chi-square statistical analysis result was $p = 0.071$, indicating that there was no significant association between patients with Ki-67 expression of ≥40% and <40% with metastasis within 2 years with an OR value of 3.152 [confidence interval (CI) 95% 0.875–11.362].

Table 1. Study subjects' characteristics

Variable	Metastasis ≤2 years, n (%)	Metastasis >2 years, n (%)	*p*
Age			
>50 years	13 (48.1)	14 (51.9)	0.802
≤50 years	20 (51.3)	19 (48.7)	
Menopausal status			
Post Menopause	17 (53.1)	15 (46.9)	0.708
Pre-Menopause	16 (48.5)	17 (51.5)	
Histopathology type			
No specific type (NST)	26 (49.1)	27 (50.9)	
Invasive lobular carcinoma	3 (33.3)	6 (66.7)	0.170
Metastatic carcinoma NST	1 (100)	0 (0)	
Special type carcinoma	3 (100)	0 (0)	
Staging			
IIIA	2 (50)	2 (50)	0.197
IIIB	24 (45.3)	29 (54.7)	
IIIC	7 (77.8)	2 (22.2)	
Tumor grading			
Grade 3	22 (52.4)	20 (47.6)	0.609
Grade 1-2	11 (45.8)	13 (54.2)	
TIL			
Moderate – strong positive	9 (40.9)	13 (59.1)	0.296
Negative – positive mild	24 (54.5)	20 (45.5)	
LVI			
Positive	18 (62.1)	11 (37.9)	0.083
Negative	15 (40.5)	22 (59.5)	

Discussion and Conclusion

Generally TNBC is characterized as an aggressive breast tumor and has poor prognosis compared with the luminal subtype. Moreover, TNBC has a tendency to develop distant metastasis, particularly brain metastasis, which significantly reduces the OS of patients with this form of breat cancer (1). Ki-67 expression, as one of the proliferation indices, was been widely used as a breast cancer prognostic factor in previous studies (4-7). However, in contrast to the luminal subtype which is divided into luminal A and B based on teh Ki-67 value, TNBC has no different classifications according to Ki-67 expression. Whether higher Ki-67 expressions in TNBC results in a worse prognosis or not is still a matter for ongoing debate. Hence the rationale behind the present study. The Ki-67 index cut-off of 40% was derived from the meta-analysis of Wu et al. (8) in 2019. These authors reported that Ki-67 expression ≥ 40% in resected TNBC patients was linked with a higher chance of recurrence and death (8). The present study focused on locally advanced TNBC and the relationship between Ki-67 expression levels and distant metastasis events inside two years of diagnosis.

Several studies, including retrospective evaluations from randomized clinical trials and meta-analyses, have shown that increased Ki-67 expression is independently associated with poor outcomes in patients with breast cancer. One of the studies, that included the most patients, was conducted by Petrelli et al. (9) in 2015 who undertook a systematic literature review and meta-analysis of several studies. A total of 41 studies, including 64,196 patients, were identified. Although the cut-off value of Ki-67 in the study varied, ranging from 10 to over 25%, the strongest prognostic significance in determining OS was shown in Ki-67 measurement with a cut-off value of over 25% [with a hazard ratio (HR) of 2.05; CI 95% 1.7–2.5; $p<0.00001$] (9). However, the low cut-off value of Ki-67 was not based on scientific evidence and research; rather, it was based on expert opinions. Until standardized research is available, Ki-67 measurement should adhere to previously published recommendations from the International Ki-67 in Breast Cancer Working Group (10).

Bivariate analysis in the present study showed a non-significant association between Ki-67 expression with a cut-off value of 40% and metastasis within two years ($p = 0.071$) and OR 3.152 (95% CI 0.875–11.362). Another study using Ki-67 expression in TNBC patients in order to attempt to predict progression of the breast cancer was performed by Hao et al. (11) in 2016. These authors used a Ki-67 cut-off value of 35%, which was the median value of Ki-67 expression from their sample. Overall, Ki-67 expression of over 35% had a similar disease-free survival (DFS) with patients with Ki-67 expression of ≤35% ($p = 0.481$). Although their study reported a similar result to the present study, their were several methodological differences: (1) the 35% cut-off value; (2) the use of survival analysis for determining prognostic factors of Ki-67 expression; (3) classifications of survival analysis based on age group; and (4) outcome in relation to breast-cancer-specific survival, which was not described in detail.

Table 2. The association between Ki-67 with a cut-off value of 40% and metastasis timing

Ki67 Expression	Metastasis ≤2 years (n; %)	Metastasis >2 years (n; %)	OR (95% CI)	*p*-value
≥40%	29 (55.8%)	23 (44.2%)	3.152 (0.875–11.362)	0.071
<40%	4 (28.6%)	10 (71.4%)		

OR: odds ratio; CI: confidence interval

Munzone et al. (12) peformed a study investigating Ki-67 expression, and drew a similar conclusion to the present study. Munzone et al. (12) used a cut-off value of 35% and compared DFS between patients with Ki-67 >35% and ≤35% in the six years following diagnosis. Over this period the DFS was similar between these two groups [p = 0.192 and HR 1.3 (95% CI 0.7–2.3)] (12). Another study that reported a similar analysis result using Ki-67 cut-off value of 30% was performed by Pistelli et al who compared DFS and OS between Ki-67 >30% and ≤30% within a median of 52.4 months. In this observational period, Ki-67 expression of over 30% had a statistically similar DFS [p = 0.71 and HR 0.8 (95% CI 0.23–2.71)] and OS (p = 0.99 and HR 1; 95% 0.21–4.73) with Ki-67 of ≤30% (13). Both of these studies used a survival analysis study design.

A retrospective study analyzing the association between Ki-67 and local recurrence and metastasis was conducted by Wang et al. (14) in 2019. This study used a cut-off value of >30% and ≤30%. Ki-67 expression of >30% had a statistically similar recurrence-free survival rate with Ki-67 expression of ≤30% (p = 0.112) (14). Another retrospective study by Gonçalves et al. (15) in 2018 with a cut-off value of 25% reported that Ki-67 of >25% had a statistically similar recurrence-survival with Ki-67 of <25% (HR 0.91; 95% CI 0.39–2.11; p = 0.83).

Previously, Wang et al. (6) in 2016 used the same Ki-67 expression cut-off as our study of 40% in the same population, although with a different analysis conclusion. They analyzed OS and DFS in patients with TNBC with Ki-67 expression of over and under 40%. Wang et al. (6) concluded that patients with Ki-67 expression of ≤40% had a significantly better DFS compared to Ki-67 >40% within 3 years (90.8% compared to 78.4%, log-rank p = 0.001) (6). Another study by Masuda et al. (16) in 2011 evaluated DFS in pre- and post-chemotherapy TNBC patients, stratified by Ki-67 of < and ≥50%. In both pre-chemotherapy TNBC patients and post-chemotherapy patients who did not achieve pathological complete response, both survival analyses showed a similar result, in which patients with a higher Ki-67 expression (≥50%) had a worse DFS compared to those with low Ki-67 expression (<50%) within two years with p values of 0.04 and 0.002 (16).

Other potential prognostic biomarkers have recently been investigated. One of these was circular RNAs (circRNA). circRNAs are known to be involved in TNBC cell proliferation, apoptosis, migration, and invasion, and have also been found to be involved in colorectal cancer and prostate cancer (17, 18). Recent studies have also shown the correlation between disease specificity and clincial relevance in TBCA and the expression of circRNAs. circRNAs are highly stable and thus have a long half-life, are resistant to Rnase R digestion, and can be detected by cost-effective methods (quantitative real-time PCR). Tian et al. (17) reviewed the use of circRNAs as a potential prognostic biomarker for TNBC. These authors showed that several upregulated circRNAS were associated with poor survival in TNBC patients but further studies are still required to standardized the collection timing and cut-off values. Another potential prognostic biomarker is the epidermal growth factor receptor (EGFR), which has been shown to be an independent indicator of prognosis for worse DFS and OS. Immunotherapy biomarkers, such as the programmed cell death protein 1, have also been shown to be commonly expressed in TNBC patients and are associated with poor prognoses (18). Furthermore, besides biomarkers, other prognostic factors also include clinical and radiological findings. Costa et al. (19) found that clinical findings such as large tumor size, angiolymphatic invasion, axillary node involvement, smoking and advanced clinical stage, were significantly related to lower OS and/or DFS and recurrence in patients with TNBC. Moreover, certain MRI features of TNBC have been shown to be useful in determining the prognosis of patients. Choi et al. (20) reported that MRI features, including heterogeneous/rim enhancement, very high intratumoral signal intensity on T2 images and peritumoral edema were significantly associated with standarized uptake value maximum from 18F-fluorodeoxyglucose positron emission tomography/computed tomography, indicating poor prognosis for TNBC.

The present study had several limitations. First, the study design was retrospective observational with case-control hypothesis testing. Based on literature review, there are only a few case-control retrospective studies that assessed Ki-67 expression as a risk factor for metastasis in patients with TNBC. Most of the available studies used a prospective survival analysis as their design and so the conclusions of this study have a poorer evidence base. Second, due to incomplete data in medical records, there were fewer study participants who met the inclusion criteria, which may have biased the results further. This missing data included details of chemotherapy agents and duration of chemotherapy or radiotherapy, which constitutes substatial data omission.

In conclusion, in this cohort Ki-67 protein expression of over 40% in patients with locally-advanced TNBC did not indicate a greater risk of distant metastasis in under two years of diagnosis compared to patients with a Ki-67 level of <40%. It should be noted that there are still inconsistencies between Ki-67 expression and the impact on survival in patients with breast cancer. These may be due to the assay precision, the difference in methods in measuring Ki-67 and different cut-off values in differentiating tumors with high and low concentrations of Ki-67 expression. Until standardized research is available, Ki-67 measurement should adhere to previously published recommendations from the International Ki-67 in Breast Cancer Working Group.

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Udayana (no: 2021.02.1.1086, date: 09.09.2021).

Informed Consent: Written informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.S., I.B.S.; Concept: K.S.; Design: K.S., I.K.W., I.W.S.; Data Collection or Processing: K.S., I.B.S.; Analysis or Interpretation: K.S., I.B.S., I.W.S.; Literature Search: K.S., I.K.W.; Writing: K.S., I.B.S., I.K.W., I.W.S.

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Original Article

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Investigation of the Effect of Women's Breast Cancer Worry Levels on Breast Cancer Prevention Behavior

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ABSTRACT

Objective: The aim of this study was to investigate the extent of worry about breast cancer (BC) amongst a sample of women and to examine the effect of this on behavior to prevent BC.

Materials and Methods: This cross-sectional study was conducted in 271 women aged 18 years and above who attended the Family Medicine Outpatient Clinic of a tertiary hospital and met the inclusion criteria. Data were collected using the following tools: Patient Information Form; Breast Cancer Worry Scale (BCWS); Breast Cancer Prevention Behaviors Identification Scale (BCPBIS); and Mammography Processes of Change Scale (MPCS).

Results: When evaluated according to BCWS scores (mean 8.43±3.36), the BC worry levels were found to be low. The behavior adopted for prevention was also found to be positive according to BCPBIS (mean 119±15.26) and MPCS (mean 82.38±12.81) scores. A significant correlation was found between the BCWS and both the BCPBIS and MPCS scores, and again between the BCPBIS and MPCS scores (p<0.001 for all). There was a correlation with three scale scores in those who had knowledge about BC, and those who had regular clinical breast examination (BE) (p<0.05 for all). The BCPBIS score was found to be higher in those aged between 41-65 years, those who had mammography, and performed p self-BE (p = 0.002; p<0.001; p<0.001, respectively). According to the MPCS score, mammography behaviors was found to be more positive in those who had regular gynecological examinations and those who had mammography (p = 0.08 and p = 0.011).

Conclusion: The participants generally had low BC worry levels and had adopted positive behavior for prevention. Being informed about BC and screening and having regular BE increased BC worry. Those with high BC worry, those who had mammography before, those who had knowledge about BC and screening, and those who regularly performed BE showed more positive behaviors toward preventing BC.

Keywords: Breast cancer screenings; mammography; preventive behaviors; worry

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Key Points

- Concern about breast cancer (BC) can positively affect participation in screening, as well as cause avoidance of screening.
- Having knowledge about BC and screening tests and having regular breast examination are factors that may increase BC anxiety.
- However, although these factors will increase BC anxiety, they are important in terms of exhibiting more positive behaviors of women to participate in screening and prevent BC.

Introduction

Breast cancer (BC), is the most common type of cancer in women and the most common cause of cancer-related deaths, especially in low- and middle-income populations (1). Detection of BC at an early stage and reducing mortality rates are thus important for public health (2). In this context, it is recommended to perform BC screening both by self-examination and clinical breast examination (BE) and mammographic imaging (3).

Although BC screening is planned according to age and risk factors, there are many factors that affect the participation of women. First of all, differences in socio-cultural status may affect risk perception of BC differently and may lead to the development of different attitudes towards screening programs. In particular those with a low socio-cultural level may have a low awareness of BC (4, 5). Having BC risk factors, having a family history of BC, fear of being diagnosed with BC and losing the breast may increase levels of BC anxiety and positively affect participation in BC screening. However, these same factors can

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also lead to screening avoidance, depending on individual perceptions. Thus, it has also been shown that fear of being diagnosed with BC may also cause avoidance of mammographic imaging (6, 7).

In addition, the lack of sufficient knowledge about BC screening programs, concern about privacy during BE and mammographic imaging, and the fact that mammographic imaging is performed with a painful technique cause mammographic imaging avoidance behavior. These negative attitudes towards mammographic imaging, which can detect cancerous tissue even when very small, hinder BC screening programs (8, 9).

The evidence has shown that worry about BC may both positively affect participation in screenings, as well as cause avoidance of screening. The aim of the present study was to investigate the anxiety levels of women towards BC and to examine the effect on their behavior towards preventative measures for BC.

Materials and Methods

This cross-sectional study was carried out with female individuals who were admitted to the Family Medicine Outpatient Clinic of a tertiary hospital between 23 December 2021 and 15 May 2022, and who met the inclusion criteria. A brief pre-assessment interview was conducted with volunteers aged 18 years and over and without a personal or family history of cancer in their first-degree relatives. Their personal medical history and their initial anxiety levels were investigated. Information about previous chronic metabolic and psychiatric diseases and medications was checked via the online health system. The participants were also questioned in terms of feeling nervous, anxious and tense in the two weeks preceding the appointment. Women who do not describe these symptoms and who did not have a known psychiatric disease or drug use were included in the study.

Exclusion Criteria

Those under the age of 18 years, those with either a personal or family history of cancer in their first-degree relatives, those who were considered to have anxiety in the brief pre-assessment interview, who had a known psychiatric disease and who used drugs for it, and those with a disability to communicate (hearing and speech impairment, cognitive dysfunction) were excluded from the study.

After the participants were informed in detail about the study, their verbal and written consent was obtained. All procedures were carried out in compliance with the Declaration of Helsinki. The study was performed with the approval of the local ethics committee (date: 22.12.2021, no: 396 - Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee).

Data Collection Tools

Patient Information Form, Breast Cancer Worry Scale (BCWS), Breast Cancer Prevention Behaviors Identification Scale (BCPBIS), and Mammography Processes of Change Scale (MPCS) were used to obtain data.

Patient Information Form

The Patient Information Form was created by the researchers using published studies as a basis. The form collected sociodemographic characteristics (age, marital status, educational status) of the participants, the presence of chronic diseases, any history of gynecological examination, and factors related to BC screening, such as having knowledge about BC screening, and performance of clinical and self-BE and mammographic imaging.

Breast Cancer Worry Scale

Lerman et al. (10) developed the scale as a 3-item form in 1991 to measure the effect of BC anxiety on daily activities and mood. Later, this form was made applicable to all types of cancer by increasing the number of questions and was renamed the Cancer Worry Scale (10). Timur Taşhan et al. (11) modified the 6-question form for BC to Turkish and conducted a validity and reliability study (Cronbach $\alpha = 0.78$). The BCWS is a 5-point Likert-type scale, and the total score is in the range of 0-24. A total score of 12 and above indicates high BC anxiety.

Breast Cancer Prevention Behaviors Identification Scale

Khazaee-Pool et al. (12) developed in the BCPBIS in 2016 to determine the factors affecting women's BC prevention behavior. The Turkish validity and reliability study was undertaken by Turan and Yiğit (13) in 2019. The BCPBIS consists of 33 items with seven sub-dimensions: attitude; motivation; self-efficacy; supportive systems; information seeking; self-care; and stress management. The BCPBIS is a 5-point Likert type scale. Items 1, 2, 3, 18, 19, 21, 22, and 23 are reverse scored. A total of 33 to 165 points can be obtained from the scale, and a higher score from the relevant dimension indicates that more positive behavior is displayed in that direction (13).

Mammography Processes of Change Scale

The validity and reliability study of the MPCS, which was created to evaluate the mammography behavior change process, was conducted by Pruitt et al. in 2010 (14, 15). The Turkish validity and reliability study was conducted by Sezen (16) in 2017. The MPCS consists of four sub-dimensions which include 22 items, and these sub-dimensions are: Information sharing and communication; consistency of regular screening; avoidance of contact with the health care system; and process of regular screening. A total of 43-100 points can be obtained from the 5-point Likert-type scale.

Statistical Analysis

SPSS, version 25 was used for statistical analysis (IBM Inc., Armonk, NY, USA). Descriptive data on the sociodemographic information of the participants are given as frequency tables. Parametric tests were used in the study since the number of participants was over 200 (17). The Pearson correlation analysis, a parametric test, was used to investigate the relationship between the scale and subscale scores. In addition, the Independent Samples t-test and One-Way ANOVA test, which are also parametric tests, were used to investigate if there was a significant difference between the scale and subscales and the sociodemographic data of the participants. In case of a significant difference between the groups, the Least Significant Difference test, a Post-hoc tests, was used to determine between which groups the significant difference occurred. A $p<0.05$ was considered statistically significant.

Results

This study was conducted with 271 women, aged between 18 and 65 with a mean of 38.59±12.22 years. More than three-quarters (78.2%, n = 212) did not have regular gynecological examinations and 85.2% (231) did not have regular clinical BE. A majority, 69.0% (n = 187), stated that they have never had a mammographic imaging. In those who had mammography, the mean age of having the first mammographic imaging was 43.95±5.91 years and this ranged from 30 to 57 years of age. The sociodemographic, medical, and BC screening characteristics of the participants are presented in Table 1.

Table 1. Sociodemographic and screening behavior characteristics of the participants

Variables		n	%
Age	18–40 years	151	55.7
	41–65 years	120	44.3
Education level	Middle school and low	118	43.5
	High school	55	20.3
	University	98	36.2
Marital status	Single	87	32.1
	Married	184	67.9
Income level	Low	101	37.3
	Middle	151	55.7
	High	19	7.0
Regular gynecological examination	Yes	59	21.8
	No	212	78.2
Had information about BC screening	Yes	154	56.8
	No	117	43.2
Regular clinic BE	Yes	40	14.8
	No	231	85.2
Self BE	Never	59	21.8
	Sometimes	164	60.5
	Regularly	48	17.7
History of mammographic imaging	Yes	84	31.0
	No	187	69.0
Mammographic imaging results (n=82)	Normal	79	96.3
	Abnormal	3	3.7

Data presented as n (%) of the participants, BC: breast cancer; BE: breast examination

Table 2. Descriptive statistics of the total and sub-dimension scores of the scales

	Min-Max	Mean ± SD
BCWS score	1.00–19.00	8.43±3.36
MPCS total score	39.00–108.00	82.38±12.81
Information sharing and communication	12.00–50.00	37.49±7.06
Consistency of regular screening	7.00–25.00	17.38±3.90
Avoidence of getting in contact with the health care system	3.00–15.00	10.65±2.74
Process of regular screening	8.00–20.00	16.84±2.59
BCPBIS total score	65.00–158.00	119.19±15.26
Supportive systems	4.00–20.00	13.01±3.69
Motivation	8.00–20.00	16.22±2.37
Attitude	17.00–40.00	32.32±4.81
Self-efficacy	5.00–20.00	15.24±2.82
Self-care	6.00–30.00	17.33±4.06
Stress management	3.00–15.00	11.13±2.21
Information seeking	4.00–20.00	13.91±2.84

Data presented as Min-Max, Mean ± SD, BCPBIS: Breast Cancer Prevention Behaviors Identification Scale; BCWS: Breast Cancer Worry Scale; MPCS: Mammography Processes of Change Scale; Min: minimum; Max: maximum; SD: standard deviation

The mean scores obtained from the scales were: 8.43±3.36 for BCWS; 119±15.26 for BCPBIS, and 82.38±12.81 for MPCS. The mean score obtained from the BCWS suggested that BC worry levels were low in this cohort. Descriptive statistics regarding the total and sub-dimension scores of the scales used in the study are given in Table 2.

Table 3 shows the correlation analysis between the scores obtained from the scales and subscales. A significant positive correlation was found between the BCWS total score and the MPCS total score (r = 0.452; p<0.001) and the BCWS and the BCPBIS total score (r = 0.340; p<0.001). There was also a significant positive correlation between the MPCS total score and the BCPBIS total score (r = 0.613; p<0.001).

Table 4 presents the comparison of the total scores of the scales according to the various characteristics of the participants. The BCWS total score was significant different between women who did and did not have information about BC and screening tests (p = 0.005) and having regular clinical BE (p<0.001). The BCWS total score, indicating greater worry concerning BC, was found to be higher in those who had knowledge about BC and screening tests and those with regular clinical BE. Similarly, the MPCS score was significantly higher in those who had knowledge of BC and screening tests (p = 0.004), those who had regular clinical BE (p<0.001), who had regular gynecological examinations (p = 0.08), and had a history of mammographic imaging (p = 0.011). Finally, the BCPBIS total score was significantly higher in the over 40-year age group (p = 0.002). There was a statistically significant difference in BCPBIS total score between women who did or did not get information about BC and screening tests (p<0.001), did or did not have regular clinical BE (p = 0.002), did or did not perform self-BE (p<0.001), and did or did not have a history of mammographic imaging (p<0.001) (Table 4).

Discussion and Conclusion

In the present study, in which the effect of women's worry levels about BC and the effect this had on their BC prevention behavior was examined, the participants generally reported low levels of worry about BC and also exhibited positive behavior for prevention of BC. Those who were more worried about BC reported more positive behavior towards BC prevention. Those who had knowledge of BC and BC screening tests and those who had regular BE had higher levels of anxiety about BC. More positive behaviors toward BC prevention were observed in older women (aged 41–65 years), who knew about BC and screening tests, who had regular BE, and who had previous mammographic imaging.

Studies have shown that patients with BC have higher anxiety and depression levels than healthy individuals (18). These findings are more marked in the pre-treatment phase than post-treatment phase (19).

Table 3. Correlation between the scores obtained from the scales and subscales

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1- BCWS score	r	1													
	p														
2- MPCS total score	r	0.452**	1												
	p	**<0.001**													
3- MPCS-ISC	r	0.366**	0.909**	1											
	p	**<0.001**	**<0.001**												
4- MPCS-CRS	r	0.461**	0.776**	0.552**	1										
	p	**<0.001**	<0.001	<0.001											
5- MPCS-AGCH	r	0.229**	0.502**	0.296**	0.259**	1									
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**										
6- MPCS-PRS	r	0.299**	0.765**	0.626**	0.555**	0.227**	1								
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**									
7- BCPBIS total score	r	0.340**	0.613**	0.525**	0.547**	0.252**	0.510**	1							
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**								
8- BCPBIS-SS	r	0.345**	0.471**	0.417**	0.451**	0.111	0.394**	0.677**	1						
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.067	**<0.001**	**<0.001**							
9- BCPBIS-MOT	r	0.333**	0.503**	0.431**	0.461**	0.217**	0.388**	0.660**	0.471**	1					
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**						
10-BCPBIS-A	r	0.016	0.241**	0.132*	0.279**	0.164**	0.238**	0.598**	0.219**	0.169**	1				
	p	0.794	**<0.001**	**0.030**	**<0.001**	**0.007**	**<0.001**	**<0.001**	**<0.001**	0.005					
11-BCPBIS-SE	r	0.301**	0.443**	0.400**	0.374**	0.148*	0.381**	0.722**	0.381**	0.481**	0.306**	1			
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.015**	**<0.001**	**<0.001**	**<0.001**	<0.001	<0.001				
12- BCPBIS-SC	r	0.300**	0.482**	0.449**	0.410**	0.189**	0.342**	0.738**	0.397**	0.424**	0.217**	0.500**	1		
	p	**<0.001**	<0.001	<0.001	<0.001	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001			
13- BCPBIS-SM	r	0.118	0.278**	0.227**	0.210**	0.164**	0.267**	0.557**	0.267**	0.331**	0.268**	0.328**	0.352**	1	
	p	0.053	**<0.001**	**<0.001**	**<0.001**	**0.007**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**		
14- BCPBIS-IS	r	0.253**	0.504**	0.476**	0.371**	0.203**	0.422**	0.719**	0.416**	0.468**	0.268**	0.495**	0.522**	0.307**	1
	p	**<0.001**	**<0.001**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

*The correlation is significant at the 0.05 level (Pearson correlation test), **The correlation is significant at the 0.01 level (Pearson correlation test), A: attitude, AGCH: avoidance of getting in contact with the health care system; BCPBIS: Breast Cancer Prevention Behaviors Identification Scale; BCWS: Breast Cancer Worry Scale; CRS: consistency of regular screening; IS: information seeking, ISC: information sharing and communication; MPCS: Mammography Processes of Change Scale; MOT: motivation; PRS: process of regular screening; SC: self-care; SE: self-efficacy; SM: stress management; SS: supportive systems

Similar to people who have been diagnosed with BC, people who do not have BC may still worry about BC. Although the worry about BC may have an effect on adopting a healthy lifestyle, it may have a negative effect on prevention behavior for BC. Nacar (20) investigated the relationship between BC anxiety level and attendance for early diagnosis behavior in healthy women. In the study by Nacar (20), 75.7% of the participants had low BC anxiety, while the rate of self-BE was higher (39.7%) and mammographic imaging rate was lower (15.8%) compared to clinical BE (18.3%). Gözüyeşil et al. (21) observed that 69.6% of their participants had low BC anxiety. Nevertheless, the rates of clinical

Table 4. Comparison of the total scores of the scales, by a number of the sociodemographic variables examined

Variables	BCWS total score	MPCS Total score	BCPBIS Total score
Age	Mean ± SD	Mean ± SD	Mean ± SD
18–40 years	8.49±3.60	82.89±12.45	116.60±15.35
41–65 years	8.37±3.06	81.74±13.30	122.46±14.59
p=	0.765	0.466	**0.002**
Education level	Mean ± SD	Mean ± SD	Mean ± SD
1) Middle school and low	8.28±2.99	80.98±13.41	119.69±14.67
2) High school	8.47±3.48	83.25±12.50	120.36±14.68
3) University	8.60±3.73	83.57±12.22	117.94±16.32
p=	0.780	0.287	0.575
Income level	Mean ± SD	Mean ± SD	Mean ± SD
1) Low	9.02±3.57	81.91±13.30	118.69±15.83
2) Middle	8.18±3.09	82.89±12.52	119.46±15.00
3) High	7.37±3.93	80.79±13.05	119.79±15.07
p=	0.054	0.717	0.913
Regular gynecological examination	Mean ± SD	Mean ± SD	Mean ± SD
Yes	9.07±3.44	86.29±13.71	122.29±15.70
No	8.26±3.33	81.29±12.38	118.33±15.07
p=	0.103	**0.008**	0.079
Getting information about screening	Mean ± SD	Mean ± SD	Mean ± SD
Yes	8.93±3.45	84.31±12.31	123.31±15.08
No	7.79±3.15	79.84±13.08	113.78±13.80
p=	**0.005**	**0.004**	**<0.001**
Clinical BE	Mean ± SD	Mean ± SD	Mean ± SD
Yes	10.68±2.79	91.15±11.71	127.35±17.51
No	8.05±3.31	80.86±12.41	117.78±14.43
p=	**<0.001**	**<0.001**	**0.002**
Self BE	Mean ± SD	Mean ± SD	Mean ± SD
1) Never	7.80±3.24	79.86±13.62	113.56±15.29
2) Sometimes	8.40±3.14	82.51±12.47	119.14±14.41
3) Regularly	9.33±4.09	85.04±12.68	126.31±15.46
p=	0.062	0.113	**<0.001**
Post-hoc tests=			1-2&3, 2-3
Having mammographic imaging	Mean ± SD	Mean ± SD	Mean ± SD
Yes	8.92±2.97	85.33±12.28	124.76±15.46
No	8.22±3.51	81.05±12.87	116.70±14.54
p=	0.115	**0.011**	**<0.001**

Data presented as Mean ± SD, Independent Samples t-test, ANOVA test, Post-hoc; LSD test, LSD: Least Significant Difference; BC: breast cancer; BCWS: Breast Cancer Worry Scale; BCPBIS: Breast Cancer Prevention Behaviors Identification Scale; BE: breast examination; MPCS: Mammography Processes of Change Scale

and self-BE were only 7.1%–21.9%, and the rate of mammographic imaging was 14.1%. According to another study conducted with the participation of 2000 women, 49.1% of women had concerns about BC. The rate of anxiety about BC was higher in women who had experienced mammographic imaging (22). In keeping with these earlier studies, the BC anxiety levels of the women who participated in the present study were low, based on BCWS scores. The rate of clinical BE was 14.8%, the rate of self-BE was 17.7%, and the rate of having mammographic imaging was 31%. Although the rate of having mammographic imaging was higher than in these earlier studies, because both the general participation rates in screenings and the level of concern about BC were low, it suggests that women with low socio-cultural level, who made up the majority of the study population of the present study, also had low awareness of BC.

In the study in which the validity and reliability of the BCPBIS were examined, the participants' BC prevention behaviors were evaluated as moderately positive (13). In Bostancı's (23) thesis study in which female health professionals examined the relationship between BC fear and BC prevention behaviors, BC prevention behaviors were found to be moderately positive. Similarly, the attitudes of the present study population in terms of BC prevention behaviors were moderately positive. With appropriate interventions, women should be encouraged to adopt behaviors to prevent BC, although it should be noted that the etiology of preventative behavior adoption or avoidance is multifactorial.

Previously, it was predicted that MPCS would be successful in identifying women who were considering or not considering having a mammographic imaging in the next two years, and the total MPCS score was higher in women considering a mammographic imaging within two years. The total MPCS scores of those who had mammographic imaging before were lower (16). Ozmen et al. (24) previously reported that women aged between 40 and 49 years, who were most likely to have had mammographic imaging within the last two years were characterized by a higher educational level, periodic gynecologic examinations, and a first or second degree family history of BC. In contrast, women aged between 50 and 69 years were more likely to have undergone mammographic imaging within the previous 2 years if they had also undergone periodic gynecologic examinations (24). In the present study, those who had mammographic imaging at any point in their lives had higher MPCS scores. When the relationship between mammographic imaging status and the sub-dimensions of MPCS (information sharing and communication, regular screening stability, and regular screening behavior) were compared, although there was a significant difference, no significant difference was found with avoidance of health care services when compared to women who had never had mammography. While trust in physicians and health services positively affects participation in BC screening, previous negative mammographic imaging experience, low rate of referral of doctors to mammographic imaging, and negative beliefs about mammographic imaging prevented BC screening behavior.

BC incidence and BC-related death rates increase with increasing age (25). In previous studies, it was striking that different relationships have been detected between age and BC anxiety. Nacar (20) reported BC anxiety was higher in women younger than 40 years of age, whereas in the study of Gözüyeşil et al. (21), BC anxiety was higher at older ages. Although protective behaviors against BC were not significantly associated with age, in the study of Çuhadar (26), it was shown that women exhibited more positive BC prevention behavior as age increased. Similarly, in the present study, no significant correlation was found between the age of the women, anxiety about BC and the total MPCS score. In contrast to the earlier literature, the BCPBIS total score was higher between the ages of 18–40 years rather than in the older age group. There will likely be an increase in awareness of a range of diseases with advancing age. This may be associated with an increase in anxiety about having BC. Although advanced age is accepted as an important risk factor in the development of BC, it was thought that the observation of positive behaviors to prevent BC at younger ages might be due to the higher awareness and knowledge level of young people about BC and health behaviors.

Although increased education level has a positive effect on women's awareness of health, no relationship has been reported in the literature in association with anxiety about BC (21, 27, 28). However, as the level of knowledge about BC increases, women's anxiety levels about BC may decrease (29). In fact, Dinçel et al. (30) showed that, despite their low education level, women who were made aware of BC had a decreased fear level of BC. In the present study, and similar to earlier reports, no significant relationship was found between BC anxiety and education level. However, BC anxiety was higher in those who had previously received information about BC and screening tests. The high level of knowledge and awareness of the participants about BC may lead to the fear of being diagnosed with cancer and may lead to avoidance of screening programs. One remedy for this unwanted association would be to stress the importance and effectiveness of early diagnosis.

In contrast, in a study investigating women's level of knowledge about BC, mammographic imaging rates increased in the last two years in direct proportion to the increase in education level. It was found that university-graduate women had undergone more mammographic imaging (31). The level of confidence in the benefits of self-BE and mammographic imaging behavior was higher among women with higher education levels (32). In the present study, no significant association was found between the level of education and the total score of BCPBIS and MPCS. This may be related to the fact that adopting health behaviors to prevent BC and increasing women's awareness, and awareness in participating in screening programs play a more important role compared to women's current education levels.

Nacar (20) reported that 0.4 times more BC anxiety was found in those who had clinical BE, but no significant relationship was found between self-BE and mammographic imaging and BC anxiety. In another study, the BC anxiety level of those who performed self-BE was approximately three times higher than those who did not (27). In the study of Bostancı (23), female health professionals examining the relationship between BC fear and BC prevention behaviors, BCPBIS scores were found to be higher in those who had BE and those who had mammographic imaging. In the present study, while BC anxiety was higher in those with regular clinical BE, no significant relationship was found between self-BE and mammographic imaging and BC anxiety. High levels of anxiety toward BC positively affected participants' attitudes and behaviors toward BC prevention and mammographic imaging. In line with the findings of Bostancı (23), the BCPBIS score was higher in those with regular BE and those who had mammographic imaging. The results we obtained suggest that the importance of self-BE and mammographic imaging is not sufficiently known. Being examined by a physician may be perceived by patients as a more important or effective behavior than self-examination.

However, it was thought that the information given to the patients during the examination might increase the level of anxiety, as stated above. Concerns about BC should be addressed, and awareness should be raised about BC and screening methods.

The present study has some limitations. Since our study was conducted in a single center, the results obtained cannot be generalized beyond the study population. Also, women may have avoided giving honest answers to some questions for fear of being exposed to social pressure.

In conclusion, this study showed that worry levels about BC were generally found to be low. Knowing about BC and screening tests and having regular BE were factors that increased anxiety about BC. Those with higher anxiety about BC, those aged between 41 and 65 years, those who had previously received information about BC and screening tests, and those who had regular BE and had had mammographic imaging previously reported more positive behavior towards BC prevention. Although it will increase the level of concern, participation in BC screening programs should be increased by providing the necessary information about BC screening methods.

Ethics Committee Approval: The study was performed with the approval of the local ethics committee (date: 22.12.2021, no: 396 - Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee).

Informed Consent: After the participants were informed in detail about the study, their verbal and written consent was obtained.

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Authorship Contributions

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

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Original Article

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Impact of Radiotherapy Volumes on Late-Term Cosmetic Outcomes and Quality of Life in Patients With Unifocal and Multifocal/Multicentric Breast Cancer After Breast-Conserving Surgery

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ABSTRACT

Objective: Breast-conserving surgery (BCS) followed by radiotherapy (RT) is the standard treatment for early-stage breast cancer. The use of an additional RT dose (boost) to the tumour bed improves local control but may worsen quality of life (QOL) and cosmetic results. Multifocal/multicentric tumours (MMTs) pose a challenge as they require larger boost volumes. This study investigated the impact of RT volumes on late-term cosmetic outcomes and QOL in patients with unifocal and MMTs who underwent adjuvant RT after BCS.

Materials and Methods: Retrospective data of 367 patients who underwent BCS between 2012 and 2014 were reviewed. A cohort of 121 patients with at least six months of completed RT were prospectively included in the study. Cosmetic results were evaluated using a modified scoring system, and QOL was assessed using The European Cancer Treatment and Organization Committee tools.

Results: The results showed that the inclusion of regional lymphatics in the RT treatment field significantly affected QOL, particularly in terms of role functioning and social functioning. Higher boost volume ratios were associated with increased pain-related symptoms. However, the presence of MMTs did not significantly affect cosmetic outcomes compared to unifocal tumours.

Conclusion: The size of the boost and inclusion of regional lymphatics in RT significantly impact QOL in patients undergoing BCS. Tumour foci number does not affect cosmetic outcomes. These findings emphasize the need for careful consideration of RT volumes to minimize long-term adverse effects on QOL. Future prospective studies should evaluate early side effects and baseline QOL scores to provide a comprehensive assessment.

Keywords: Breast conserving surgery; cosmetic outcome; quality-of-life; radiotherapy

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Key Points

- Breast-conserving surgery followed by whole-breast radiotherapy ± boost is the current standard treatment for early-stage breast cancer.
- Regardless of the focality of the tumor, the expansion of the boost area and the addition of lymphatic areas to the treatment fields negatively affect the quality of life.
- The presence of multicentric/multifocal tumors does not affect cosmetic results.
- Using standard dosimetric parameters in treatment planning and recommending appropriate lifestyle changes after treatment will improve quality of life.

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Introduction

The current standard treatment for early-stage breast cancer is breast-conserving surgery (BCS) followed by whole-breast radiotherapy (RT) (1-3). The general approach is to give an additional dose (boost) to the tumour bed in high-risk cases, based on individual clinical and pathological features. Studies show that the use of boost increases local control at the expense of worsening quality of life (QOL) and cosmetic results (4). The most important factor that increases the negative effects on cosmetic results is large boost volumes. However, enlargement of the boost field is inevitable in breasts with multicentric/multifocal tumours (MMTs) that have undergone BCS. Thirteen to sixty percent of newly diagnosed breast cancers are MMTs (5). Although mastectomy has been performed in MMTs for many years, Hartsell et al. (6) published the rules used today regarding BCS in multicentric tumours in 1994. Thus, it has been included in the basic guideline that BCS can be applied in multicentric tumours if all clinical and radiological abnormal findings are cleared, a clean surgical margin is provided, and there is no widespread intraductal component. The results of the Alliance Z11102 study revealed that BCS and RT are possible in the presence of more than one tumour focus in the same breast, and that increased boost volume does not adversely affect long-term cosmetic results (7).

Based on these results, the aim of the present study was to investigate the effect of RT volumes on late-term cosmetic outcomes in patients with unifocal and MMTs who underwent adjuvant RT after BCS in a single center. In addition, since they have not been discussed in the literature, the effect of RT volumes and cosmetic results on QOL was examined using the European Cancer Treatment and Organization Committee (EORTC) QOL assessment tools (8).

Materials and Methods

For the study, the data of 367 patients aged 18 years and older who underwent BCS and were treated in a single centre between 2012 and 2014 were retrospectively reviewed. In those years, oncoplastic surgery had not entered routine surgical practice, so conventional BCS was performed. Computed tomography of thorax, abdomen and pelvis, plus bone scan or fluorodeoxyglucose-positron emission tomography was done for staging purposes. All patients with suspicion of multicentricity/multifocality after mammography+breast ultrasound were evaluated with magnetic resonance imaging.

Patients who received neoadjuvant systemic therapy, patients with another malignancy other than basal cell skin cancer, and patients who had undergone hypofractionated RT were excluded, in order to homogenize the group as much as possible. A final cohort of 121 patients who had completed RT and were followed up for at least six months (the minimum time required for late side effects of RT to appear) and met the study criteria were prospectively included in the study. When these patients came to routine outpatient clinic controls, they were asked to sign the study consent form, cosmetic result evaluations were made, and they were asked to fill in the questionnaire forms.

Clinical characteristics of patients (age, menopausal status), type of approach to the axilla during BCS (sentinel lymph node sampling, axillary dissection), pathological features of the disease (type, number and diameter of foci, stage, grade, receptor and human epidermal growth factor receptor two status, presence of lymphatic space invasion), adjuvant systemic treatments (chemotherapy, hormone therapy), RT fields (breast, breast+regional lymphatics), breast RT volumes (breast and additional dose volumes, in cc) were noted. The presence of tumours located less than 5 cm in the same quadrant was considered multifocal, and the presence of tumours located more than 5 cm in different quadrants was considered multicentric.

Radiotherapy: In all patients, breast (±lymphatic fields) irradiation was applied as 50 Gy in 25 fractions and 10 Gy in 5 fractions as an additional dose (boost) to the tumour bed. To use the standard tangential field-in-field technique and to ensure dose homogeneity, 6 and 18 MV photon beams were used. The Radiation Therapy Oncology Group breast contouring atlas was used as a guide for contouring RT volumes (9). Treatments were recorded according to reports 50 and 62 of the International Commission on Radiotherapy Units (10, 11).

Each patient with positive nodes on histopathological examination was evaluated for regional nodal irradiation. Isolated tumour cells, sub-micrometastases and micrometastases were not included in the regional irradiation field. pN2, pN3 disease and extra nodal involvement were certain indications for irradiation of supraclavicular nodes and level 1-2-3 axilla (supra+axilla). For internal quadrant tumours over 3 cm, the mammary interna was also included in the field (full regional lymphatics=RL). Supraclavicular region plus level 3 only irradiation was not performed in any patient.

Cosmetic Evaluation and Quality of Life Analysis: The patients were evaluated for cosmetic results at their first admission following the start of the study, and they were asked to complete breast cancer QOL questionnaires. For cosmetic scoring, the 4-point scoring system described by Winchester and Cox (12) in 1998 was modified and used. Accordingly, cosmetic results were recorded as "good" with little or no change in the treated breast compared to the untreated breast, recorded as "moderate" with clear difference between the treated and untreated breasts, and recorded as "poor" with significant functional and aesthetic sequelae in the treated breast.

The EORTC's 30-item general QOL scale (EORTC QLQ-C30) and the 23-item breast cancer-specific QOL scale (EORTC QOL-BR23) were used to evaluate and score QOL. EORTC-30 scoring includes global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) were evaluated. Functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss) were evaluated in the EORTC-23 module, which was prepared specifically for breast cancer. In scoring out of 100, higher scores for the functional scales indicates better results, and higher scores for the symptom scales indicates worse results.

This study was approved by the Bezmialem Vakif University Non-Invasive Clinical Research Ethics Committee (date: 04.04.2017, no: 7/63).

Statistical Analysis

While evaluating the findings of the study, the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Whether the scores obtained from each continuous variable were normally distributed was analysed using descriptive, graphical, and statistical methods. Kolmogorov-

Smirnov test was used to assess the normality of the scores obtained from a continuous variable with the statistical method. The reliability of the measurement tool in this study was tested with Cronbach's alpha coefficient used in internal consistency control. While evaluating the study data, comparisons between the two groups in quantitative data were made with the Mann-Whitney U test, as well as descriptive statistical methods (number, percentage, mean, median, standard deviation, etc.). Fisher's exact test was used for qualitative comparisons between groups. Survival calculations were made using the Kaplan-Meier analysis method. Results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$.

Results

The median time for enrollment in the study was 48 (12–75) months after the completion of RT. Patient and pathological tumour characteristics are summarized in Table 1.

In 24 patients with MMTs, the number of foci varied between 2-11 and tumour sizes between 3–40 mm. In 97 patients with unifocal tumours, the mean tumour size was 22.21 mm. While the median boost/breast volume ratios were 3.25% (0.24–29.11) in unifocal patients, this mean ratio was 5.52% (0.75–14.61) in multifocal/multicentric patients.

The surgical, systemic treatment and details of RT applied to the patients and the follow-up results are summarized in Table 2.

The median follow-up period was 99 (32–127) months. In the analyses performed, no statistically significant correlation was found between the presence of local/regional and systemic recurrence and the RT field, RT volume ratio, axillary surgery type and tumour focal status ($p>0.05$). Since the number of patients was not sufficient for survival analysis, the results were given as proportional difference, according to cut-off quarters. There was no difference in survival rates (Table 3).

Mean EORTC QLQ-C30 Scores of the Patients

The mean EORTC QLQ-C30 global health status score of the patients was 67.77. For functional scales, physical functioning average was 73.22, role functioning average was 88.84, emotional functioning average was 76.17, cognitive functioning average was 80.72, and social functioning average was 86.64 points. In terms of symptoms scales the average score for fatigue was 34.16, for nausea-vomiting was 9.37, for pain was 23.42, for dyspnoea was 15.43, for insomnia was 30.85, appetite loss was 11.02, constipation was 19.56, diarrhoea was 5.51, financial difficulties were 20.66. Cronbach's alpha (α) coefficients of the EORTC QLQ-C30 global health status, physical functioning scales and symptom scales were 0.96, 0.76 and 0.79, respectively. With these findings, the scale reliability level was found to be at an acceptable level (Table 4).

Mean EORTC QLQ-BR23 Scores of the Patients

The QLQ-BR23 functional scales of the patients, the mean body image, sexual functioning, sexual enjoyment, and future perspective averaged 84.16, 12.81, 40.83 and 58.95 points, respectively. The mean scores of the symptom scales were 27.94 for systemic therapy side effects, 21.14 for breast symptoms, 23.05 for arm symptoms and 22.04 for upset by hair loss. Cronbach's alpha (α) coefficients of the EORTC QLQ-BR23 functional scales and symptom scales were 0.60 and 0.76, respectively. With these findings, the scale reliability level was found to be at an acceptable level (Table 4).

Mean EORTC QLQ-C30 Scores of Patients Based on Tumour and RT Characteristics

There was no significant difference in EORTC QLQ-C30 scores according to tumour focus status, RT volume ratio and cosmetic results ($p>0.05$). When associated with the RT field, there was a significant difference in role functioning ($p = 0.017$), social functioning ($p = 0.002$) and financial difficulties ($p = 0.028$) scales. Patients irradiated to the breast+regional lymphatics (RL) field had lower role functioning

Table 1. Patient and pathological tumour characteristics (n = 121)

Variables	Categories	n (%)
Age, median (range)	All	52 (35–78)
Age group	≤50	55 (45.5)
	>50	66 (54.5)
Menopausal status	Premenopausal	50 (41.3)
	Postmenopausal	71 (58.7)
Tumour type	Ductal	94 (77.7)
	Other	27 (22.3)
Tumour focal status	Unifocal	97 (80.2)
	Multifocal/multicentric	24 (19.8)
pT Stage	pT1	56 (46.3)
	$pT2_{(n=63)}$-$3_{(n=2)}$	65 (53.7)
pN Stage	pN0	75 (62.0)
	pN1	30 (24.8)
	$pN2_{(n=12)}$-$3_{(n=4)}$	16 (13.2)
p Stage	p Stage-1	48 (39.7)
	p Stage-2	56 (46.3)
	p Stage-3	17 (14.0)
Tumour diameter (mm), median (range)	All	22 (1-80)
Grade	$I_{(n=20)}$-$II_{(n=51)}$	71 (58.7)
	III	50 (41.3)
LVI	Positive	32 (26.4)
	Negative	89 (73.6)
DCIS	Positive	97 (80.2)
	Negative	24 (19.8)
ER	Positive	103 (85.1)
	Negative	18 (14.9)
PR	Positive	94 (77.7)
	Negative	27 (22.3)
HER2	Positive	10 (8.3)
	Negative	111 (91.7)
Molecular subtype	Luminal	104 (86.0)
	Non-luminal	17 (14.0)

LVI: lymphovascular invasion; DCIS: ductal carcinoma *in situ*; ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor two

Table 2. The treatment information applied to the patients and the follow-up results (n = 121)

Variables	Categories	n (%)
Axillary surgery	SLNB	71 (58.7)
	Axillary dissection	50 (41.3)
Adjuvant chemotherapy	Yes	81 (66.9)
	No	40 (33.1)
Hormone therapy	Yes	104 (86.0)
	No	17 (14.0)
Radiotherapy field	Breast	82 (67.8)
	Breast+supra+axilla+MI	7 (5.8)
	Breast+supra+axilla	32 (26.4)
RT breast volume, median (IQR)	All	786 (511–1127)
RT boost volume, median (IQR)	All	25.9 (12.8–44.8)
RT volume ratio median (IQR)	All	3.3 (1.9–5.6)
Breast cosmetic outcome	Good	81 (66.9)
	Moderate	36 (29.8)
	Poor	4 (3.3)
Local regional recurrence	Yes	4 (3.3)
	No	117 (96.7)
Systemic recurrence	Yes	6 (5.0)
	No	115 (95.0)
Follow-up period (month), median (range)	All	99 (32–127)

RT: radiotherapy; IQR: interquartile range; SLNB: sentinel lymph node biopsy; MI: mammaria interna

and social functioning QOL, and more financial problems compared to patients irradiated to the breast only (Table 5).

When the RT volume ratio (RTVR) was classified according to the 75% quartile, the RTVR was 5% or less in 90 patients (74.4%) and above 5% in 31 patients (25.6%). Among breast+RL irradiated patients (n = 39), those with RTVR above 5% (n = 13) had significantly lower QOL scores related to role functioning (p = 0.12) and emotional functioning (p = 0.048) and significantly higher pain-related symptoms (p = 0.019). There was no significant difference in the QOL of the patients according to RTVR classification in multifocal tumours (p>0.05). However, in unifocal tumours, patients with RTVR above 5% (n = 22) had significantly higher pain-related symptoms (p = 0.018) (Table 6).

Mean QLQ-BR23 Scores of Patients According to Tumour and RT Characteristics

There was no significant difference in QLQ-BR23 scores according to RT treatment fields and RTVR (p>0.05). Compared to unifocal tumours, patients with MMTs had lower body image-related QOL (p = 0.021) and patients with moderate/poor cosmetic results had worse arm-related symptoms (p = 0.029) compared to patients with good breast cosmetic results after RT (Table 5).

Among breast+RL irradiated patients (n = 39), those with RTVR above 5% (n = 13) had significantly higher breast (p = 0.019) and arm (p = 0.028) related symptoms. In MMTs, no significant difference was found in the QLQ-BR23 scores of patients according to RTVR classification (p>0.05). However, in unifocal tumours, patients with RTVR above 5% had significantly worse scores for arm-related symptoms (p = 0.041) (Table 6).

Discussion and Conclusion

It is now generally accepted that BCS and RT can be performed in multifocal tumours, just as in unifocal tumours (13, 14). However, there is concern that increased boost volumes, especially in multifocal tumours, may worsen cosmetic results and have a negative impact

Table 3. Relapse outcomes in relation to study parameters

	All	Local regional recurrence (n = 4, 3.3%)		Systemic recurrence (n = 6, 5%)	
Variables	**n**	**n (%)**	***p****	**n (%)**	***p****
Radiotherapy field			0.999		0.084
Breast	82	3 (3.7)		2 (2.4)	
Breast+RL	39	1 (2.6)		4 (10.3)	
RT volume ratio			0.271		0.646
≤5%	90	2 (2.2)		4 (4.4)	
>5%	31	2 (6.5)		2 (6.5)	
Axillary surgery			0.642		0.690
SLNB	71	3 (4.2)		3 (4.2)	
Axillary dissection	50	1 (2.0)		3 (6.0)	
Tumour focal status			0.176		0.340
Unifocal	97	2 (2.1)		4 (4.1)	
Multifocal/multicentric	24	2 (8.3)		2 (8.3)	

p>0.05; ***:** Fisher's exact test; RT: radiotherapy; SLNB: sentinel lymph node biopsy; RL: regional lymphatics

Table 4. EORTC QLQ-C30 and EORTC QLQ-BR23 quality of life scores

QLQ-C30	No. of items	Mean ± SD	95% CI	α
Global health status/QOL	2	67.77±24.88	63.29–72.25	0.96
Functional scales				0.76
Physical functioning	5	73.22±20.20	69.59–76.86	
Role functioning	2	88.84±21.45	84.98–92.70	
Emotional functioning	4	76.17±24.42	71.78–80.57	
Cognitive functioning	2	80.72±20.86	76.96–84.47	
Social functioning	2	86.64±20.60	82.93–90.35	
Symptom scales				0.79
Fatigue	3	34.16±24.93	29.67–38.65	
Nausea & vomiting	2	9.37±20.29	5.72–13.02	
Pain	2	23.42±24.40	19.02–27.81	
Dyspnoea	1	15.43±25.11	10.91–19.95	
Insomnia	1	30.85±35.00	24.55–37.15	
Appetite loss	1	11.02±21.68	7.12–14.92	
Constipation	1	19.56±29.08	14.32–24.79	
Diarrhoea	1	5.51±15.72	2.68–8.34	
Financial problems	1	20.66±27.64	15.69–25.64	
QLQ-BR23	**No. of items**	**Mean ± SD**	**95% CI**	
Functional scales				0.60
Body image functioning	4	84.16±20.96	80.39–87.93	
Sexual functioning	2	12.81±18.73	9.44–16.18	
Sexual enjoyment	1	40.83±23.25	33.40–48.27	
Future health function	1	58.95±32.99	53.02–64.89	
Symptom scales				0.76
Systemic therapy side effects	7	27.94±20.04	24.33–31.55	
Breast symptoms	4	21.14±20.10	17.53–24.76	
Arm symptoms	3	23.05±22.69	18.97–27.13	
Hair loss	1	22.04±34.31	15.86–28.21	

SD: standard deviation; CI: confidence interval; α: Cronbach alpha coefficient; EORTC: European Cancer Treatment and Organization Committee

on QOL (15). In the recently published analysis of the ACOSOG Z11102 (Alliance) study, it was stated that RT after BCS did not adversely affect long-term cosmetic results in multifocal tumours, and poor cosmetic results were observed in 3.6% of patients (7). In the present study, the rate of poor cosmetic result was 3.3%.

In the ACOSOG Z11102 study, it was observed that absolute and relative boost volume did not significantly affect the overall cosmetic appearance, but worsening of breast QOL scores was observed with the expansion of absolute boost volume. In the Dutch cohort, larger tumour size, axillary lymph node dissection, locoregional RT, and boost to the tumour bed were associated with breast oedema (16). Breast oedema was independently associated with more breast pain and worse QOL, physical functioning and body image. Our study revealed that the number of foci and boost/breast volume ratio were not significant in terms of cosmetic outcomes in patients who underwent only breast RT after BCS. Pain and arm-related symptoms were more common in unifocal tumours with a relative boost volume above 5%. The main factor that negatively affected QOL was irradiation of regional lymphatics. Breast and arm symptoms were particularly adversely affected.

In the present study, we did not include patients who underwent different fractionation regimens to avoid bias in the evaluation of the results. However, there are studies in the literature that examined this issue. Jacobs et al. (17) examined the effects of different RT schemes on QOL in 1512 patients in five prospective cohorts and found no difference between RT schemes, with the exception of breast symptoms. Those who underwent intraoperative RT and external accelerated partial breast irradiation had fewer breast symptoms than those who underwent whole breast irradiation. In the 5-year QOL review of the START A and B trials using hypofractionated regimens, arm and shoulder pain affected one-third of patients. But this was related to previous surgery rather than RT (18). These results suggest that the extent of surgery (e.g., addition of lymphatic dissection) and the increase in irradiated volume (partial vs whole breast vs breast+boost)

Table 5. Mean EORTC QLQ-C30 and QLQ-BR23 scores according to tumour focus status, RT volume ratio and cosmetic results

	Tumour focal status				RT volume ratio			
	Unifocal	Multifocal			≤5%	>5%		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	68.4±25.0	65.3±24.9	-0.54	0.587	68.8±25.3	64.8±23.6	-0.96	0.339
Functional scales								
Physical functioning	74.4±20.1	68.3±20.4	-1.65	0.099	73.7±20.9	71.8±18.3	-0.83	0.404
Role functioning	90.2±19.2	83.3±28.7	-0.86	0.392	90.2±20.7	84.9±23.3	-1.19	0.233
Emotional functioning	77.0±24.3	72.9±25.3	-0.88	0.381	76.3±25.0	75.8±23.2	-0.26	0.797
Cognitive functioning	79.4±21.6	86.1±16.8	-1.42	0.155	80.7±21.2	80.6±20.2	-0.05	0.960
Social functioning	87.6±19.3	82.6±25.3	-0.50	0.618	86.9±21.3	86.0±18.8	-0.47	0.636
Symptom scales								
Fatigue	33.6±24.3	36.6±27.7	-0.31	0.753	33.8±24.5	35.1±26.5	-0.17	0.866
Nausea & vomiting	10.5±22.0	4.9±10.4	-0.72	0.471	8.7±19.4	11.3±22.9	-0.34	0.733
Pain	23.4±24.5	23.6±24.5	-0.17	0.863	20.0±20.0	33.3±32.5	-1.82	0.068
Dyspnoea	17.2±26.8	8.3±14.7	-1.22	0.222	14.8±25.0	17.2±25.6	-0.64	0.520
Insomnia	29.9±35.5	34.7±33.3	-0.90	0.367	30.7±34.7	31.2±36.4	-0.03	0.980
Appetite loss	11.0±22.4	11.1±18.8	-0.48	0.635	10.0±20.9	14.0±24.0	-0.84	0.399
Constipation	18.9±27.6	22.2±35.0	-0.03	0.979	18.9±29.2	21.5±29.2	-0.63	0.526
Diarrhoea	6.2±16.9	2.8±9.4	-0.82	0.413	5.6±16.8	5.4±12.5	-0.48	0.635
Financial problems	19.6±27.1	25.0±29.9	-0.86	0.391	19.3±26.0	24.7±32.2	-0.63	0.526
QLQ-BR23								
Functional scales								
Body image functioning	86.2±19.8	76.0±23.9	-2.30	0.021*	85.5±19.9	80.4±23.7	-0.88	0.379
Sexual functioning	12.7±19.5	13.2±15.5	-0.59	0.556	13.0±18.2	12.4±20.6	-0.51	0.610
Sexual enjoyment	40.6±25.0	41.7±15.4	-0.08	0.940	38.9±23.3	46.7±23.3	-1.10	0.273
Future health function	59.8±31.5	55.6±38.9	-0.31	0.754	59.3±33.4	58.1±32.2	-0.24	0.811
Symptom scales								
Systemic therapy side effects	26.4±20.1	34.3±19.1	-1.96	0.050	26.9±19.1	31.0±22.6	-0.75	0.454
Breast symptoms	20.4±19.8	24.3±21.3	-0.86	0.389	19.7±19.4	25.3±21.9	-1.19	0.233
Arm symptoms	22.6±22.8	25.0±22.8	-0.75	0.452	20.4±19.7	30.8±28.6	-1.65	0.098
Hair loss	19.6±32.2	31.9±41.1	-1.34	0.181	21.9±33.9	22.6±35.9	-0.02	0.981

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

	Cosmetic outcome				RT field			
	Good	Moderate/ Poor			Breast	Breast/RL		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	69.4±25.0	64.4±24.5	-1.14	0.254	69.7±24.7	63.7±25.1	-1.31	0.191
Functional scales								
Physical functioning	73.5±21.3	72.7±18.1	-0.75	0.456	74.6±20.2	70.4±20.2	-1.10	0.270
Role functioning	89.3±22.9	87.9±18.5	-1.02	0.306	91.7±18.9	82.9±25.2	-2.39	0.017*
Emotional functioning	77.8±23.8	72.9±25.7	-0.93	0.355	75.1±25.8	78.4±21.4	-0.33	0.746
Cognitive functioning	80.5±20.5	81.3±21.7	-0.37	0.711	79.9±21.6	82.5±19.5	-0.72	0.471
Social functioning	85.8±21.7	88.3±18.2	-0.53	0.596	90.4±17.6	78.6±24.2	-3.04	0.002*
Symptom scales								
Fatigue	33.3±26.1	35.8±22.6	-1.00	0.317	33.7±23.8	35.0±27.5	-0.06	0.955
Nausea & vomiting	9.7±21.9	8.8±16.9	-0.35	0.727	8.9±19.8	10.3±21.5	-0.24	0.812
Pain	21.4±23.0	27.5±26.8	-1.18	0.239	23.0±21.9	24.4±29.3	-0.48	0.633
Dyspnoea	13.6±24.0	19.2±27.1	-1.21	0.228	15.9±26.3	14.5±22.7	-0.03	0.979
Insomnia	28.0±33.9	36.7±36.8	-1.32	0.186	30.5±35.2	31.6±35.0	-0.25	0.806
Appetite loss	10.7±21.6	11.7±22.1	-0.23	0.819	10.2±21.4	12.8±22.4	-0.75	0.453
Constipation	17.7±28.4	23.3±30.4	-1.20	0.231	17.9±26.8	23.1±33.5	-0.65	0.514
Diarrhoea	4.9±14.1	6.7±18.8	-0.40	0.687	4.5±12.6	7.7±20.9	-0.55	0.581
Financial problems	18.1±25.3	25.8±31.6	-1.24	0.215	16.7±24.7	29.1±31.7	-2.20	0.028*
QLQ-BR23								
Functional scales								
Body image functioning	85.7±17.7	81.0±26.3	-0.13	0.898	85.6±19.2	81.2±24.2	-1.01	0.312
Sexual functioning	13.6±19.0	11.3±18.3	-0.74	0.457	13.0±18.9	12.4±18.6	-0.11	0.911
Sexual enjoyment	36.9±21.0	50.0±26.6	-1.55	0.122	39.3±20.4	44.4±29.6	-0.54	0.587
Future health function	60.5±33.0	55.8±33.2	-0.71	0.481	57.3±33.2	62.4±32.6	-0.83	0.407
Symptom scales								
Systemic therapy side effects	26.3±19.2	31.2±21.5	-1.14	0.256	27.1±19.7	29.7±20.9	-0.50	0.618
Breast symptoms	19.1±19.1	25.2±21.6	-1.59	0.111	20.5±19.9	22.4±20.8	-0.41	0.681
Arm symptoms	19.3±19.3	30.6±27.1	-2.19	0.029*	20.1±20.6	29.3±25.7	-1.94	0.053
Hair loss	19.8±32.0	26.7±38.6	-0.80	0.425	17.9±29.7	30.8±41.5	-1.31	0.191

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

Table 6. Mean EORTC QLQ-C30 and QLQ-BR23 scores in tumour focus status and RT field groups classified according to RT volume

	Unifocal				Multifocal			
	RTVR ≤5% (n = 75)	RTVR >5% (n = 22)			RTVR ≤5% (n = 15)	RTVR >5% (n = 9)		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	70.1±25.3	62.5±23.5	-1.45	0.147	62.2±25.6	70.4±24.3	-0.63	0.526
Functional scales								
Physical functioning	74.6±21.3	73.9±15.8	-0.67	0.505	69.3±19.0	66.7±23.6	0.00	1.000
Role functioning	90.7±19.6	88.6±18.1	-0.76	0.445	87.8±26.3	75.9±32.4	-0.76	0.449
Emotional functioning	77.6±25.0	75.0±21.8	-0.75	0.456	70.0±24.4	77.8±27.6	-0.94	0.347
Cognitive functioning	80.2±22.0	76.5±20.4	-1.01	0.312	83.3±16.7	90.7±16.9	-1.23	0.221
Social functioning	87.8±20.4	87.1±15.4	-0.64	0.524	82.2±25.6	83.3±26.4	-0.21	0.837
Symptom scales								
Fatigue	32.7±24.2	36.4±25.2	-0.57	0.569	39.3±26.5	32.1±30.7	-0.67	0.502
Nausea & vomiting	8.9±20.6	15.9±26.0	-1.40	0.161	7.8±12.4	0.0±0.0	-1.89	0.058
Pain	19.3±20.1	37.1±32.5	-2.37	0.018*	23.3±19.7	24.1±32.4	-0.50	0.617
Dyspnoea	16.4±26.5	19.7±28.5	-0.58	0.561	6.7±13.8	11.1±16.7	-0.72	0.475
Insomnia	28.4±34.1	34.8±40.5	-0.59	0.559	42.2±36.7	22.2±23.6	-1.30	0.195
Appetite loss	10.2±21.9	13.6±24.5	-0.63	0.529	8.9±15.3	14.8±24.2	-0.49	0.625
Constipation	17.8±26.5	22.7±31.5	-0.62	0.534	24.4±40.8	18.5±24.2	-0.17	0.863
Diarrhoea	6.2±17.9	6.1±13.2	-0.48	0.631	2.2±8.6	3.7±11.1	-0.37	0.709
Financial problems	17.3±25.9	27.3±30.2	-1.54	0.124	28.9±24.8	18.5±37.7	-1.39	0.164
QLQ-BR23								
Functional scales								
Body image functioning	87.8±19.0	80.7±21.7	-1.39	0.165	73.9±20.6	79.6±29.5	-1.09	0.275
Sexual functioning	12.2±18.7	14.4±22.6	-0.20	0.844	16.7±15.4	7.4±14.7	-1.50	0.134
Sexual enjoyment	38.9±25.4	45.8±24.8	-0.83	0.406	38.9±13.6	50.0±23.6	-0.88	0.378
Future health function	61.3±31.5	54.5±31.8	-0.92	0.357	48.9±41.5	66.7±33.3	-0.99	0.320
Symptom scales								
Systemic therapy side effects	24.8±18.9	31.8±23.3	-1.22	0.224	37.5±17.3	29.1±21.9	-1.05	0.294
Breast symptoms	18.4±19.3	26.9±20.7	-1.85	0.064	26.1±19.1	21.3±25.4	-0.94	0.349
Arm symptoms	19.9±20.8	31.8±27.1	-2.05	0.041*	23.0±13.6	28.4±33.8	-0.43	0.669
Hair loss	19.1±31.1	21.2±36.4	-0.06	0.955	35.6±44.5	25.9±36.4	-0.39	0.694

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

	Breast				Breast/RL			
	RTVR ≤5% (n = 64)	RTVR >5% (n = 18)			RTVR ≤5% (n = 26)	RTVR >5% (n = 13)		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	70.6±25.4	66.7±22.5	-0.77	0.445	64.4±25.2	62.2±25.8	-0.36	0.718
Functional scales								
Physical functioning	74.0±21.8	76.7±13.0	-0.18	0.856	73.1±18.8	65.1±22.6	-1.04	0.298
Role functioning	90.4±20.7	96.3±9.1	-0.99	0.322	89.7±21.1	69.2±27.9	-2.51	0.012*
Emotional functioning	73.6±26.5	80.6±23.2	-1.14	0.256	83.0±19.6	69.2±22.4	-1.98	0.048*
Cognitive functioning	79.2±22.2	82.4±19.4	-0.53	0.599	84.6±18.2	78.2±21.9	-0.82	0.411
Social functioning	89.3±18.9	94.4±11.4	-0.97	0.334	80.8±25.7	74.4±21.1	-1.15	0.250
Symptom scales								
Fatigue	35.8±24.6	26.5±19.5	-1.25	0.210	29.1±24.2	47.0±30.8	-1.81	0.070
Nausea & vomiting	9.6±21.4	6.5±13.0	-0.26	0.794	6.4±13.4	17.9±31.5	-0.86	0.393
Pain	22.1±20.6	25.9±26.3	-0.45	0.650	14.7±17.8	43.6±38.2	-2.35	0.019*
Dyspnoea	14.6±25.8	20.4±28.3	-1.05	0.295	15.4±23.5	12.8±21.7	-0.29	0.774
Insomnia	30.2±35.0	31.5±37.0	-0.14	0.885	32.1±34.6	30.8±37.2	-0.19	0.849
Appetite loss	10.4±22.1	9.3±19.2	-0.02	0.981	9.0±17.8	20.5±29.0	-1.23	0.220
Constipation	16.1±25.9	24.1±29.8	-1.20	0.232	25.6±35.7	17.9±29.2	-0.57	0.569
Diarrhoea	4.7±13.1	3.7±10.8	-0.18	0.859	7.7±23.7	7.7±14.6	-0.78	0.433
Financial problems	16.1±23.8	18.5±28.5	-0.21	0.834	26.9±29.8	33.3±36.0	-0.45	0.656
QLQ-BR23								
Functional scales								
Body image functioning	86.3±18.4	82.9±22.0	-0.32	0.750	83.3±23.3	76.9±26.4	-0.86	0.391
Sexual functioning	13.0±18.4	13.0±21.0	-0.24	0.811	12.8±17.8	11.5±20.8	-0.51	0.607
Sexual enjoyment	36.4±20.3	50.0±18.3	-1.45	0.146	45.8±30.5	41.7±31.9	-0.09	0.928
Future health function	55.7±33.1	63.0±34.1	-0.83	0.406	67.9±33.3	51.3±29.2	-1.72	0.085
Symptom scales								
Systemic therapy side effects	26.9±19.8	28.0±19.8	-0.34	0.731	26.9±17.6	35.2±26.3	-0.87	0.386
Breast symptoms	20.8±20.0	19.4±20.0	-0.38	0.707	17.0±17.9	33.3±22.6	-2.34	0.019*
Arm symptoms	19.8±20.1	21.0±22.8	-0.17	0.868	21.8±19.0	44.4±31.1	-2.19	0.028*
Hair loss	20.3±30.6	9.3±25.1	-1.71	0.087	25.6±41.4	41.0±41.2	-1.41	0.158

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

do not significantly change the cosmetic results, but negatively affect QOL scores. When combined with the data of the present study, we suggest that the factors that negatively affect QOL will be the same, regardless of which fractionation is used.

There are a few limitations of the present study. Since the main aim was to demonstrate the effects of RT, the negative cosmetic effect of surgery was not analysed separately. In any case, a study designed as post-surgery, pre-RT and post-RT would be the most accurate. Therefore, it is planned to add evaluation before RT in future patients. Second, the number of patients with MMTs was only 24 and statistical corrections were made to account for this. Nevertheless, as a result of our study, we believe that breast/boost ratios give an idea about how the tumour focal status may affect the cosmetic results. We hope that more effective and informative QOL studies will be performed with larger series. Another critical limitation is the retrospective nature of the treatment phase of the study. However, the fact that it was planned by the same team of physicians and physicists is an important factor that ensures standardisation in terms of patient treatment quality.

In summary, the major factors affecting QOL in patients receiving RT after BCS are the size of the boost fields and whether regional lymphatics are included in the treatment field. If the disease is multicentric it will not change the cosmetic effect of boost size. These factors inevitably affect long-term QOL. Therefore, standard dosimetry parameters should be determined in treatment planning and necessary lifestyle approaches should be recommended to improve QOL after treatment.

Ethics Committee Approval: This study was approved by the Bezmialem Vakif University Non-Invasive Clinical Research Ethics Committee (date: 04.04.2017, no: 7/63).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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The Mediating Role of Psychological Resilience in the Relationship Between Spiritual Well-Being and Supportive Care Needs in Women With Breast Cancer

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ABSTRACT

Objective: The aim of this study was to examine the mediating role of psychological resilience as part of the effect of spiritual well-being in the supportive care needs of women with breast cancer.

Materials and Methods: Cross-sectional design. The Connor-Davidson Resilience Scale Short Form, the Spiritual Well-Being Scale, and the Supportive Care Needs Survey Short Form were completed women with breast cancer treated at the oncology clinic of a university hospital. For the mediation model, Bootstrap methods with PROCESS Macro were used.

Results: The study was conducted with 126 breast cancer patients. A significant negative, moderate relationship was found between supportive care needs and psychological resilience (r = -0.560). There was a significant negative, but weak relationship between supportive care needs and spiritual well-being (r = -0.385). The indirect effect of spiritual well-being on supportive care needs was significant, thus, psychological resilience was shown to have a mediating effect on the relationship between spiritual well-being and supportive care needs [*b* = -0.370, 95% confidence interval (- 0.5568, -0.1911)].

Conclusion: Psychological resilience appears to contribute to a reduction in supportive care needs of breast cancer patients by affecting spiritual well-being.

Keywords: Breast cancer; psycho-oncology; resilience; spiritual well-being; supportive care

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Key Points

- Psychological resilience contributes to the reduction of supportive care needs of breast cancer patients by affecting spiritual well-being.

Introduction

Breast cancer is the most commonly diagnosed cancer among women globally, with an estimated 2.3 million new cases annually, making it the most prevalent type of cancer in women (1). Breast cancer is the most common type of cancer in women in Turkey with an incidence of 47.7/100.000 people (2). Despite the frequent diagnosis of breast cancer, mortality rates have either remained stable or decreased since the 1990s, due to advanced early detection and treatment methods (3). However, breast cancer patients experience varying degrees of psychological distress during both the pre-treatment and post-treatment processes (4). Spirituality, in this context, is an important source of strength and coping for cancer patients to adapt to their illness (5). Thus, the well-being of individuals in the physical, social, psychological, and spiritual domains can be improved through spiritual well-being. Spiritual well-being is defined as individuals' ability to establish relationships with others, discover the meaning of life and purpose of life, and believe in and relate to a higher power (6). There is a positive relationship between spiritual well-being and mental health during cancer (7). It has been determined that spiritual well-being has a positive effect on hope in women with cancer. This effect is explained through the mediating role of psychological resilience and perceived social support (8). It is known that spiritual well-being also enhances the quality of life (5, 9). High levels of spiritual well-being are associated with fewer physical symptoms and reduced levels of depression in patients (9). Furthermore, it has been reported that spirituality increases psychological resilience in breast cancer patients (10).

Resilience is the ability of an individual to maintain or improve psychological and physical well-being during or after exposure to stressful situations in life (11). For cancer patients, resilience refers to a dynamic process in which successful adaptation to cancer-related problems is developed (12). It has been shown that resilience may independently contribute to lower levels of depression in breast cancer patients (13). Breast cancer survivors tend to have higher levels

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of psychological resilience compared to healthy women (14). There is a strong negative correlation between the severity of symptoms experienced by breast cancer patients and resilience. In other words, as the severity of symptoms increases, resilience tends to decrease (13).

Advances in cancer treatment make supportive care an important part of excellence in oncological care due the an increase in recovery rates and quality of life (15). Supportive care encompasses interventions aimed at improving overall well-being, including physiological, psychological, social, and spiritual aspects, to enhance quality of life. It requires screening for specific symptoms and tools to allow patients to effectively report their outcomes. Supportive care should be evidence-based, highlighting the need for further research in this field (16). Psychological resilience is a personal characteristics that involves emotional strength, courage, and the ability to adapt, mitigating the negative impact of illness and supporting the process of adaptation. It includes characteristics such as perseverance, having a sense of purpose in life, and self-belief (14). Spiritual well-being, on the other hand, is a subjective experience of having a purpose in life, involving both emotional health and concerns about the meaning of life (17). The pursuit of spiritual well-being through the development of psychological resilience, which plays a key role in the process of coping with the disease, may reduce supportive care needs in patients. Determining the meaning of life is therefore believed to be a way that psychological resilience, a personal characteristics, might contribute to the relationship between spiritual well-being and the need for supporting care. There is no published research showing how psychological resilience affects this relationship. Therefore, the aim of this study was to clarify the connection between psychological resilience, spiritual well-being, and supportive care needs in female breast cancer patients.

The Hypothesis of the Research:

H_1: There is a difference between spiritual well-being, psychological resilience, and supportive care needs according to the sociodemographic and clinical characteristics of the patients.

H_2: Spiritual well-being will be positively associated with psychological resilience.

H_3: Psychological resilience being will be negatively associated with supportive care needs.

H_4: Spiritual well-being being will be negatively associated with supportive care needs.

H_5: Psychological resilience mediates the relationship between spiritual well-being and supportive care needs.

Materials and Methods

Study Design

This study was of cross-sectional design and was planned to determine the effects of psychological resilience and spiritual well-being on supportive care needs in breast cancer patients.

Setting and Participants

This study was carried out between July 27 and September 29, 2022, in the Adult Oncology Outpatient Clinic of a university hospital. The population of the study consisted of breast cancer patients who received care between the specified dates. The sample size calculation for the study was based on published evidence (18). In the sample analysis, the calculation was made based on the rate of need for supportive care in cancer patients (54%) by calculating the population from the unknown formula. Since the population was not known in sample size calculation in studies conducted on a single sample, = 126 people were calculated from the calculation formula (19). Therefore, 126 patients over 18 years of age, willing to participate in the study, diagnosed with breast cancer at least one month earlier, and without any psychiatric diagnosis, were included in the study.

Data Collection

Patients were first evaluated according to the inclusion criteria. Firstly, patient medical records were checked for previous diagnosis of psychiatric illness. Then, the patient was informed about the study, and written consent was obtained. The following tools were used to assess the patients (see below). The Sociodemographic and Clinical Characteristics Form was used to determine individual characteristics, The Connor-Davidson Psychological Resilience Short Form to evaluate psychological resilience, The Spiritual Well-Being Scale to evaluate spiritual well-being, and The Supportive Care Needs Scale Short Form to determine supportive care needs. Data were collected through face-to-face interviews before patients received chemotherapy.

Measurements

The Sociodemographic and Clinical Characteristics Form, Connor-Davidson Resilience Scale Short Form, Spiritual Well-Being Scale, and Supportive Care Needs Scale Short Form were used to collect data.

The Sociodemographic and Clinical Characteristics Form: This form was developed by researchers in line with the literature (13, 14). This form includes variables such as age, gender, marital status, number and status of having children, education level, time elapsed since diagnosis, diagnosis stage, and treatment.

The Connor-Davidson Resilience Scale Short Form (CD-RISC-10) was developed to determine the psychological resilience of individuals. It is a 5-point Likert-type scale with 25 items. Afterwards, as a result of the factor analysis for the scale items, short forms of the scale emerged, and reliability and validity studies of the 10-item short form were conducted. Kaya and Odacı (20) determined that the Turkish version of the scale was a valid and reliable measurement tool for determining psychological resilience. Responses on the scale are "Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree". The scale has a single-factor structure and the higher the score, the higher the psychological resilience (20). The Cronbach's alpha value of the scale was found to be 0.910.

The Spiritual Well-Being Scale (SWBS) was developed by Ekşi and Kardaş (21) to make sense of life in line with the values of individuals. It is a 5-point Likert-type, 29-item scale. Responses on the scale are "1 = Not applicable to me at all; 2 = Not applicable to me; 3 = Somewhat applicable to me; 4 = Quite applicable to me; 5 = Completely applicable to me". A minimum of 29 and a maximum of 145 points are obtained from the scale. The scale consists of three sub-dimensions: "Transcendence", "Harmony with Nature", and "Anomie (it as a situation that causes the loss of understanding that provides clues about the purpose and meaning of life on earth)". The higher the scores, the higher the spiritual well-being. Getting a high score on the scale sub-score items indicates that it has that sub-dimension feature The Cronbach alpha value of the scale was 0.886 (21). In this study, the Cronbach alpha value of the scale was found to be 0.680.

The Supportive Care Needs Scale Short Form (SCNS-SF), The Supportive Care Needs Scale Short Form was developed by the New South Wales Cancer Council Health Research and Psycho-Oncology Center and the Turkish adaptation was carried out by Özbayır et al. (22). The Turkish form consists of 29 items. Cronbach's alpha values were found to be between 0.83 and 0.95. The scale is rated on a 5-point Likert scale (1=not applicable, 2=satisfied, 3=low need, 4=moderate need, 5=high need). The score that can be obtained from the scale varies between 29 and 145 points. The Turkish form of the scale consists of four sub-dimensions: "Health Service and Informing", "Psychology", "Sexuality", and "Daily Life" (22). The Cronbach alpha value of the scale was 0.853.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0 (IBM Inc., Armonk, NY, USA) was used to analyze the data obtained from the research. The sociodemographic and clinical characteristics of the patients were described with frequency, percentage distribution, mean, and standard deviation values. To examine the effects of sociodemographic and clinical characteristics on the level of resilience, spiritual well-being, and supportive care needs, t-test, One-Way ANOVA for data that fit the normal distribution, and Kruskal-Wallis and Mann-Whitney U test for data that were non-parametric were used. A regression analysis based on the bootstrap method was performed to determine whether psychological resilience had a mediating role in the spiritual well-being and supportive care needs of women with breast cancer. P values less than 0.05 were considered statistically significant in all results (p<0.05).

Ethical Considerations

For the study, the approval of the Non-Clinical Interventional Research Ethics Committee of Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (dated: July 01, 2022, and numbered: 2022/372) was obtained. Permission was obtained from the hospital where the study was conducted (dated June 21, 2022, and numbered E.91953). Before the application, the patients were informed about the purpose of the study and how it would be conducted, and their written consent was obtained. Permission was obtained from the authors for the use of scales.

Results

The mean age of the participants was 55.6±21.5 years and 35.0% of the participants were over 60 years old. Of the women with breast cancer, 67.5% were married, 36.5% had two or fewer children and the same percentage had three children. In terms of education,18.3% were illiterate, while 58.7% graduated from schools below a high school degree. Most (61.9%) were not employed. Of the participants, 71.4% were diagnosed with breast cancer, 18.3% with operated breast cancer, and 10.3% with metastatic breast cancer. The time elapsed since diagnosis in 61.9% of the women was between 2 months and 1 year and more than three-quarters (75.4%) were receiving chemotherapy treatment (Table 1).

Breast cancer was found to significantly affect the psychological resilience levels of women in terms of age, marital status, number of children, education and employment status, medical diagnoses, duration and stage of diagnosis, and treatments (p<0.05). As age, number of children, duration of diagnosis, and stage of cancer increased, psychological resilience decreased. Married individuals, those with higher education levels, employed individuals, those diagnosed only with breast cancer, and those undergoing rational drug treatment were found to have higher levels of psychological resilience (Table 1).

The level of spiritual well-being was significantly affected by women's age, marital status, medical diagnoses, duration of diagnosis, and stage of diagnosis (all p<0.05). However, the number of children, education and employment status, and treatments were found to have no significant effect on spiritual well-being. It was found that as age, duration of diagnosis, and stage of cancer increased, spiritual well-being decreased. Married individuals and those diagnosed with operable breast cancer had higher levels of spiritual well-being (Table 1).

Supportive care needs were significantly affected by age, education, employment status, and cancer stage (all p<0.05), while there was no significant effect on supportive care needs in terms of marital status, number of children, medical diagnosis, duration of diagnosis, and treatment options. As age and cancer stage increased, the need for supportive care also increased. In contrast, as the level of education increased, the need for supportive care decreased. Retired people had a higher need for supportive care than employed and unemployed people (Table 1).

The correlation values between the supportive care needs and sub-dimensions of the participants and the sub-dimensions of psychological resilience and spiritual well-being are given in Table 2. There was a significant negative and moderate correlation between supportive care needs and resilience (r = -0.560). There was a very weak but significant positive relationship between sexuality and resilience, one of the sub-dimensions of supportive care needs, and a weak and moderately significant negative relationship between other sub-dimensions. There was a significant negative but weak correlation between supportive care needs and spiritual well-being (r = -0.385). There was no relationship between sexuality and spiritual well-being, which are both sub-dimensions of supportive care needs. There was a significant very weak positive relationship between health services and information and spiritual well-being, which are also sub-dimensions of supportive care needs, and a weak and negative correlation between the other sub-dimensions (Table 3).

In the analysis conducted to determine the mediating role of psychological resilience in the effect of the sub-dimensions of spiritual well-being and supportive care needs, it was found that in the sub-dimensions of psychology and daily life, spiritual well-being mediated the relationship between the sub-dimensions of transcendence, harmony with nature, and anomie. Psychological resilience was shown to mediate the relationship between the sexuality sub-dimension, which is included in the supportive care needs sub-dimensions, and the transcendence and anomie dimensions of spiritual well-being. Psychological resilience also had a mediating role in the relationship between transcendence and anomie, which are sub-dimensions of spiritual well-being, and supportive care needs (Table 4).

Discussion and Conclusion

The aim of this study was to determine the mediating role of psychological resilience on the effects of spiritual well-being and supportive care needs, and the findings obtained explained the contribution of resilience to spiritual well-being and the effect of supportive care needs.

Spiritual care has an important place in health services for patients who are faced with cancer (23). Studies have focused on the quality

Table 1. Characteristics of the patients and scale score means (n = 126)

Variables	n (%)	CD-RISC-10 (Mean ± SD)	*p*	SWBS (Mean ± SD)	*p*	SCNS-SF (Mean ± SD)	*p*
Age (Mean ± SD) 55.6±21.5							
<50	40 (31.7)	34.5±6.0	26.135* **<0.001**	84.6±10.1	3.171*** **0.045**	77.7±13.4	3.765*** **0.026**
50–60	42 (33.3)	30.0±7.1		82.7±8.9		81.9±12.1	
>60	44 (35.0)	25.2±6.5		79.5±8.9		84.5±8.7	
Martial status							
Married	85 (67.5)	31.5±6.8	945.500** **<0.001**	83.7±9.3	2.658**** **0.009**	81.3±12.7	-0.280**** 0.780
Single	41 (32.5)	25.7±7.2		79.0±9.1		81.9±9.6	
Number of children (n = 125)							
Two and under	46 (36.5)	32.4±6.1	4.877*** **0.003**	81.9±10.1	0.530*** 0.662	77.9±12.4	2.284*** 0.082
Three	46 (36.5)	29.3±8.0		83.4±10.2		83.7±13.4	
Over three	33 (26.2)	26.3±6.9		81.0±7.7		83.1±6.6	
Education							
Illiterate	23 (18.3)	22.8±4.6	19.454*** **<0.001**	79.4±8.5	1.334*** 0.267	85.7±8.6	11.457*** **<0.001**
Below high school	74 (58.7)	30.0±7.1		82.5±9.2		83.4±11.1	
High school and above	29 (23.0)	34.1±6.2		83.6±10.8		73.1±11.9	
Working							
Employed	21 (16.7)	34.8±6.9	10.992*** **<0.001**	84.1±12.2	1.930*** 0.149	72.3±12.6	8.632*** **<0.001**
Unemployed	78 (61.9)	29.7±7.1		82.7±9.2		83.0±11.5	
Retired	27 (21.4)	25.0±6.0		79.1±7.5		84.1±8.5	
Medical diagnosis							
Breast cancer	90 (71.4)	31.2±6.9	11.160*** **<0.001**	82.9±9.5	6.145*** **0.003**	80.1±12.4	2.436*** 0.092
Operated breast cancer	23 (18.3)	27.6±7.1		84.0±6.9		83.5±10.4	
Metastatic breast cancer	13 (10.3)	22.0±6.5		73.8±9.9		87.1±7.4	
Diagnosis time							
2 months- 1 year	78 (61.9)	32.0±6.7	982.000** **<0.001**	85.0±8.9	4.642**** **<0.001**	80.5±11.6	-1.155**** 0.250
More than 1 year-2 years	48 (38.1)	25.7±6.8		77.5±8.6		83.0±12.0	
Diagnosis stage							
Stage 1	9 (7.1)	35.8±3.5	19.830*** **<0.001**	91.1±6.2	9.567*** **<0.001**	69.5±7.8	4.566*** **0.002**
Stage 2	40 (31.7)	34.5±6.0		85.5±9.5		78.8±10.2	
Stage 3	29 (23.0)	30.0±6.5		82.4±8.6		82.8±15.8	
Stage 4	30 (23.8)	23.5±5.4		75.0±8.0		85.5±8.8	
Unknown	18 (14.3)	25.3±5.8		81.8±6.8		84.6±8.6	
Treatment							
Chemotherapy	95 (75.4)	30.1±7.5	0.550*** **0.699**	82.4±9.8	2.079*** 0.088	81.2±12.0	1.640*** 0.169
Chemotherapy + surgery	20 (15.9)	27.6±6.9		83.2±6.6		82.6±9.5	
Chemotherapy + hormone therapy	6 (4.8)	28.8±7.6		73.0±10.5		83.3±11.2	
Chemotherapy + surgery + hormone therapy	3 (2.4)	28.0±10.5		89.3±7.5		89.6±16.1	
Smart drug use	2 (1.6)	31.0±9.8		77.5±3.5		63.5±4.9	

n: number; %: percentage; SD: standard deviation; CD-RISC-10: Connor-Davidson Resilience Scale Short Form; SWBS: Spiritual Well-Being Scale; SCNS-SF: Supportive Care Needs Scale Short Form; *KW: Kruskal-Wallis; **Mann-Whitney U; ***One-Way ANOVA; ****t-test

of life of spiritual well-being in cancer patients, and its positive effect on quality of life has been reported (5, 9). In addition, it has been stated that spiritual well-being reduces the symptoms of depression in patients (24). There are no studies into the effect of spiritual well-being on supportive care needs. The present study showed that, as the level of spiritual well-being increased, the supportive care needs of breast cancer patients decreased. Spiritual well-being may have a reducing effect on the supportive care needs of patients or given the same level of supportive care needs there may be better outcomes for those with stronger spiritiual well-being.

Spirituality is a characterisitic that improves quality of life by supporting adaptation and resilience in cancer patients. Supporting spirituality improves the ability to cope with negative circumstances,

Table 2. Pearson correlations between all variables (n = 126)

	1	2	3	4	5	6	7	8	9	10
1. Psychological resilience (CD-RISC-10)	1									
2. Transcendence (SWBS)	0.247**	1								
3. Harmony with nature (SWBS)	0.134	0.464**	1							
4. Anomie (SWBS)	- 0.666**	- 0.193*	- 0.233**	1						
5. Spiritual well-being (SWBS)	0.587**	0.730**	0.568**	-0.795**	1					
6. Healthcare service and informing (SCNS-SF)	-0.314**	-0.200*	-0.172	-0.269**	0.205*	1				
7. Psychology (SCNS-SF)	-0.573**	-0.051	-0.083	0.528**	-0.386**	0.317**	1			
8. Sexuality (SCNS-SF)	0.201*	-0.069	-0.046	-0.276*	0.136	0.123	0.006	1		
9. Daily life (SCNS-SF)	-0.628**	0.059	-0.022	0.613**	-0.374**	0.262**	0.586**	-0.264**	1	
10. Supportive care needs (SCNS-SF)	-0.560**	-0.113	-0.136	0.462**	-0.385**	0.719**	0.804**	0.273**	654**	1

CD-RISC-10: 10-item Connor–Davidson Resilience Scale; SWBS: Spiritual Well-Being Scale; SCNS-SF: Short-Form Supportive Care Needs Survey Questionnaire; *: $p<0.05$, **: $p<0.01$

Table 3. Regression analysis results for mediation test (n = 126)

		M (psychological resilience)			Y (supportive care needs)	
Prediction variables		**b**	**S.E.**		**b**	**S.E.**
X (spiritual well-being)	α	0.460***	0.056	c′	- 0.106	0.114
M (psychological resilience)	-			b	- 0.805***	0.145
Constant	i_M=-8.160, 4.708			i_Y = 114.136***, 7.726		
	R^2 = 0.345			R^2 = 0.317		
	F(1;124) = 65.35; $p<0.001$			F(2;123) = 28.66; $p<0.001$		

*$p<0.05$; **$p<0.01$; ***$p<0.001$; S.E.: standard error; b: unstandardized beta coefficients

such as cancer (25). It was reported that the psychological resilience of patients with advanced gastrointestinal cancer increased with increased spiritual well-being (26). Psychological resilience can be improved by supporting it with spirituality (25). In another study conducted with cancer patients, it was stated that as spiritual well-being increased, psychological resilience also increased (27). A strong correlation was found between religious beliefs and psychological resilience in patients with breast cancer (28). The present study was compatible with these earlier reports and a significant effect of spiritual well-being on resilience was found. As spiritual well-being increased, psychological resilience may also increase in female breast cancer patients.

For cancer patients, psychological resilience is a dynamic process that involves confronting the evolving challenges associated with the cancer experience (29). Nursing interventions for these challenges can facilitate the process (12). In other words, the aim of improving psychological resilience is to increase quality of life rather than survival. Supportive care needs were found to be less in patients with higher personal flexibility levels. Unsupported care needs decreased as psychological resilience increased in breast cancer patients (29). In the present study, greateer psychological resilience appered to reduce supportive care needs. Thus, interventions that increase psychological resilience may reduce supportive care needs.

The most unsupported care need in cancer patients is in the field of psychological needs (29). It has been shown that spiritual well-being has a positive effect on hope through the mediating role of psychological resilience and social support in female cancer patients (8). In a study examining the effect of psychological resilience on the fear of cancer through spiritual well-being, it was concluded that stronger psychological resilience reduced the fear of cancer (30). In the present study, greater psychological resilience had a reducing effect on all aspects of spiritual well-being, especially on the psychology and daily life of supportive care needs. Therefore, interventions that increase psychological resilience can contribute to spiritual well-being and reduce the psychological care needs of breast cancer patients, simproving their anxiety, worry, future uncertainty, and fear of death. It may also contribute to spiritual well-being in the daily care needs when dealing with pain, weakness, well-being, and doing work. The present study found that spiritual well-being was not affected by the clinical test results, treatment options, health workers, and psychological resilience in the hospital processes, which are among health services and information care of supportive care needs.

Table 4. Indirect effects of spiritual well-being on the sub-dimensions of supportive care needs through psychological resilience (n = 126)

	Point estimate	S.E.	BCa 95% CI	
			Lower	Upper
Health service and informing				
Transcendence	-0.010	0.133	-0.1104	0.1242
Harmony with nature	-0.093	0.336	-0.1019	0.0646
Anomie	-0.020	0.120	-0.1570	0.1613
Psychological resilience	-0.1681	0.073	-0.1630	0.0080
Psychology				
Transcendence	**0.534*****	0.122	0.0819	0.3078
Harmony with nature	**0.658***	0.325	0.0028	0.1303
Anomie	**0.519*****	0.108	-0.3937	-0.1457
Psychological resilience	**-0.381*****	0.065	-0.2484	-0.1058
Sexuality				
Transcendence	**-0.263****	0.092	-0.1725	-0.0321
Harmony with nature	-0.401	0.236	-0.0980	0.0100
Anomie	**-0.265****	0.082	0.0572	0.2413
Psychological resilience	0.090	0.053	-0.0069	0.0952
Daily life				
Transcendence	**0.589*****	0.086	0.1493	0.2947
Harmony with nature	**0.707****	0.247	0.0195	0.1253
Anomie	**0.571*****	0.076	-0.3806	-0.2247
Psychological resilience	**-0.346*****	0.048	-0.2189	-0.1030
Supportive care needs				
Transcendence	**0.851****	0.277	0.1084	0.5253
Harmony with nature	0.871	0.720	-0.0717	0.2435
Anomie	**0.805****	0.249	-0.7050	-0.1587

Specific and total indirect effects: 5000 bootstrap samples; BCa bias-corrected and accelerated

Significant indirect effects, i.e., zero is not included in the confidence intervals (*p<0.05, **p<0.01, ***p<0.001); CI: confidence interval

Finally, spiritual well-being was shown to positively affect psychological resilience in breast cancer patients, and psychological resilience and spirituality also reduced supportive care needs. Thus psychological resilience appears to contribute to reducing the supportive care needs of patients with breast cancer, by affecting spiritual well-being.

Study Limitations

This study has some limitations. First, due to the cross-sectional design of the study, no change over time could be observed in the relationship between clinical characteristics, spiritual well-being, psychological resilience, and supportive care needs of female breast cancer patients. Second, although this study was conducted in groups specific to breast cancer patients, it included a small sample group. Since breast cancer patients were female in the participant group, no results could be obtained for male patients. Third, the results of the study explained approximately 32% of the effect of spiritual well-being through psychological resilience on supportive care needs. For the unexplained 68%, models with different variables should be created. These limitations should be taken into account when generalizing the findings of the study.

Ethics Committee Approval: For the study, the approval of the Non-Clinical Interventional Research Ethics Committee of Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (dated: July 01, 2022, and numbered: 2022/372) was obtained.

Informed Consent: The patient was informed about the study, and written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.S.E., H.N.E.; Concept: Ö.S.E.; Design: Ö.S.E.; Data Collection or Processing: Ö.S.E., H.N.E.; Analysis or Interpretation: Ö.S.E.; Literature Search: Ö.S.E., H.N.E.; Writing: Ö.S.E., H.N.E.

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Original Article

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Is Breast Imaging in Male Patients With Benign Lumps Necessary? A Retrospective Study to Assess Concordance Between Clinical Diagnosis and Imaging Findings

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ABSTRACT

Objective: Breast imaging for male patients is a controversial topic due to the high prevalence of gynecomastia compared to male breast cancer. Worldwide, men are undergoing more breast imaging despite the low incidence of male breast cancer. Gynecomastia is a benign condition, but the anxiety it causes and unnecessary medical costs are still high.

Materials and Methods: In accordance with Royal College of Radiology guidelines, a retrospective study was performed in two cycles to determine if mammography or ultrasound should be included in the workup of male patients who were referred to a breast care unit for a lump that was deemed benign by doctors.

Results: There was 100% concordance between clinical diagnosis and imaging findings.

Conclusion: In this population imaging was not necessary in cases of probable gynecomastia and benign conditions found during a clinical assessment. Standardised patient assessment methods can improve care and ensure accurate evaluation.

Keywords: Breast imaging; gynaecomastia; male breast

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Key Points

- Breast imaging for men is controversial due to the high prevalence of gynecomastia compared to male breast cancer.
- Most male breast lumps are diagnosed as gynecomastia, but other benign conditions include lipoma, epidermal inclusion cyst, breast hematoma, fat necrosis, and abscess.
- Malignancy was detected in only 1.65% of cases in the first cycle, and 0.8% of cases in the second cycle, with breast cancer in men being relatively rare.
- Gynecomastia is a benign condition that can affect between 32% and 66% of men in their lifetime.
- Comprehensive evaluation of male breast symptoms requires thorough history and examination to avoid unnecessary imaging and patient anxiety.

Introduction

In the last few years, the number of male patients who complain of breast lumps and discomfort has increased significantly (1). Recent epidemiological studies show that in the last 20 years the number of men who complain about breast discomfort has increased from 0.8% up to 2.4% (2). About 57% of men older than 44 years have a palpable breast (3).

The most frequent male breast condition is gynecomastia, a benign growth of glandular tissue, followed by lipomas and epidermal inclusion cysts (4). Men can also develop angiolipoma, schwannoma, and intraductal papillomas, which are benign breast diseases (5). In addition to these pathologies, several benign non-cancerous diseases can affect the male breast, including secondary syphilis, nodular fasciitis, hematoma, fat necrosis, subareolar abscess, venous malformation, intramammary lymph node, and diabetic mastopathy (6).

The use of breast imaging in male patients has become a topic for discussion due to the rising prevalence of male breast complaints (7, 8). Numerous studies have demonstrated that the majority of male breast problems can be diagnosed just by clinical examination (9). However, some scientists have argued that imaging may be required

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when the clinical diagnosis is ambiguous or the patient is at a high risk of breast cancer (3).

"Triple assessment", which combines clinical evaluation, imaging, and needle biopsy has been used for diagnostic evaluation in men with breast complaints (10).

The tests conducted in each situation depend on the patient's age, clinical results, and symptoms (10). The first-line imaging technique for patients under 40 years old is ultrasound (US) (11). Patients between the ages of 35 and 39 who have clinically suspicious findings (P4 or P5) and/or ultrasonically suspicious findings (U4 or U5) should get a mammogram, ideally before getting a biopsy (3). When a palpable mass on mammography is hidden or only partially imaged, targeted US is necessary (11). US is reported to have higher sensitivity and specificity than mammography and is therefore the most sensitive for male breast cancer (11). For suspected or uncertain masses, a biopsy is required and is frequently attainable with US guidance (12).

Objective

This study sought to determine whether mammography or US should be included in the diagnostic workup of men with gynecomastia referred with a breast lump to the breast care center. The study also aimed to determine whether men referred because of a breast lump met the guidelines of the Royal College of Radiology (RCR), and the Association of Breast Surgery (ABS) (13, 14).

Standards

According to guidelines developed by the RCR and the ABS, mammography and/or ultrasonography are recommended in cases of unaccounted for or suspicious unilateral breast growth (P4 or 5) of the male breast. Imaging may be used in cases where there is clinical uncertainty (P3) regarding the difference between gynecomastia or fatty breast enlargement.

In males younger than 50 years, the preferred method of imaging is US, whereas bilateral mammography or US is recommended in those older than 50. Following imaging, needle core biopsy should be performed in cases where radiological findings are uncertain or suspicious (P3–5 and or R3–5), or when indeterminate clinical findings (P3) are not sufficiently explained by benign imaging findings (13-15).

Materials and Methods

A retrospective audit was conducted involving male patients who attended the two-week wait clinic in the Breast Care Unit at our institute between January 2019 and October 2019 (n = 303) for the first cycle, and between December 2021 and June 2022 (n = 117) for the second cycle.

The second audit cycle was conducted following the presentation and awareness of audit findings. The 'rolled-nipple' technique, which is a well-known method, can be used to visualize subareolar ducts and was recommended for use in evaluation in suspected cases of gynaecomastia. Excluded cases included axillary lump, post-surgery surveillance cases, and paediatric cases. Depending on the age of the patient, radiological imaging was done either as mammography, or US. The P (Palpable) value grade given by a breast surgeon was recorded, as well as the M/U/R (Mammography/US/Radiological) values reported by radiologists. The pathological results of biopsies have also been recorded. The concordance between radiological and clinical diagnoses was assessed.

Results

In the first cycle (n = 303), the majority of cases (75.6%, n = 229) were diagnosed with gynaecomastia followed by lipoma 7.6% (n = 23), and normal breast tissue 7.6% (n = 23). The remaining cases were: abscess 1.0% (n = 3); sebaceous cyst 1.0% (n = 3); fat necrosis 0.3% (n = 1); lipoma with gynecomastia 1.0% (n = 3); lymph node 1.0% (n = 3); resolving bruise 0.3% (n = 1); pseudogynaecomastia 1.32% (n = 4); haematoma 0.6% (n = 2); oedematous breast 0.3% (n = 1); and cyst 0.6% (n = 2). Malignancy was detected in only 1.65% of cases (n = 5), of which two were incidentally detected on routine computed tomography (CT). Biopsy was performed in a total of eight patients (2.6%), which confirmed five cases of malignancy, four of which were invasive breast carcinomas, and one Hodgkin's lymphoma. The other three biopsied patients were histologically proven as gynaecomastia.

The second cycle (n = 117), following presentation of the audit findings and recommended practice change, showed a decline in the proportion of gynaecomastia cases to 58.1% (n = 68) and a rise in lipoma cases to 15.4% (n = 18) compared to the first cycle. The remaining cases were: abscess 1.7% (n = 2); sebaceous cyst 2.6% (n = 3), epidermoid cyst 1.7% (n = 2), lymph node 0.85% (n = 1), pseudogynaecomastia 1.7% (n = 2), haematoma 3.4% (n = 4), oedematous breast 0.85% (n = 1), simple cyst 1.7% (n = 2) and normal breast tissue 11.1% (n = 13). Malignancy was detected in only 0.85% of cases (n = 1), which was proven to be papillary ductal carcinoma *in situ* (DCIS) with no invasive disease. Biopsy was performed in four cases (3.4%) and only one was proven to be malignant. The P grading for the malignant case was P5. Among the other three, two were histologically proven as epidermoid cyst and one gynaecomastia.

In the first cycle, four of the malignant cases were in the age group of 60–80 years and one between 40–50 years, the latter being a case of Hodgkin's lymphoma. The one malignant case in the second cycle was in the age group of >90 years.

We observed 100% concordance in both audit cycles between clinical diagnosis and imaging results when comparing the P grading given by clinicians for benign lesions as P2 and were concordantly found to be benign on imaging with R grading of R2. Thirty-seven (31.6%) patients were graded as P3 by the clinicians in the second cycle. Of these, only three were graded as R3 on imaging and underwent a biopsy, although none proved to be malignant and demonstrated results of benign findings. In contrast in the first cycle, ten (3%) patients were graded as P3 by the clinicians but only one was graded as R3 and underwent a biopsy which proved to be non-malignant (Table 1).

In the first cycle, 45% of patients had a mammogram, 32% had US only, and 23% had both imaging modalities. In the second cycle, 31% of patients had a mammogram, 33% had US only, and 36% had both imaging modalities. The *p*-value 0.0001 indicated that, significantly,

Table 1. Comparison of clinical grading (P) given by clinicians between the first and second audit cycle

P grading	P1/2	P3	P4/5	Biopsy
First cycle	288 (95%)	10 (3%)	5 (2%)	14 (4.2%)
Second cycle	79 (67.5%)	37 (31.6%)	1 (0.85%)	4 (3.4%)

despite the change in proportion of patients who is undergoing different imaging modalities, consistently similar results were observed in both the audit cycles as mentioned in Table 2.

Following the second cycle, there was a decline in P1/P2 referrals (-29.5%) and a steep rise in P3 grading referrals (+28.6%), increasing from 3% to 31.6%. However, only 8% of the P3 referrals were radiologically considered indeterminate/suspicious. Further, the p-value of 0.001 suggested similar proportion to the first cycle as mentioned in Table 3.

Discussion and Conclusion

Seventy five percent of cases in the first cycle were diagnosed with gynaecomastia, followed by smaller proportions for lipoma and normal breast tissue. Malignancy was detected in only five of 303 cases, and among the five malignant cases, two were detected on prior CT as incidental findings. The second cycle showed a decline in the proportion of gynaecomastia cases and a rise in lipoma cases compared to the first cycle, although the gynaecomastia cases outnumbered the lipoma cases by almost 4:1. Malignancy was detected in only 0.85% of cases, which was proven to be papillary DCIS with no invasive disease. Results show that breast cancer in men is less common than in women (7, 16).

Breast cancer in men is relatively rare, affecting only around 1% and not being included in the top 20 cancers (16). Gynecomastia, on the other hand, is a condition that can affect up to two-thirds of men in their lifetime (17). It is therefore important to distinguish this group from other patients with lower malignant conditions (18).

Table 2. Chi-square test through SPSS. Referral patterns * change in imaging modality chi-square tests

	value	df	asymptotic significance (2-sided)
Pearson chi-square	218.900[a]	99	0.000
Likelihood ratio	148.653	99	0.001
Linear-by-Linear association	45.587	1	0.000
N of valid cases	100		

[a]: 118 cells (98.3%) have expected count less than 5. The minimum expected count is 0.02

Table 3. Chi-square test through SPSS. Referral patterns * radiological assessment chi-square tests

	value	df	asymptotic significance (2-sided)
Pearson chi-square	218.900[a]	99	0.000
Likelihood ratio	148.653	99	0.001
Linear-by-Linear association	45.587	1	0.000
N of valid cases	100		

[a]: 118 cells (98.3%) have expected count less than 5. The minimum expected count is 0.02

A soft, tender, mobile subareolar mass is the classic presentation of gynecomastia (Figure 1-4) (19). A mass outside of the subareolar region is not considered to be gynecomastia (20). Moreover, gynecomastia does not increase the risk of developing male breast carcinoma (16). Patients with palpable breast tissues who are asymptomatic need only to undergo a thorough physical exam and a detailed history (8). For patients with symptoms of gynecomastia, laboratory blood tests may be performed to determine the underlying cause (21). It will reduce unnecessary anxiety among patients (7, 8). This will also improve the cost-effectiveness of the imaging department (7).

The prevalence of gynecomastia increases with age (21). Most patients presenting with breast symptoms were 51–70 years in the present study (22). The prevalence of gynecomastia is known to increase with age, and studies have shown that the majority of patients presenting with breast symptoms are between the ages of 51 to 70. A study conducted by Johnson and Murad (20) found a similar prevalence of 57% of gynecomastia in men over the age of 44. These findings indicate that the risk for developing gynecomastia is higher with age, and that

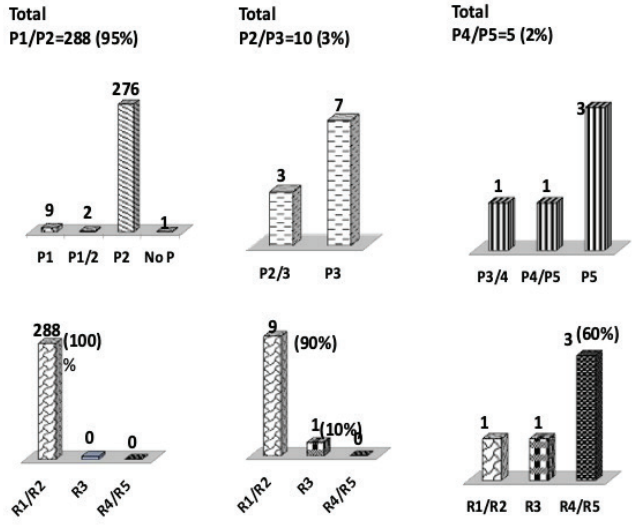

Figure 1. Evaluating concordance between clinical grading (P) and radiological grading (R) in the first audit cycle

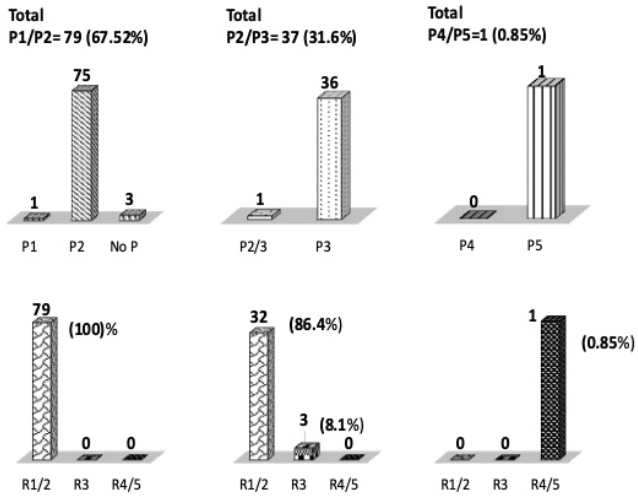

Figure 2. Evaluating concordance between clinical grading (P) and radiological grading (R) in the second audit cycle

healthcare professionals should be aware of that when evaluating males with breast symptoms (18). In addition, it has been reported that breast tissue may be palpable in 30% or more of the middle-aged adult male population, which increased to 60% or more by the seventh decade (23). In addition, the study found that gynecomastia is the leading cause of breast tissue enlargement in men older than 50 years (18). These findings emphasize the importance of taking patient age into account when evaluating males with breast symptoms (17).

Recent studies suggest that certain medications and medical conditions may also increase the risk for developing gynecomastia (20). Gynecomastia has been linked to obesity, liver disease and testicular tumours (17, 19). Some medications, including spironolactone and cimetidine, as well as some antipsychotics have been associated with the development of gynecomastia (24, 25). A comprehensive evaluation of males with breast symptoms should include a detailed medical history and physical examination that can determine the cause (26).

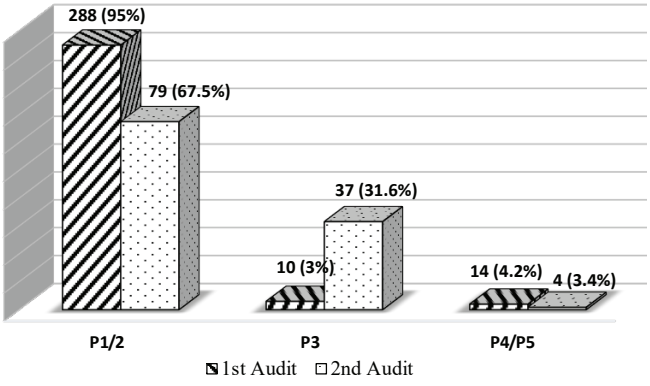

Figure 3. Comparison of clinical grading (P) given by clinicians between the first and second audit cycles

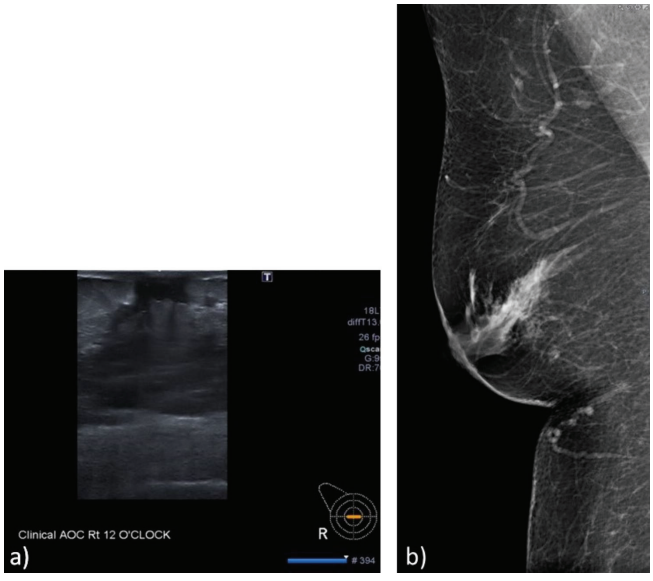

Figure 4. Gynaecomastia. A 56-year-old male patient presented with a three-week history of painful swelling in his right breast. The patient had a known history of excessive alcohol intake. a) On the ultrasound, the breast tissue appears to be hypoechoic, with scattered glandular tissue and fibrous strands. b) The mammogram shows "flame-like" features emanating from the right nipple at the 12 o'clock position, consistent with gynaecomastia. No evidence of suspicious microcalcifications or masses

Lipoma, epidermal inclusion cyst, breast hematoma, fat necrosis, diabetic mastopathy, intramammary lymph nodes, and subareolar abscess are some of the other benign and rare conditions that may be encountered in the male breast (27). These conditions present with varying clinical characteristics, and a proper clinical history is necessary to establish the correct diagnosis (1). In our study these pathologies accounted cumulatively for 15.8% in the first cycle and 33.7% in the second cycle. Sebaceous cysts or epidermal inclusion cysts are benign intradermal lesions that present as a firm non-tender lump (Figure 5) (28). Lipomas are benign mesenchymal lesions made up of mature adipose tissues (Figure 6) (29). They typically appear as a soft, mobile and painless lump that can be palpated in the breast (30). This is the second most common cause for male breast lumps after gynaecomastia (29, 30). Our study found 7.5% in first cycle and 13.3% in second

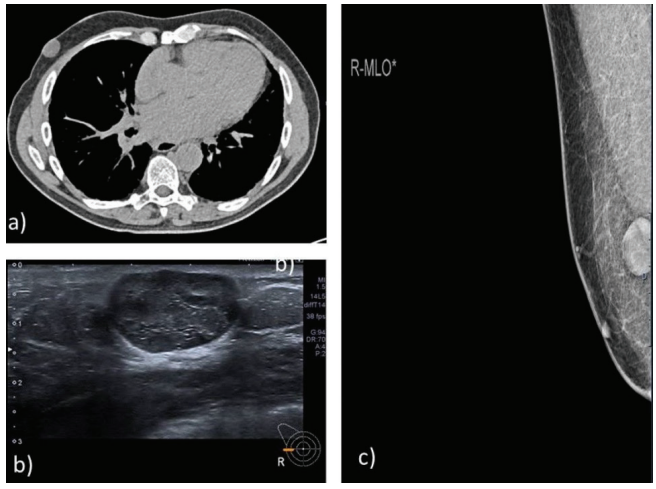

Figure 5. Epidermal inclusion cyst. a) Non-contrast CT scan revealed an incidental, oval-shaped lesion with well-defined margins located in the epidermis of the right breast. b) Ultrasound of the same lesion, demonstrated a well-defined, hypoechoic lesion with internal echoes caused by the presence of keratin and sebaceous material and a small central punctum/tract at the superficial aspect. c) Mammogram showed a well-defined lesion in the same breast with slightly increased density compared to the surrounding tissue. No other suspicious lesions or microcalcifications were present

CT: Computed tomography

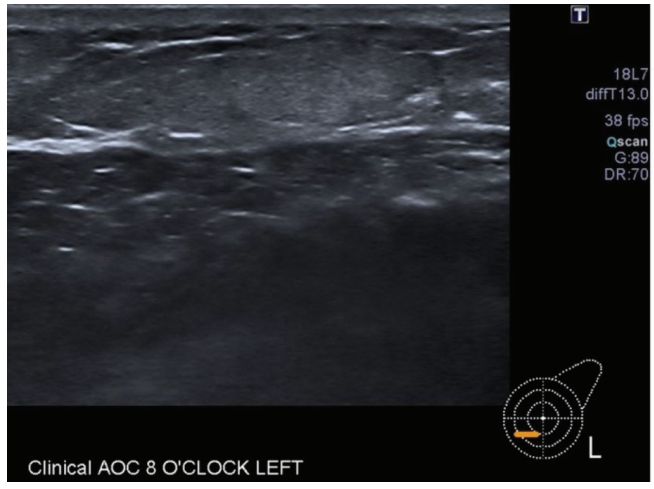

Figure 6. Lipoma. A well-defined hyperechoic lesion consistent with a lipoma observed on ultrasound. This was found in a 64-year-old man who presented with a lump in his left breast that had been present for four months

cycle. Pseudogynecomastia, which is caused by excessive fat deposits in the breast region, is rare (31). It is bilateral and has no palpable lump (31). Intramammary lymph nodes are typically found in the upper outer quadrant of the breast (Figure 7) (1). Breast hematomas can be mistaken for breast cancer if they are not interpreted correctly (30, 32). This includes hematomas that result from surgery, direct trauma, biopsy or contusion (Figure 8) (32). Fat necrosis in male breasts is rare and can be caused by a variety of factors, such as blunt trauma, prior breast surgery, radiotherapy or anticoagulant usage (33). Subareolar abscesses can present as a localized abscess or infection secondary to chronic obstruction and inflammation, and/or pain and swelling of the nipples (Figure 9) (34).

Our data showed that referrals for P1/P2 decreased during the second phase. This decline may be due to increased awareness of benign male disease by clinicians and radiologists after the presentation of the audit findings, as well as implementation of recommended change.

During the second phase, there was also a substantial rise in referrals for P3 grading, ten times higher in the second cycle compared to the first. However, the proportion of P3 referrals that were radiologically classified as indeterminate or suspicious remained relatively low at 8%, similar to the first cycle at 10%, where, p-value of 0.0001 which is less than the significant level of 0.005, indicated the similarity in both cycles It suggests that the increase in referrals for P3 was more due to over-caution by clinicians and an overuse than to a rise in suspicious cases.

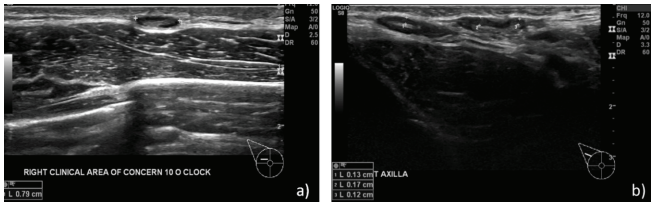

Figure 7. Intramammary lymph node. A 21-year-old male presented with a lump that had been noticed 12 months earlier. At the 10 o'clock position on the chest wall close to the nipple, there is a well-defined, oval-shaped lesion with an isoechoic center encircled by a hypoechoic rim, measuring 8x8x2 mm. These features are consistent with a normal intramammary lymph node, with a cortical measurement of 1 mm. b) shows a scan of the right axilla to confirm completeness, and similar lymph nodes of normal size and morphology are seen. Together, these images suggest that the lump noticed by the patient was likely due to a normal intramammary lymph node, rather than a malignant or benign mass

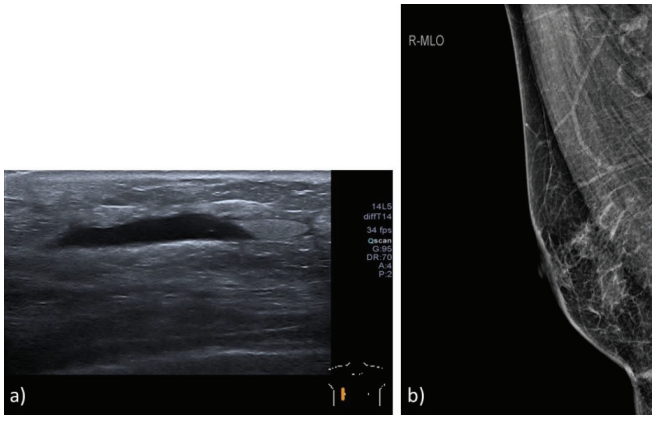

Figure 8. Resolving hematoma. A 67-year-old male patient presented with a lump in his right breast following an injury four weeks earlier. a) The ultrasound reveals a hyperechoic area within the outer breast tissue, with an irregular shape and indistinct borders associated with an anechoic component. b) The mammogram shows diffuse density in the right breast. No other suspicious findings are seen in either breast. These findings are consistent with the patient's history of breast injury and suggest that the lump is likely due to a benign post-traumatic hematoma

The importance of radiological imaging in male breast assessment becomes apparent when considering the 37 patients who were referred as suspicious or indeterminate by clinicians in first cycle and 10 in second cycle (P3). Remarkably, only three of them were finally categorized as indeterminate following radiological imaging in the first cycle and only one in the second cycle (R3). This finding underscores the pivotal role that radiological imaging plays in evaluating patients falling within this ambiguous category. By offering objective and precise information, radiological imaging serves as a powerful tool in distinguishing between benign and malignant findings, ultimately facilitating well-informed management decisions and minimizing the need for unnecessary interventions.

The present study also showed that the concordance between clinical diagnosis (P1/2) and imaging results (R1/2) was 100% in both audit cycles for lesions thought to be benign by the clinicians. This suggests that the clinical examination was reliable and accurate in diagnosing benign breast diseases in men.

It is important to note that false positives and negatives can be a potential downside of the imaging methods used to diagnose breast disease in men (18). False positives may lead to an unnecessary biopsy or increased anxiety among patients (8). False negatives could result in a delayed diagnosis and treatment that leads to worse outcomes (7). It is important to weigh the pros and cons of male imaging to provide the best care for patients (7, 8).

In the last few years, there has been a notable increase in males presenting with breast complaints, with gynecomastia being the most prevalent condition. Other benign non-neoplastic entities can also affect the male breast. The role of imaging for male breast assessment is still a matter of debate. However, a clinical examination may be sufficient in most cases. Imaging may be used in cases where there

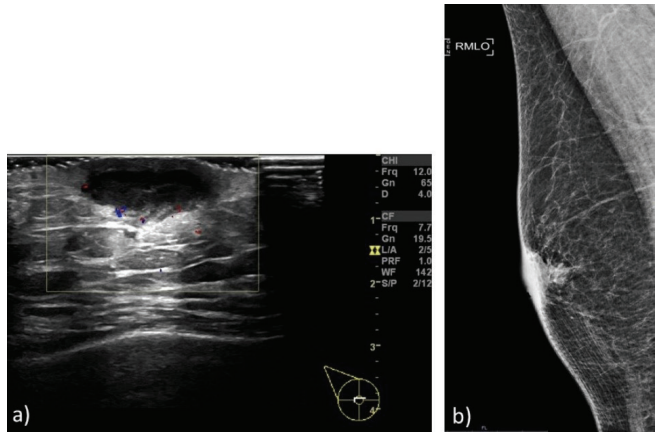

Figure 9. Abscess. A 43-year-old male patient presented with right breast pain and nipple discharge, and a history of previous nipple piercing on that side. a) The ultrasound reveals a retroareolar collection measuring 22x7x22 mm, with surrounding hyperemia and edematous tissues in keeping with inflammation. b) Mammogram, shows a focal area of increased density in the retroareolar with indistinct margins and associated skin thickening

is suspicion of malignancy, or if the physical examination results are inconclusive. Imaging is not recommended for gynecomastia, or lumps that have benign characteristics on clinical examination. Further research is required to elucidate the optimal role of imaging in male breast assessment. This will ensure that patients receive the best possible care.

Ethics Committee Approval: Not necessary.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: C.F., A.S., J.K., M.K., Z.M.I.; Concept: S.B., Z.M.I.; Design: C.F., A.S., Z.M.I.; Data Collection or Processing: C.F., A.S., J.K., M.K., S.B.; Analysis or Interpretation: C.F., A.S., J.K., S.B., Z.M.I.; Literature Search: C.F., A.S., J.K., M.K.; Writing: C.F., A.S., J.K., M.K., Z.M.I.

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Original Article

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Evaluating Efficiency of Time Use and Operational Costs in a Breast Clinic Workflow: A Comparative Analysis Between Automated Breast Ultrasound and Handheld Ultrasound

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ABSTRACT

Objective: The aim of this study was to evaluate efficiency of time use for radiologists and operational costs of automated breast ultrasound (ABUS) versus handheld breast ultrasound (HHUS).

Materials and Methods: This study was approved by the Institutional Review Board, and informed consent was waived. One hundred and fifty-three patients, aged 21–81 years, underwent both ABUS and HHUS. The time required for the ABUS scanning and radiologist interpretation and the combined scanning and interpretation time for HHUS were recorded for screening and diagnostic exams. One-Way ANOVA test was used to compare the methods, and Cohen Kappa statistics were used to achieve the agreement levels. Finally, the cost of the methods and return of interest were compared by completing a cost analysis.

Results: The overall mean ± standard deviation examination time required for ABUS examination was 676.2±145.42 seconds while mean scan time performed by radiographers was 411.76±67.79 seconds, and the mean radiologist time was 234.01±81.88 seconds. The overall mean examination time required for HHUS was 452.52±171.26 seconds, and the mean scan time and radiologist time were 419.62±143.24 seconds. The reduced time translated into savings of 7.369 TL/month, and savings of 22% in operational costs was achieved with ABUS.

Conclusion: The radiologist's time was reduced with ABUS in both screening and diagnostic scenarios. Although a second-look HHUS is required for diagnostic cases, ABUS still saves radiologists time by enabling a focused approach instead of a complete evaluation of both breasts. Thus, ABUS appears to save both medical staff time and operational costs.

Keywords: Automated breast ultrasound; handheld ultrasound; radiologist; time savings; operational cost

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Key Points

- Total time needed for the ultrasound examination was greater with automated breast ultrasound (ABUS), yet it demands less time from radiologists compared to handheld breast ultrasound.
- Radiologist time is reduced across both screening and diagnostic scenarios with ABUS by allowing a targeted approach to certain breast areas rather than necessitating a thorough evaluation of the entire breast.
- ABUS has the potential to enhance the efficiency of human resource allocation and result in cost savings.

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Introduction

Screening mammography in women with large breasts may have a sensitivity as low as 30%–48% (1). Furthermore, studies show that women with extremely dense breast tissue have a lifetime risk of developing breast cancer up to six-fold higher than those with fatty breast tissue (2). Breast cancer screening with handheld breast ultrasonography (HHUS) in women with dense breast tissue has been shown to increase breast cancer detection rates by approximately three to four cancers per 1.000 women (3). Moreover, ultrasonography is the primary technique used in diagnostic settings to differentiate benign and malignant breast tumors.

There are several significant drawbacks to HHUS, including operator dependence, lack of standardization and repeatability, and long acquisition periods. Another restriction is the time required for the US screening exam, which was reported as a mean of 19 minutes in the ACRIN trial (4). Engaging in manual ultrasonography by a radiologist proves to be both time-intensive and costly. The cumulative time taken by a radiologist for conducting, interpreting, and dictating a report for ultrasonographic screening might extend up to 25 to 30 minutes. Additionally, a shortage of available radiologists presents another challenge.

Automatic breast ultrasound (ABUS) was designed to eliminate some of the drawbacks of HHUS. This novel ultrasonography technique makes reproducibility feasible by delegating data acquisition to the technician while reserving data interpretation for the radiologist. Moreover, standardizing breast ultrasound procedures and conserving valuable radiologist time offer additional advantages. ABUS was approved by the Food and Drug Administration in 2012 as a complementary screening tool for women with heterogeneous and extremely dense breasts. It has been shown that there is no statistically significant difference between ABUS and HHUS in terms of diagnostic performance (5). Although ABUS detects fewer lesions than HHUS, it is a reliable method for detecting malignancy in dense breasts (6-8).

Recent research has demonstrated that ABUS can also be used for diagnostic applications, including staging breast cancer, evaluating the tumor response to neoadjuvant chemotherapy, and a second look tool to complement magnetic resonance imaging (9-11). However, this approach lacks some advantages of HHUS, such as better axillary imaging and the ability to assess a lesion's elasticity and vascularization. Second-look HHUS may be needed to verify some lesions detected after ABUS and to evaluate further parameters, such as Doppler US imaging and US elastography.

Within the existing literature, the examination time of ABUS is reported to range between 10–30 minutes, although a consistent estimate is often reported at 15 minutes (12-14). This duration tends to decrease as technicians develop familiarity with breast sonographic anatomy and accumulate experience during the learning phase (14). In different studies, the interpretation time of ABUS varies between 2.9 and 9 minutes (12, 15, 16).

The aim of this study was to compare HHUS and ABUS examination times, observe the change in radiologists' time when ABUS is included in the workflow, and compare the operation costs of the two methods regarding time-saving.

Materials and Methods

Study Design

This prospective, single-center study was approved by the Institutional Review Board, and patient consent was obtained from each participant. Four breast radiologists with 5–25 years of experience in breast imaging and three well-trained radiology technicians/radiographers participated in this study. All patients were evaluated by one of four radiologists. One radiologist examined the patient with HHUS, and another radiologist evaluated the same patient with ABUS images blindly. The time required for the ABUS scanning and radiologist interpretation and the combined scanning and interpretation time for HHUS were recorded for screening and diagnostic exams.

A stopwatch was employed to determine the duration of examination and reading times for both ABUS and HHUS. In the case of ABUS, timing commenced once the probe was positioned on the patient and concluded upon the completion of all acquisitions. Secondly, timing started when the radiologist began the assessment of images on the workstation and ceased when all images were interpreted, and data was sent to the PACS. For HHUS, the timing commenced when the radiologist placed the probe on the breast and persisted until the image acquisition was finalized. To measure the reading time for each case using ABUS and HHUS, the radiologist's initiation of opening the patient file on the workstation marked the start, and the conclusion of report dictation marked the end. In summary, the acquisition, interpretation, and reading times were evaluated individually for ABUS. In contrast, for HHUS, only the examination and reading times were documented, with no measurement of interpretation time since the radiologist conducted interpretation simultaneously with the HHUS examination itself.

This study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (date: 12.03.2020, no: 2020-04/17).

Study Population

The study included women who consecutively attended a single clinic for opportunistic screening or diagnostic workup between 1st July 2021 and 1st August 2021. One hundred and fifty-three patients, aged from 21 to 81 years, underwent both HHUS and ABUS examinations. Women who had a history of breast cancer, who had breast implants, who were lactating, or who had inflammatory skin conditions were excluded. Patients who refused to undergo both procedures were also excluded.

Ultrasound Imaging

HHUS examinations were performed with GE LOGIQ S8 and GE LOGIQ E10S plus (GE Healthcare, WI, USA) using a linear high-frequency probe (6–15MHz and 4–20 MHz, respectively). The subjects were examined in the supine position in at least two orthogonal views for each breast. All the lesions detected during the examination were recorded with at least two orthogonal views. Necessary additional examination methods, such as Doppler US, were used if needed.

The subjects underwent imaging of the breasts using ABUS (Invenia™ ABUS, GE Healthcare, WI, USA) scanner performed by radiographers. Standard images of both breasts (anteroposterior, lateral, and medial views) were acquired in the supine posture. Additional superior and inferior images are also obtained for large breasts. The ABUS Invenia system consists of a scan station with a linear transducer

that automatically operates at a 6–14 MHz frequency and has a wide field of view (15.4 cm). The images have a 0.5 mm thickness. To accurately locate the nipple position in each position, a nipple marker was placed on the coronal view. These images are immediately routed to a dedicated workstation (sonoVIEWer Workstation) for post-processing. On the workstation's monitor, two dimensional (2D) pictures and three dimensional (3D), multiplanar reconstructions of three orthogonal planes were assessed.

Data Collection and Statistical Analysis

The examination time and the radiologist's interpretation times were recorded separately for ABUS. For HHUS, examination time, which is a combination of scanning and interpretation times, was recorded. The reporting time was recorded for each method separately.

The results were evaluated under four main headings: overall examination time, exam type (ABUS/HHUS), breast density (BI-RADS category A/B/C/D), and breast volume (cup size A/B/C/D). The radiologist's overall time for each patient according to exam type and breast density categories was cross-tabulated. During cross-tabulation, time (minutes) was classified into five groups: 0–3, 3–6, 6–9, 9–12, and 12–15 minutes. Cohen Kappa statistics were used to achieve the agreement levels. According to Cohen's approach, negative kappa ratios indicate no agreement or disagreement, 0–0.20 as slight agreement, 0.21–0.39 as minimal agreement, 0.40–0.59 as weak agreement, 0.60–0.79 as moderate agreement, 0.80–0.90 as strong agreement, and above 0.90 as almost perfect agreement.

The one-way ANOVA test was used to determine p values with a confidence interval of 95% and a $p<0.05$ considered statistically significant.

Cost Analysis

Radiologist costs per patient and fixed technician salaries were considered in the financial analysis. The cost of the methods was compared by completing a cost analysis, which focused on the calculation of return of investment (ROI) of both screening methods.

To compare the ROI of ABUS and HHUS, net profits and total investments of both methods were used. In detail, ROI is calculated as follows: *ROI = (Net Profit * 100) / Total Investment.* The depreciation expenses are calculated via a linear amortization method, assuming a useful life of 10 years and zero book value. In detail, the total investment was divided by the number of years, which leads to yearly depreciation expense.

HHUS revenue was determined by factoring in the absence of ABUS and incorporating additional HHUS examinations beyond ABUS, which was estimated as 62 more examinations per month.

For the respective salary expenses, the calculation was as follows:

For ABUS: Salary Expenses = patient number * median radiologist evaluation time = total radiologist spent time as hours * radiologist hourly fee and additionally technician salary was added.

For HHUS: HHUS revenue was determined by factoring in the absence of ABUS and incorporating additional HHUS examinations beyond ABUS, (62 extra per month). Salary Expenses = patient number * median radiologist examination time = total radiologist spent time as hours * radiologist hourly fee and additional HHUS examinations * median radiologist examination time and radiologist hourly fee was added.

For USD/TL currency, we used the end of January 2022 spot rate which was USD/TL = 13.567.

Results

Time Savings

The mean time required for ABUS examination (scanning, interpretation, and reporting time) and for HHUS examination

(scanning and reporting time) are given in Table 1. The median reporting time is 13s (range 4–265s) for HHUS and 14s (range 6–212s) for ABUS. For screening group of patients, the median reporting time was 13s (4–118s) for HHUS and 16s (6–145s) for ABUS. For diagnostic group the median reporting time was 53s (6–265s) for HHUS and 44s (7–212s) for ABUS.

In terms of the radiologists' overall time for each patient, there was a significant difference between ABUS and HHUS (kappa= -0.07, $p<0.01$). ABUS requires a longer process for each patient while providing a significantly shorter involvement time for radiologists ($p<0.05$, see Figure 1). Radiologists saved a mean of 158.44 sec

Table 1. Comparison between the mean time for various elements of the ABUS versus HHUS examinations

	Mean (seconds)	Standard deviation	*p*
Reporting time			
HHUS	32.90	37.93	0.55
ABUS	30.42	34.59	
Radiologist's time			
HHUS	419.62	143.24	<0.05
ABUS	234.01	81.88	
Scan time			
HHUS	419.62	143.24	0.54
ABUS	411.76	67.79	

ABUS: automated breast ultrasound; HHUS: handheld breast ultrasound

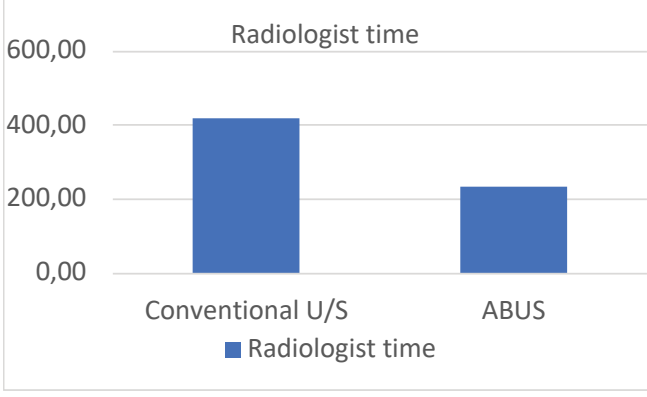

Figure 1. ABUS vs conventional US (HHUS) in regard of radiologist time

ABUS: automated breast ultrasound; HHUS: handheld breast ultrasound

Table 2. Statistical analysis of ABUS and HHUS times in minutes according to examination type

	Screening			Diagnostic		
	Mean	**Standard deviation**	***p*-value**	**Mean**	**Standard deviation**	***p*-value**
Report time						
HHUS	21.14	23.14	0.97	54.02	50.11	0.44
ABUS	21.26	19.64		44.38	43.82	
Radiologist time						
HHUS	375.38	110.03	<0.05	496.29	164.62	<0.05
ABUS	217.15	57.95		253.75	93.18	
Scan time						
HHUS	375.38	110.03	0.05	496.29	110.03	0.005
ABUS	401.51	70.72		430.88	70.72	
Overall examination time						
HHUS	396.53	125.05	<0.05	550.31	200.62	<0.05
ABUS	639.92	112.85		729.02	157.33	

ABUS: automated breast ultrasound; HHUS: handheld breast ultrasound

(approximately 3 minutes) for each case using ABUS; 2.6 minutes for screening exams and 4.04 minutes for diagnostic exams (Table 2, Figure 2). A summary of the findings for screening cases is given in Table 3.

Reporting time was similar for ABUS and HHUS (kappa=0.29, p=0.13).

As breast density increased, the scanning and interpretation times significantly increased using HHUS (Figure 3). Whereas when using ABUS, the radiologist interpretation time increased, but the scanning time remained similar.

The same pattern of findings was also observed for each breast volume. ABUS had a significantly shorter processing time for each size compared to HHUS (p<0.05).

Cost Savings

The reduced time translated into an annual savings of 7369 TL/month (based on 665 patients/month). That included the radiologist time cost and 5.500 TL for technician time cost. This would translate to a 22% savings in operational costs using ABUS. The details of net profit calculation for both methods is summarized in Table 4.

ABUS and HHUS costs were calculated as 256.614 TL and 282.514 TL, respectively.

For the respective salary expenses, the following details are given below:

For ABUS - Salary Expenses for 665 patients (each 3'45" radiologist time) = 149,625 seconds = 41.56 hours; thus, 350 x 41.56 = 14,546 TL; in total plus technician salary altogether 14,546 + 5,500 = 20,046 TL

For HHUS - Salary Expenses for 665 patients (each 16'37" radiologist time) = 663,005 seconds = 184.17 hours; thus, 350 x 184.17 = 64,460 TL and for 62 patients (each 17'10") = 63,860 seconds = 17.74 hours; therefore, 350*17.74 = 6,209 TL; in total 64,460 + 6,209 = 70,669 TL

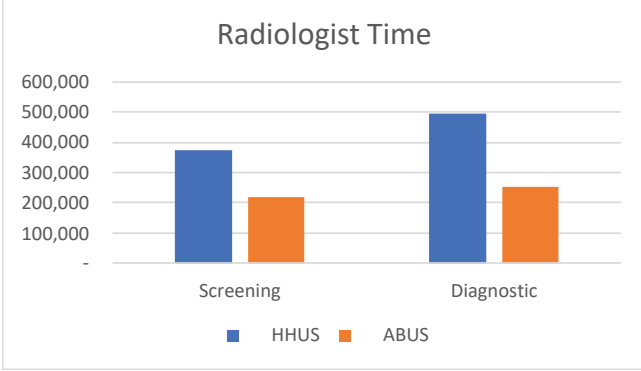

Figure 2. Radiologist time for screening and diagnostic cases compared for ABUS and HHUS

ABUS: automated breast ultrasound; HHUS: handheld breast ultrasound

Thus, the ROI for both methods can be calculated as follows;

ROI (ABUS) = (Net Profit (ABUS) * 100)/Total Investment (ABUS) =194,769.8*100/(200,000*13.567) = 7.18%

ROI (HHUS) = (Net Profit (HHUS) * 100)/Total Investment (HHUS) = 186,909.9*100/(65,000*13.567) = 21.2%

Discussion and Conclusion

ABUS has become used increasingly for the diagnosis of breast cancer in adjunct screening. As ABUS becomes more common, concerns have been raised about the time needed for radiologist interpretation of the test. Few studies have compared the examination times of HHUS and ABUS. However, comparison between the two techniques is essential, especially if time is a limiting issue. In this prospective study, comprehensive ABUS examination, encompassing both scanning and interpretation, required more time compared to HHUS, where radiologists conducted and interpreted the examination simultaneously due to the nature of HHUS interpretation occurring alongside the exam. The present study showed that adoption of ABUS, rather

Table 3. Summary table of screening cases

					HHUS		ABUS	
	Kappa	*p*-value	F	F crit	Mean	Standard deviation	Mean	Standard deviation
Exam type								
Screening	-0.08	0.00	157.04	3.89	375.38	12106.07	217.15	3357.76
Diagnostic	0.07	0.00	10.54	4.23	431.43	13603.49	271.50	20359.65
Breast volume								
A	-0.08	0.00	11.16	4.60	406.25	24974.50	198.88	5864.41
B	-0.03	0.00	47.60	3.94	363.35	11755.23	224.61	8057.70
C	-0.04	0.00	124.06	3.99	384.59	4490.19	230.74	1996.81
D	-0.15	0.00	25.44	4.10	416.10	23420.83	221.15	6456.03
Breast density								
A	0.25	0.01	10.41	4.60	365.25	1763.64	266.38	5748.27
B	-0.10	0.00	20.31	4.04	371.24	17529.11	241.12	3313.94
C	-0.10	0.00	85.76	3.92	380.36	11990.37	216.57	7091.55
D	-0.12	0.00	47.73	4.15	414.53	12607.76	205.59	2941.76
Report time	0.29	0.72	0.13	3.88	23.05	553.01	24.24	697.97

ABUS: automated breast ultrasound; HHUS: handheld breast ultrasound

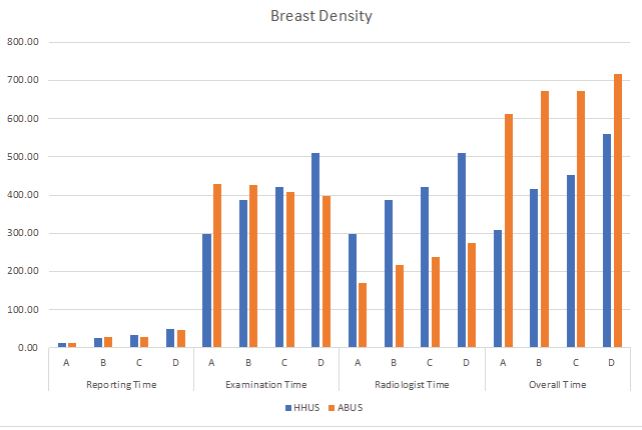

Figure 3. Time required for scanning and interpretation based on breast density

Table 4. Profit calculations of ABUS and HHUS (in Turkish Lira)

	HHUS	ABUS
Revenue	282.514	256.614
Salary expenses	70.669	20.046
Maintenance expenses	1.333,3	2.250
EBITDA	210.511,7	234.318
Depreciation expenses	7.348,8	22.611,7
EBIT	203.162,9	211.706,3
Interest expenses	0	0
EBT	203.162,9	211.706,3
Tax	16.253	16.936,5
Net profit	186.909,9	194.769,8

EBITDA: Earnings Before Interest, Tax, Depreciation, Amortization; EBIT: Earnings Before Interest, Tax; EBT: Earnings Before Tax; ABUS: automated breast ultrasound; HHUS: handheld breast ultrasound

than HHUS, for breast ultrasound examinations, led to an average radiologist's time saving of 3.06 minutes per patient. Further detailed assessment of the data showed this was made up of 2.6 minutes for screening exams and 4.04 minutes for diagnostic exams. Both screening and diagnostic cases benefited from this reduction in waiting time. ABUS nevertheless showed time-saving benefits for radiologists by allowing a targeted approach to certain breast areas rather than necessitating a thorough evaluation of the entire breast, even though there may be a need for a secondary conventional ultrasound in some diagnostic cases.

Brunetti et al. (17) observed that ABUS examination and combined examination and interpretation times were longer than HHUS and that the time required by radiologists was longer for ABUS. They reported that even the interpretation time of ABUS alone took longer than the execution time for HHUS, varying between 4.5 and 11 minutes for ABUS and 5.2±1.5 minutes for HHUS. Nonetheless, the research involved performing HHUS by radiologists of moderate experience, whereas ABUS assessments were conducted by radiologists who lacked familiarity with ABUS. In contrast, in the present study, all the ABUS readers had more than three years of experience with ABUS evaluation. A recent study of ABUS found a reduction in evaluation time as experience accumulated (18). We believe that the difference in ABUS evaluation time between the present study and that of Brunetti et al. (17) arises from disparities in radiologist experience with the system. Furthermore, in the Brunetti et al. (17) protocol, HHUS interpretation was carried out with the benefit of mammography

findings differently from ABUS interpretation, which may have decreased HHUS time. However, in other studies (6, 13, 16, 19), the interpretation time of ABUS (around 3 minutes) was much less than the time needed for HHUS. Some other studies reported ABUS reading time of 2.9 and 9 min (15, 20). To summarize, the presence of various lesions, varying levels of experience of the observer, different devices and hardware, and different workflows could all contribute to this diversity.

In a daily workflow, ABUS saves the radiologist time when dealing with screening cases (6). These cases can be examined, and the images can be evaluated after the patient leaves the clinic, allowing an evaluation during less busy hours of the day. Radiologists use HHUS to confirm suspicious results. The initial ABUS screening reduces the workload enabling the radiologist to focus on the problem rather than performing a whole breast scanning. In diagnostic cases, an online evaluation was necessary, and a second look HHUS may be needed in some cases for assessment of the requirement for further workup, such as Doppler US, elastography, or biopsy. ABUS aids in saving radiologists' time by enabling a focused approach instead of a thorough evaluation of both breasts.

In the present study, when using HHUS scanning time and radiologist interpretation time both increased considerably when breast density increased. However, using ABUS, the radiologist interpretation time increased while the technician's scanning time remains relatively constant. In contrast, cup size had an effect on radiologists' times using both HHUS and ABUS. HHUS execution and ABUS interpretation times increased in parallel with the breast volume.

The reduced time spent by radiologists in performing scans translated into an annual saving of 22% in operational costs with ABUS. Based on the data, a ROI calculation for January 2022 indicated that the investment in HHUS, five years previously, had a return almost three-fold higher than that of ABUS. We expect this gap between the returns to decrease in the medium and long run due to the recovery of the investment over its lifetime. Additionally, it would be more accurate to calculate the ROI over the years for this type of investment. However, financial expenses (interest, etc.) of the relevant company were not included in the analysis. If there are such expenses, adding them may enable us to highlight the "positive" effect of ROI on ABUS. While the initial ROI assessment of ABUS stands at one-third of HHUS, this evaluation was preliminary, without factoring in the influence of ABUS on patient experience, workflow optimization, and reduced radiologist workload. Taking into consideration improved work conditions and the potential for better ROI over time in the long run, ABUS could be deemed a substantial investment. However, examination fees were standardized for both ABUS and HHUS. It might be necessary to consider a downward adjustment for ABUS examination fees.

Our study has some limitations. Firstly, it is a single-center experience and a multicenter approach would provide a more comprehensive depiction of study timelines. Second, the number of patients included in the study was limited. A study involving a larger volume of subjects would offer a more accurate representation of real-life scenarios. Third, the awareness among staff carrying out clinical interpretation that time was being monitored might have introduced a bias towards either method. Fourth, the revenue calculations were conducted generally, potentially resulting in a significant disparity in ROI between the methods. Lastly, this study was designed in a setting where HHUS is performed by radiologists only. This circumstance emphasizes the need for an automated system to relieve radiologists from performing numerous screening US that are likely to show normal or benign results in the majority of cases. In a setting where ultrasonographers perform HHUS, the savings found in this study may not apply.

In conclusion, the present study demonstrated that the total time needed for the procedure was longer with ABUS, yet it demands less radiologist's time compared to HHUS. Radiologist time is reduced across both screening and diagnostic scenarios with ABUS. Therefore, we suggest that ABUS has the potential to improve expert human resource allocation and result in overall cost savings.

Ethics Committee Approval: This study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (date: 12.03.2020, no: 2020-04/17).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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Axillary Surgical Attitude Changing with Retrospective Application of *ACOSOG Z0011* Eligible Criteria: An Institutional Evaluation

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ABSTRACT

Objective: Sentinel lymph node biopsy (SLNB) represents the gold standard for axillary surgical staging. The aim of this study was to assess the proportion of axillary lymph node dissection (ALND) that could be avoided after retrospective application of the *ACOSOG Z0011* criteria and to evaluate the short-term complications associated with axillary surgery.

Materials and Methods: We reviewed breast cancer (BC) patients treated by primary breast-conserving surgery from 2012 to 2015. The percentage of SLNB vs ALND performed before and after the application of the *ACOSOG Z0011* criteria was calculated. Complications were analyzed using crosstabs, with $p<0.05$ considered significant.

Results: Two hundred fifty one patients with a median age of 59.3 years were included. BC tumors had a median size of 13 mm and were mostly unifocal (83.9%). There were 30.3% with 1-2 metastatic lymph nodes (MLN). ALND was performed in 44.2%. The patients with 1-2 MLN, had only SLNB in 14.5% of cases. By applying the *ACOSOG Z0011* criteria, ALND would have been avoided in 40.2% of patients. At least one postoperative complication was reported after SLNB or ALND for 45.7% and 74.7% of patients respectively. Seroma was the most frequent complication, and occurred in 29.3% of cases after SLNB and in 59.5% after ALND.

Conclusion: SNLB is the most commonly used axillary surgical staging procedure in this series (55.8%). With a retrospective application of the *ACOSOG Z0011* criteria in our population, ALND could have been avoided for 40.2% patients. Post-operative complications rate was higher after ALND, with a seroma rate at 59.5%.

Keywords: Breast-conserving surgery; sentinel lymph node biopsy; axillary surgery; axillary lymph node dissection; seroma

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Key Points

- The *ACOSOG Z0011* trial results have set a new standard for surgical management of the axilla.
- The results of Z0011 trial were received with some reluctance in the daily practice.
- By applying the Z0011 criteria, axillary lymph node dissection would have been avoided in 40.2% of patients.
- In our opinion surgical teams should not look with so much reluctance at the results of trials that may led to a change in surgical practice.

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women (1). Its management is complex and can involve a combination of different modalities such as surgery, radiotherapy, and various systemic treatments (2).

Surgical excision of the tumor remains an essential step in the therapeutic scheme for the treatment of BC. Surgical staging of the axilla is necessary for optimal treatment planning.

Until the early 2000s, axillary lymph node dissection (ALND) was the standard procedure used for the treatment and staging of axillary lymph nodes (ALN) (3-5). Nearly thirty years ago, the sentinel lymph

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node (LN) biopsy (SLNB) technique opened new perspectives in the management of patients with early BC (6). Since then, there has been an evident de-escalation of axillary surgical staging, giving way to the SLNB technique, which has become the gold standard in the management of BC at the early stage cT1-2N0 (7-9).

The short- and long-term side effects associated with ALND (seroma, wound healing problems, infection, neuropathy and especially lymphedema of the arm) have always been a concern. Comparative studies of morbidity with different types of axillary surgery (AS), such as that of Giuliano et al. (11), have shown that SLNB leads to fewer side effects than ALND, with an overall complication rate of 3% after SLNB compared to 35% after ALND (10, 11).

The pathological stage of the ALN represents a major prognostic factor for BC, but it is less commonly used for deciding adjuvant treatment (12). In this context and given the high morbidity rate of ALND, management strategies for micro- or macro-metastatic ALN have evolved considerably over time (3).

In 2011, the publication of the results of the *ACOSOG Z0011* trial led to a change in the axillary management of early-stage BC (7). They demonstrated that completion ALND (cALND) in patients with clinical T1-2 N0 tumors treated with breast-conserving surgery (BCS) and external radiotherapy (ER), with a maximum of two micro- or macro-metastatic SLN's, did not provide benefit in terms of overall survival (OS) or disease-free survival (DFS), especially in the case of adjuvant treatment with chemotherapy (CT) and/or endocrine therapy (ET) (9, 13, 14).

Following the publication of these results, some teams (mainly in the United States) quickly changed their clinical practices and decided to no longer perform cALND in this specific situation (15). On the other hand, in Europe, and at our institution, Institute Jules Bordet (IJB) in particular, the results of this study were received with some reluctance and raised many questions about the export of the *ACOSOG Z0011* criteria in the daily clinical situations and the risk of under-treatment linked to ignorance of complete ALN status (16, 17). Currently, the *ACOSOG Z0011* trial results have set the standard for surgical management of the axilla in patients meeting the trials inclusion criteria, included in all international and national recommendations (5, 15, 18, 19).

The aim of this study was to evaluate the possible modifications in the surgical attitude of the axilla by retrospective application of the *ACOSOG Z0011* trial criteria in a cohort of patients with early-stage invasive BC treated with BCS and adjuvant ER at the IJB. We also sought to compare the OS and DFS of these patients according to the degree of ALN invasion and to evaluate the rate of short-term post-operative complications according to the type of axillary surgery.

Materials and Methods

Study Population and Design

This was a retrospective, exploratory, monocentric study of patients with early-stage invasive BC, treated by BCS (and adjuvant ER) at the IJB over a period of 4 years (January 2012-December 2015). The study was approved by the IJB Ethics Committee under approval number CE3446.

Inclusion and exclusion criteria

We only included patients over 18 years of age with invasive BC clinically classified as cT1-2N0M0, treated with BCS, whole breast radiotherapy and adjuvant systemic treatment (CT and/or HT). Patients with invasive BC treated by mastectomy or BCS and intraoperative radiotherapy, as well as patients with metastatic or in situ BC were excluded.

Clinical Data and Procedures

All clinical data were extracted from patients computerized medical records and stored in a prepared database on REDCap (Research Electronic Data Capture). For each patient, the following information was collected: Demographic data, imaging characteristics of the tumor, clinical nodal status; tumor pathology data, pathological data of ALNs (number of invaded LNs, presence of micro- or macro-metastasis); data on therapeutic management including the type of axillary surgery (SLNB, SLNB and cALND or ALND) and adjuvant treatment; the follow-up data of recurrence (local or distant) and/or death; and data on post-operative complications.

Patients were divided into two groups: One group had only SLNB and the other group had an ALND (either SLNB plus cALND or ALND alone).

Study Evaluation Criteria

The primary endpoint measures were: The percentage of ALND that could have been avoided (number of ALNDs performed when only 1-2 SLNs were positive) and the percentage of types of axillary surgery performed (SLNB vs ALND) before and after application of the *ACOSOG Z0011* criteria.

The secondary endpoint measures were OS, DFS and percentage of short-term post-operative complications. OS was defined as the time interval between the date of diagnosis and the date of last follow-up or death (related to BC or death from any cause). DFS was defined as the time interval from the date of diagnosis to the date of first recurrence or last follow-up or death, whichever occurred first. Recurrence was regarded as any local, regional, or distant tumor recurrence. Patients alive at last follow-up or lost to follow-up were censored. Data on follow-up were collected until March 31, 2022.

The post-operative complications assessed were: Wound dehiscence, hematoma (breast and/or axillary), (local) infection at the axillary surgery site divided into superficial (presence of inflammatory signs) or deep (microbial fluid culture positive), and seroma (serous and/or lymphatic collection at the axillary surgical site, clinically detected and requiring at least 1 puncture). Short-term post-operative complications were considered complications that occurred less than 3 months postoperatively. Due to the lack of systematic registration of late complications, such as lymphedema or shoulder neuropathy, their incidence could not be assessed.

Statistical Analysis

The statistical analysis was conducted using SAS software version 9.4. Descriptive statistics were employed to summarize the patient cohort and tumor characteristics, including nominal and categorical variables reported as frequencies and proportions, and continuous variables reported as means and standard deviations or medians and interquartile ranges.

Cross-tabulation was used to examine the relationship between nodal status and type of surgery. Survival rates were analyzed using Kaplan-Meier curves, and compared between patients without LN metastasis, those with 1-2 LN metastases (per *ACOSOG Z0011* criteria), and

those with ≥3 LN metastases. Time to death and time to event were calculated using the diagnosis date as a reference point, and both OS and DFS were reported at five years.

Short-term complications were analyzed based on the type of axillary surgery (SLNB vs. ALND) through cross-tabulation and statistical tests such as the chi-squared test or Fisher's Exact test. A *p*-value of less than 0.05 was considered statistically significant for all analysis.

Results

Characteristics of the study population

During the study period, 251 patients with invasive BC (cT1-2N0M0) were treated at the IJB by BCS followed by external whole breast radiotherapy and were included in the study. The clinical and pathological characteristics of the population studied are shown in Table 1. Women had a median age of 59.3 years and a median body mass index of 24.09 kg/m², 67.8% were post-menopausal. The median tumor size was 13 mm (1.00-45.00 mm), tumors were mostly unifocal (83.9%) and of the infiltrating ductal carcinoma type (70.1%). Most of the tumors were luminal A molecular subtype (66.4%). Regarding hormone receptor status, 90.8% were positive for estrogen receptor (ER) and 82% for progesterone receptor. As adjuvant systemic treatment, 45.4% of patients received CT and 92.4% ET.

Type of axillary surgery and LN status

One hundred forty (55.8%) had only a SLNB and 111/251 patients (44.2%) underwent an ALND. Among the patients with ALND, 87/111 patients had a cALND after SLNB. In our cohort, 165 patients did not present with ALN involvement. Among patients with ALN involvement, 76 patients (30.3%) had only 1-2 metastatic ALNs. The median number of SLNs removed was 2 (1-7) and the median number of LNs in the ALND specimen was 14 (2-34), with a median number of invaded ALNs of 1 (1-20, for cN0). The characteristics of removed ALNs are listed in Table 2. Among the 78 patients treated with SLNB followed by cALND because of metastasis of the SLN, 25.6% of patients had at least one positive complementary LN node in the cALND specimen.

Axillary surgical procedure and axillary LN status

Among the 165 patients whose pathologic ALN status was negative (pN0), 77.6% patients were treated with SLNB alone. Among the 76 patients with only 1-2 metastatic LNs (and thus meet the *ACOSOG Z0011* criteria), only 14.5% of patients underwent SLNB alone, while 65 of them, representing 85.5% of patients, were treated by radical axillary surgery (ALND) in IJB. The distribution of the type of axillary surgery according to axillary LN status is presented in Table 3. By applying the *ACOSOG Z0011* criteria to our entire population, only 10/251 patients (3.9%) should have had an cALND, so we could have avoided cALND in 101/251 patients (40.2%) (Figure 1).

OS and DFS

The median follow-up of patients was 7 years. At the time of analysis, 16 (6.4%) patients had died. The 5-year OS was 96.9%: 95.7% in patients without metastasis of the LNs, 98.5% in patients with metastasis of only 1-2 LNs (*ACOSOG Z0011* criteria) and 100% for in patients with metastasis of ≥3 SLNs ($p = 0.101$). In total, 18 (7.2%) patients experienced recurrence: One patient with a loco-regional relapse and 17 patients with a distant relapse. The 5-year DFS was 96% overall: 94.4% in patients without metastasis of the LNs, 98.6% in patients with metastasis of 1-2 LNs (meeting the *ACOSOG Z0011* criteria) and 100% in patients with metastasis of ≥3 SLNs ($p = 0.146$).

Table 1. Clinical, pathological and treatment characteristics of the study population

Characteristics	Entire cohort	
	n	%
Patients	251	100
Age		
Median	59.3	
Mean (range)	58.6 (26.8-85.8)	
BMI		
Median	24.09	
Mean (range)	25.01 (16.49-48.44)	
<25	152	60.56
25 - <30	64	25.50
≥30	35	13.94
Pre-menopause	79	32.11
Post-menopause	167	67.89
Pathological tumor size (mm)		
Median	13	
Mean (range)	14.24 (1.00-45.00)	
<10 mm	51	20.32
10-20 mm	168	66.93
>20 mm	32	12.75
Histological type		
IDC	176	70.10
ILC	70	27.90
Others	5	2.00
Tumor grade		
G1	78	31.08
G2	107	42.63
G3	66	26.29
Ki-67 status		
Median	10	
Mean (range)	19.34 (2.00 – 95.00)	
Molecular subtype		
Luminal A	166	66.40
Luminal B	62	24.80
HER2-enriched	5	2.06
Triple-negative	17	7.00
Type of axillary surgery		
SLNB	140	55.77
SLNB + cALND	87	34.66
ALND	24	9.57
Chemotherapy		
Yes	114	45.42
No	137	54.58
Endocrine therapy		
Yes	232	92.43
No	19	7.57

BMI: body mass index; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; HER2: human epidermal growth factor receptor 2; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection

Postoperative complications

In our cohort, 58.5% of patients experienced at least one short-term postoperative complication, 64/140 patients (45.7%) for the SLNB-only group and 83/111 (74.7%) in the ALND group. Axillary seroma was the most common complication, 29.3% in the SLNB-only group and 59.4% in the ALND group. The difference for other complications such as hematoma, wound dehiscence, and infections between the 2 groups (SLNB-only vs ALND) was not significant. Regarding infectious problems, the most common infectious agent identified was *Staphylococcus epidermidis*. A summary of complications is presented in Table 4.

Table 2. The characteristics of removed axillary lymph nodes

Characteristics	n	%
Number of SLNs		
Median (SQR)	2	(2-3)
Mean (range)	2.3	(1-7)
SLN		
Negative	141	62.11
Positive	86	37.89
Number of ALND nodes		
Median	14	
Mean (range)	13.9	(2-34)
ALND nodes		
Negative	37	33.33
Positive	74	66.67
Lymph node status		
Negative	16	65.74
1-2 positive	76	30.28
≥3 positive	10	23.74
LNs status in involved SLN and cALND		
Complementary positive LN	20	25.64
Complementary negative LN	58	74.36

SLN: sentinel lymph node; ALND: axillary lymph node dissection; LN: lymph node; cALND: completion axillary lymph node dissection

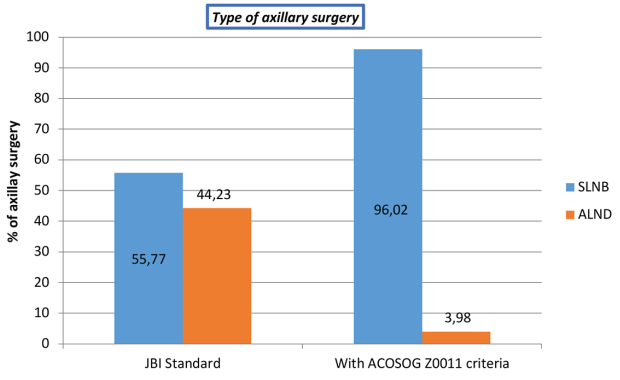

Figure 1. Comparison between the type of standard axillary surgery at IJB and according to the *ACOSOG Z001* criteria for cT1-2N0M0 patients. Figure 1 shows the comparison of the type of axillary surgery according to the standard procedure at the JBI during the study period and the possible effect of application of the *ACOSOG Z0011* criteria. The blue colons represent the patients with a sentinel lymph node biopsy and the orange colons those with axillary lymph node dissection

Discussion and Conclusion

As part of the de-escalation of BC surgical treatment, axillary surgery has undergone major changes over the past 3 decades. Our study was able to show that 40.2% of the patients in our cohort could have been spared more aggressive axillary surgery like ALND if the patient selection criteria of the *ACOSOG Z0011* study were applied. More particularly for the group of patients with 1-2 metastatic SLNs, ALND could have been avoided in almost 9 out of 10 patients (65/76 patients). This change in the axillary surgical attitude seems to be in agreement with other studies published after the adoption of the *ACOSOG Z0011* criteria in the USA and Europe (20, 21-23). Morrow and colleagues, in a prospective study that evaluated the rates of ALND in patients eligible for *ACOSOG Z0011*, showed that 84% of ALNDs were prevented in their cohort (21). Similarly, Hennigs and colleagues, in a retrospective study evaluating the impact of the *ACOSOG Z0011* criteria on the axillary management of patients with BC, reported that nearly one in two patients still had ALND in situations where it could have been avoided (22). The main argument put forward for performing an ALND when it was not recommended was the fear of under-treatment which could impact the survival of the patient. This was emphasized by the fact that he indication for adjuvant CT sometimes depended on the number of metastatic ALN, which is not actually known when an ALND is not performed (5, 23). However, this fear of under treatment led to the realization of an ALND in 37/165 patients (22.4%) who had a negative SLN status. The reasons given for the completion of the ALND in our series were either the presence of isolated tumor cells (pN0, i+) in the SLN, or a tumor size >3 cm, or the presence of a multifocal tumor.

In our cohort, among the 72 patients who had 1-2 metastatic SLNs, only 21.7% of patients had at least one additional positive LN after cALND. These results are in concordance with the data of the *ACOSOG Z0011* trial that reports in the ALND arm, a complementary positive LN rate of 27.3%, and close to that reported by Galimberti et al. (23), in which the rate was 13% (4, 13). Some studies have also demonstrated that after an additional ALND, the information obtained did not have a significant impact on survival and on the indication of systemic adjuvant treatment (CT and/or HT) (9, 13, 14). The AMAROS trial compared in patients with T1-2N0 BC, ALND to axillary radiotherapy in case of positive SLNs (1 to 2 or even 3-4), showed that the additional cALND had no impact on adjuvant treatment, and that other factors such as age, tumor grade, size of metastasis in the SLN and multifocal tumors were significantly related

Table 3. Distribution of type of axillary surgeries performed in our cohort according to pathological lymph node status

Pathological nodal status	Axillary surgical procedure			
	SLNB		ALND	
	n	%	n	%
Negative	128	77.57	37	22.43
Positive: 1-2 lymph nodes	11	14.47	65	85.53
Positive: >2 lymph nodes	1	10.00	09	90.00

SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection

Table 4. Short-term post-operative complications (<3 months) according to different type of axillary surgeries

Complication type	SLNB		ALND		*p*-value
	n	%	n	%	
Hematoma	6	4.29	9	8.11	0.2550
Axillary seroma	41	29.29	66	59.46	**<0.0001**
Wound dehiscence	6	4.29	6	5.41	0.7650
Infections - Superficial	15	10.71	20	18.02	0.1470
- Deep	2	1.43	7	6.31	0.4650
At least one complication	64	45.71	83	74.77	**<0.0001**

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

to the prescription of CT and not the number of complementary positive LNs (4, 9, 13, 14, 24).

Currently, ALND has been effectively replaced by the SLNB technique, in almost all cases of primary surgery. Even if axillary LN involvement represents one of the major prognostic factors in BC, the adoption of a more conservative axillary surgery, like SLNB is a safe attitude with respect to survival of patients (5, 11, 25).

In the current study, there was no difference in OS and DFS between patients without metastatic invasion of the LNs compared to patients with metastatic invasion of only 1-2 LNs (*ACOSOG Z0011* criteria) or with metastatic invasion of ≥3 SLNs ($p = 0.101$ and $p = 0.146$). These results are more likely the reflection of breast tumor characteristics (size, grade, molecular subtype, etc.) and probably the effect of the adjuvant treatments (used to treat our patients), than a reflection of the surgical aggressiveness.

These findings are in accordance with the *ACOSOG Z0011* trial that was able to demonstrate that removing "all" positive ALN does not improve long-term patient survival, in cases where the axillary tumor burden is low. The results updated in 2017 (10 years of follow-up) confirmed the absence of significant difference in terms of OS (83.6% for the ALND group versus 86.3% for the SLNB group, $p = 0.72$), DFS (78.2% for the ALND group versus 80.2% for the SLNB group, $p = 0.44$) and axillary recurrence (0.5% in the ALND group versus 1.5% in the SLNB group) (13, 20).

As several studies have already shown, patients treated with SLNB alone have fewer immediate and especially long-term postoperative complications compared to patients who have undergone ALND (6, 10, 11, 24, 25). In our study, we were also able to show a significant reduction ($p<0.0001$) in the rate of complications between these 2 groups. As expected, following ALND, axillary seroma was the most common complication in 59.5% of patients.

Information on short-term complications such as seromas, hematoma, wound dehiscence, and infection, is rarely reported in the literature. Nevertheless, Purushotham et al. (10) showed a significant reduction in physical arm morbidity over one year of follow-up in patients who underwent SNLB only compared to patients who underwent ALND. Numbness, paresthesia, and loss of sensitivity were also significantly reduced (10). The Milan group who compared the 2 types of axillary surgery over a period of 6 months, also showed that patients in the SLNB group had less pain and numbness and had better arm mobility than those who underwent ALND (6). Warmuth et al. (26) showed that inflammatory problems and/or infection of the arm or breast are common in patients treated with BCS and ALND. Abass et al. (27) published the results of a prospective study of patients who underwent ALND, which confirmed that more than 40% of patients experienced adverse events, primarily seroma formation and paresthesia.

Long-term complications are widely reported in the literature and that these can have a greater negative influence on the quality of life of patients, but the short time complications must not be neglected (24). Our retrospective analysis shows that complications such as chronic pain, impaired arm mobility, paresthesia or even arm lymphedema are less well documented in the follow-up of patients in everyday practice. In the future, we, like other care givers, should provide a standard evaluation of these short and long-term complications after BC and axillary surgery in order to have more precise information on their incidence, and be able to better treat or prevent them.

In an era of accelerated innovation in medicine, with new and rapidly changing clinical practices, the new surgical practice to align with evidence-based guidelines has not consistently been adopted promptly, in all surgical disciplines (28). Randomized controlled trials comparing different surgical procedures are relatively rare, due principally to methodological difficulties. Moreover, they are also most often received with scepticism and reluctance, and often criticized. This was also the situation for *ACOSOG Z0011* trial (16, 17, 28). This delay in adopting changes in surgery can have consequences especially on patients, but also on health systems. A recent retrospective evaluation of nearly 14.000 patients with *ACOSOG Z0011* criteria from 179 German breast cancer units, showed that the implementation of *ACOSOG Z0011*, resulted in gain of 335 quality-adjusted life-years and substantial cost savings for the society (1,924 EUR per patient). The authors concluded that this gain would have been more than double if all of the patients had been treated according to ACOSOG Z0011 trial recommendations (29).

Study Limitations

This study has several limitations. First, the exploratory retrospective nature of the study, second, the limited number of patients analyzed. Also, with this study design, we could not account for all the different reasons why a certain patient underwent ALND and not SLNB and vice versa. And not last, the fact that there has not been the possibility

of studying the adoption of the *ACOSOG Z0011* criteria on the change in axillary surgical attitude within our study cohort, by the absence of a real control group. Moreover, this cohort represents the real-world experience. Furthermore, we would like to highlight our opinion that surgical teams should not look with so much reluctance at the results of trials that may led to a change in surgical practice.

The SLNB was the most used axillary surgical procedure (55.8%) in our series of patients with early-stage invasive BC, and an axillary LN involvement was observed in 34.2% of patients. With the retrospective application of the ACOSOG Z0011 criteria to our study population, 40.2% of ALNDs could have been avoided in our patients. Short-term post-operative complications are higher after ALND, with an estimated seroma rate of 59.5%. Standard evaluation of these short- and long-term postoperative complications should be performed regularly for our patients in order to have more precise information on their incidence and to be able to subsequently improve the quality of life of our patients.

Ethics Committee Approval: The study was approved by the IJB Ethics Committee under approval number CE3446.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.F.P., M.R., D.L., I.V., F.D.N.; Concept: C.F.P., L.D.N., I.V., F.D.N.; Design: C.F.P., L.D.N., M.M., F.D.N.; Data Collection or Processing: C.F.P., L.D.N., E.E.H., M.M.; Analysis or Interpretation: C.F.P., L.D.N., M.M., I.V., F.D.N.; Literature Search: C.F.P., L.D.N., E.E.H.; Writing: C.F.P., L.D.N., E.E.H., M.M., M.R., D.L., I.V., F.D.N.

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Original Article

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Assessment High-Risk Breast Cancer in Older Patients: A Comparative Analysis of PREDICT Scores and TAILORx Risk Categorization

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ABSTRACT

Objective: This study aimed to evaluate the relationship between PREDICT tool overall survival (OS) scores and high-risk patients according to TAILORx risk categorization in elderly hormone reseptor (HR) positive human epidermal growth factor negative early breast-cancer patients.

Materials and Methods: We conducted a retrospective study, extracting data from medical records of 64 patients diagnosed with breast cancer. A retrospective analysis was performed on all patients who had Oncotype Dx Recurrence Scores across five medical centers between 2017 and 2022. PREDICT scores were defined as calculated 10-year OS rates via PREDICT tool.

Results: The median age of the patients was 67, with a range between 65–75 years. Low-risk patients had a slightly higher two PREDICT scores compared to high-risk patients (78% *vs.* 73%), (81% *vs.* 77%), which were statistically significant. The progesterone receptor (PR) level was significantly lower in the high-risk group (3.5% *vs.* 80%). A unit decrease in the PREDICT scores was associated with a 11% increase in the odds of being in the high-risk group. However, these effects weren't statistically significant in the multivariate analysis. A unit decrease in the PR level was significantly associated with increased odds (by 5% in the multivariate analysis) of being in the high-risk group.

Conclusion: Our study underscores the importance of using a combination of tools, including the PREDICT tool, PR levels, and TAILORx risk categorization, for a comprehensive risk assessment in these patients, especially in the older population. Accurate risk assessment is crucial for tailoring the treatment and optimizing outcomes in this vulnerable population. Future studies are warranted to further validate these findings in larger cohorts and to explore additional biomarkers and genomic signatures that may aid in the risk assessment and management of breast cancer in older patients.

Keywords: Breast cancer; PREDICT tool; oncotype DX recurrence score; TAILORx risk categorization

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Key Points

- This is first study in the literature to investigate the relationship between ODx-RS and PREDICT tool OS scores in HR-positive HER-2 negative early breast-cancer elderly patients.
- A unit decrease in PREDICT scores and PR levels was associated with increased odds of being classified as high-risk, but only the PR levels association was statistically significant in the multivariate analysis.
- Despite the PREDICT tool indicating higher survival scores for low-risk patients compared to high-risk patients, the tool did not demonstrate significant predictive value in the multivariate analysis, indicating alone its limited utility as a standalone predictive measure for high-risk classification in older patients.

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Introduction

Breast cancer has now overtaken lung cancer as the most commonly diagnosed cancer globally, with 2.3 million new cases diagnosed annually (1). In Turkey, breast cancer remains the dominant cancer among women, with 24,175 cases, or 23.9%, recorded in 2020 (1, 2). This prevalence has underscored the need for tools that can provide personalized prognostic insights, aiding clinicians in formulating treatment strategies tailored to individual patient profiles. The PREDICT tool and the Oncotype Dx Recurrence score (ODx-RS) have emerged as being important in this field (1, 3), designed to deliver nuanced prognoses by combining both tumor-specific and patient-specific factors (3). However, their efficacy and applicability, specifically in the older population (≥65 years) with breast cancer, warrants further exploration.

The PREDICT tool, originating from UK research, is geared towards forecasting post-surgical survival for invasive breast cancer. PREDICT considers variables such as tumor size, nodal status, grade, and biomarkers such as human epidermal growth factor-2 (HER-2) and Ki-67 (3-9). Several studies have highlighted its validity across a variety of patient cohorts, particularly in age-specific groups (9-14). Given that PREDICT is free, user friendly, and easily accessible, it may provide an economically feasible option to guide adjuvant chemotherapy decision-making in resource-limited settings. PREDICT is a web-based prognostication tool, which estimates the probability of survival for individual patients with breast cancer and the impact of systemic treatment choices on their survival probability (http://www.predict.nhs.uk/).,Als Furthermore, PREDICT has been endorsed by the American Joint Committee on Cancer (13). Notably, a recent study by van der Plas-Krijgsman et al. (15) introduced the PORTRET tool–a prognostic model explicitly designed for older patients (≥65 years) with breast cancer in the Netherlands. This need for the development of this tool undelines the significance of age-specific prognostic models.

The Oncotype Dx (ODx) test (Genomic Health, Redwood City, CA, USA) examines a 21-gene expression profile. It has been authenticated for patients with HR-positive, HER-2 negative, and lymph node negative breast cancer. This score segments patients into risk categories (low, intermediate, or high) primarily concerning recurrence in hormone receptor-positive breast cancer, thereby aiding the decision-making process around the need for adjuvant chemotherapy (1, 16-18). As the realm of oncology shifts towards more patient-focused care, comprehending the impact and implications of these tools, specifically for the older demographic (≥65 years), becomes increasingly important.

This study was designed to investigate the possible correlations between the PREDICT tool and the TAILORx risk classification in an older cohort of patients with hormone receptor positive/HER2 negative breast cancer, focusing on their combined prognostic value.

Materials and Methods

Study Design and Patient Population

This was a retrospective study, with data extracted from the medical records of patients diagnosed with breast cancer. A retrospective analysis was performed on all patients who had available ODx-RS across five medical centers between 2017 and 2022. The study eventually included women aged 65 years and above who were diagnosed with hormone receptor positive, HER-2 negative, early-stage breast cancer (pT1-2, pN0-N1mic, M0). These patients were treated in five different hospitals across Turkey and had ODx-RS assessments to inform the decision for adjuvant chemotherapy.

Patient demographic, clinical, and pathological details, including age, tumor size, histological grade, estrogen receptor (ER) and progesterone receptor (PR) status, Ki-67 index, and lymph node status were recorded retrospectively. The ODx-RS was examined using tissue sections taken from surgically removed, formalin-fixed, paraffin-embedded samples in a centralized laboratory. If nuclear staining was moderate to strong in at least 1% of tumor cells upon immunohistochemical (IHC) testing, ER and/or PR were considered positive. HER-2 expression was evaluated using IHC staining. A score of 0 or 1 on the IHC staining was interpreted as negative for HER-2. In cases where the IHC score was 2, further assessment was conducted using a Fluorescence *In Situ* Hybridization (FISH) test. Only those with a negative FISH test result were included in the study. Patients were divided into two groups according to ODx-RS: 0-25 and ≥26. An oncotype score cut-off value of 26 for chemotherapy administration was used, based on the TAILORx study (19, 20).

Even with the known ODx scores, the choice of adjuvant therapy was determined at a weekly tumor board meetings. Patients were split into two categories: those who received hormone therapy alone and those who received chemotherapy (taxane-based and/or adriamycin-based regimens) in combination with hormone therapy (aromatase inhibitors or tamoxifen).

Predicted 10-Year OS (PREDICT Score)

PREDICT scores were defined as calculated OS rates using the PREDICT tool. In the present study the predicted OS was calculated for each patient using version 2 of the PREDICT tool. For each patient, data on age (continuous), tumor size (continuous), number of involved lymph nodes (continuous), ER status (positive, negative, undefined), tumor grade (grade 1, grade 2, grade 3, undefined), HER-2 status (positive, negative, undefined), Ki-67 status (entered as undefined for all patients), and adjuvant chemotherapy regimen (no chemotherapy, second-generation chemotherapy, third-generation chemotherapy) were manually entered. For every entry, the program predicted 10-year OS for three different scenarios. These were, survival with no adjuvant treatment, benefit of adjuvant hormone therapy, and additional benefit of adding adjuvant chemotherapy (ChT) to adjuvant hormone therapy. We used the second and third scenarios for every patients and OS scores were recorded for each patient [(2-OS score via PREDICT only adding hormonotherapy (HT); 3- OS score via PREDICT adding combine therapy (ChT + HT)]. The survival probability corresponding to the actual treatment received by the individual patient was recorded. PREDICT score was defined as calculated OS rate derived from the PREDICT tool. In order to ensure accuracy, all the PREDICT scores were calculated by two research personnel, and further audited.

The study protocol was reviewed and performed in accordance with İstanbul Bilgi University Ethics Committee. (project number: 2023-40162-053, date: 30.03.2023).

Statistical Analysis

Data were analyzed using SPSS, version 22.0 (IBM Inc., Armonk, NY, USA). Descriptive statistics were used to summarize patient demographics and tumor characteristics in both age groups. Mean and standard deviation or median and range were computed for continuous variables as appropriate, while frequencies and percentages

were calculated for categorical variables. The Student's t-test was used in cases where the numerical demographic and clinical properties met with the standard distribution hypothesis. In cases where these criteria were not met, the Mann-Whitney U test was used to compare the distribution of ODx risk categories (high risk *vs.* not high risk). Boxplot analysis was used to evaluate the distribution of PREDICT scores between the high-risk and non-high-risk groups To control for potential confounders, a multivariate linear regression analysis was conducted with the TAILORx high risk score (ODx-RS ≥26) as the dependent variable and the PREDICT scores, tumor size, Ki-67, and tumor grade as independent variables. A *p*-value of less than 0.05 was considered statistically significant.

Table 1. Characteristics of the patients at baseline

(n = 64)	n (%)/median (min-max)
Age	67 (65–75)
PREDICT score* (only hormonotherapy)	78% (57–85)
PREDICT score* (chemoterapy + hormonotherapy)	80% (63–86)
The histological subtype	
IDC	47 (73.4%)
Other subtypes#	17 (26.6%)
ODx-RS	15 (1–37)
Ki-67	18.5 (5–50)
Histologic grade	
Grade 1	6 (9.4%)
Grade 2	41 (64.1%)
Grade 3	17 (26.6%)
Tumor diameter	1.6 (0.6–4)
PR status	
PR>10	47 (73.4%)
PR≤10	17 (26.6%)
Ki-67 status	
Ki-67 <20	33 (51.6%)
Ki-67 ≥ 20	Ki-67 <20
Ki-67 ≥ 20	
0-10	18 (30.0%)
11–25	31 (51.7%)
≥26	11 (18.3%)
pT stage	
pT1	36 (56.3%)
pT2	28 (43.8%)
pN stage	
pN0	
pN1mic	55 (85.9%)
pM	9 (14.1%)
Adjuvant treatment	
HT	48 (75.0%)
ChT+HT	16 (25.0%)

All the values presented as n (%), IDC: invasive ductal carcinoma; #: invasive lobuler carcinoma, mucinous, metaplastic, micropapiller, cribriform, papiller; *PREDICT scores were defined as calculated overall survival rates via PREDICT tool; min: minimum; max: maximum

Results

The median (range) age of the patients was 67 (65-75) years. The majority of tumors were histological grade 2 (64.1%) followed by grade 3 (26.6%) and grade 1 (9.4%). In terms of treatment, 75% received HT while 25% received combined ChT + HT. Clinicopathological details of the patients are summarized in Table 1.

Low-risk patients had slightly but significantly higher PREDICT scores compared to high-risk patients (78% *vs.* 73% and 81% *vs.* 77%, for HT only or combined ChT + HT, respectively. The PR level was significantly lower in the high-risk group (3.5% *vs.* 80%) (Table 2) (Figure 1).

A unit decrease in the PREDICT scores was associated with an 11% increase in the odds of being in the high-risk group (Table 3). However, these effects lost significance in the multivariate analysis. A unit decrease in the PR level was significantly associated with increased odds (by 5% in the multivariate analysis) of being in the high-risk group. Grade 3 tumors were about 3.72 times more likely to be high risk compared to grade 1–2 tumors in univariate analysis.

Discussion and Conclusion

The aim of this study was to categorize the risk of HR positive/HER-2 negative, early stage breast cancer patients, focusing on high-risk *vs.* not high-risk classification using the TAILORx risk categorization and the PREDICT tool for OS scores, focussing on older patients. The results revealed that low-risk patients had slightly higher PREDICT scores compared to high-risk patients, which was a significant difference. Moreover, a unit decrease in the PREDICT scores and PR level was associated with an increase in the odds of being in the high-risk group. However, the effects of PREDICT scores did not remain significant on multivariate analysis, whereas a unit decrease in the PR level continued to be significantly associated with increased odds of being in the high-risk group (14, 15).

The PREDICT tool has been previously validated in the Dutch breast cancer population (14) and our study further supports its utility in predicting the risk group of breast cancer patients. The PREDICT tool, along with other genomic signatures, such as the 21-gene recurrence score, are essential in guiding decisions on adjuvant systemic therapy for women with early-stage, invasive breast cancer (21). The 21-gene recurrence score, in particular, has been shown to be useful in determining the benefit of chemotherapy among women of different age groups with HR-positive, HER-2-negative, node-negative breast cancer (22). Our study also highlighted the significance of PR levels in determining the risk group, supporting the use of biomarkers in guiding decisions on adjuvant systemic therapy (21).

The present study is particularly relevant for older patients, as the management of breast cancer in this population presents unique challenges. Older patients often have comorbidities and may experience more side effects from chemotherapy, making it even more important to accurately assess the risk and tailor the treatment accordingly (23, 24). While many studies have reported a heightened risk of endometrial carcinoma in postmenopausal breast cancer patients undergoing tamoxifen treatment, a study by Chiofalo et al. (25), involving 1199 patients, found no significant difference in risk between those treated with tamoxifen and those either treated

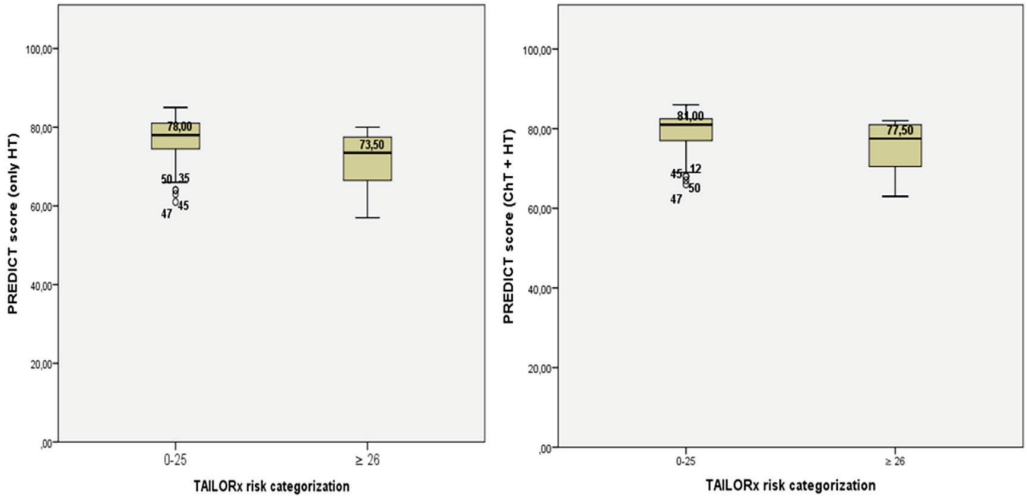

Figure 1. a. PREDICT scores (with only HT treatment) according to TAILORx risk categorization (ODX-RS<26 ODX-RS and ODX-RS ≥26) (left), 1b. PREDICT scores (with combine treatment) according to TAILORx risk categorization (right)

Table 2. Association between clinicopathological characteristics according to risk groups

	Low-risk group (n = 52) median (min-max)	High-risk group (n = 12) median (min-max)	*p*-value
PREDICT (only hormonotherapy)*	78 (61–85)	73 (57–80)	**0.02**
PREDICT (chemoterapy + hormonotherapy)*	81 (66–86)	77 (63–82)	**0.03**
Tumor size (cm)	1.65 (0.6–4.0)	1.85 (1.3–3.6)	0.21
Ki-67 level (%)	18 (5–50)	25 (10–40)	0.10
PR level (%)	80 (0–100)	3.5 (0–80)	**<0.001**

*PREDICT scores were defined as calculated overall survival rates via PREDICT tool; min: minimum; max: maximum

Table 3. Regression models of potential prognostic variables associated with the high-risk group (≥65 years)

All patients	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
PREDICT score* (only hormonotherapy)	0.89	0.81–0.97	**0.02**	0.72	0.25–2.03	0.53
PREDICT score* (chemoterapy + hormonotherapy)	0.89	0.80–0.99	**0.04**	1.22	0.39–3.82	0.72
Tumor size	1.20	0.57–2.51	0.62			
Ki-67	1.06	0.99–1.13	0.08			
ER	0.96	0.91–1.02	0.96			
PR	0.96	0.93–0.98	**0.002**	0.95	0.92–0.98	**0.002**
Grade 1-2 vs. grade 3	3.72	1.01–13.8	**0.04**	3.57	0.53–23.8	0.18

*PREDICT scores were defined as calculated overall survival rates via PREDICT tool; CI: confidence interval; OR: odds ratio

with aromatase inhibitors or receiving no treatment (26). Previous studies have shown that the use of the 21-gene recurrence score was of variable utility among older women of different races (27), and our study adds to this body of literature by highlighting the importance of using a combination of tools, such as the PREDICT scores, PR levels, and TAILORx risk categorization for a more comprehensive risk assessment in older patients (28, 29).

Interestingly, the present study found that grade 3 tumors were more likely to be high risk compared to grade 1–2 tumors in univariate analysis, although this lost significance in the multivariate analysis. This finding is in line with previous studies that have highlighted the association between higher tumor grade and worse outcomes (30, 31). The clinical utility of genomic signatures in young breast cancer patients has been previously documented (32), and our study extends these findings to older patients, underlining the importance

of incorporating genomic signatures and tools such as PREDICT in the risk assessment and management of breast cancer in older patients.

However, it is important to acknowledge certain limitations of the study. These include the relatively small sample size and the retrospective nature of the analysis. Additionally, the study did not assess the impact of these tools on clinical outcomes, such as recurrence-free survival, which would be important to evaluate in future studies.

In conclusion, the present study underscores the importance of using a combination of tools, including the PREDICT tool, PR levels, and TAILORx risk categorization, for a comprehensive risk assessment in HR positive/HER-2 negative, early stage breast cancer in older breast cancer patients. Accurate risk assessment is crucial for tailoring the treatment and optimizing outcomes in this vulnerable population. Future studies are warranted to further validate these findings in larger cohorts and to explore additional biomarkers and genomic signatures that may aid in the risk assessment and management of breast cancer in older patients.

Ethics Committee Approval: The study method was reviewed and performed in accordance with İstanbul Bilgi University Ethics Committee. (project number: 2023-40162-053, date: 30.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ç.Ü.; Design: Ç.Ü.; Data Collection or Processing: E.G., M.Ö., K.N.P., C.U., H.K., O.D., V.Ö., Ç.Ü.; Analysis or Interpretation: Ç.Ü., Ç.O., T.D.; Literature Search: Ç.Ü., Ç.O., V.Ö.; Writing: Ç.Ü., Ç.O.; Editing: Ç.Ü., T.Ö., Ç.O., V.Ö.

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Case Report

Eur J Breast Health 2023; 19(4): 331-334
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A Rare Complication Following Breast Conserving Surgery: Pyoderma Gangrenosum

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ABSTRACT

Pyoderma gangrenosum (PG) after breast-conserving surgery is rare, and its diagnosis is often delayed because of the similarity to wound infection and the broad differential diagnosis for PG, making it a diagnosis of exclusion. A 60-year-old woman who underwent breast conserving surgery and sentinel lymph node biopsy for invasive breast carcinoma presented with increasing erythema, fever and serosanguinous discharge in the lower outer quadrant of the right breast at the site of tumour excision on postoperative day (POD) 9. Fever persisted despite antibiotics and the patient was noted to have leucocytosis (0.9 x 10^9/L), neutrophilia (37.8 x 10^9/L) and elevated C-reactive protein levels (136 µg/mL) on POD 16. Microbiology and blood culture results were negative but the breast ulcer continued to expand at a rate of 1-2 cm a day. The patient underwent surgical debridement on POD 21 to rule out necrotising soft tissue infection. Persistent ulcer progression, despite debridement and antibiotics, led to clinical suspicion of PG and the patient was started on prednisolone and cyclosporin. A rapid response was seen with treatment and an optimum healing process was noted over the subsequent three-month follow-up period. Early suspicion, careful macroscopic evaluation of disease progression and appropriate use of immunosuppressive therapy are important for the management of PG. Prompt initiation of immunosuppressive therapy may avoid unnecessary treatment and aggravation of the surgical wound.

Keywords: Breast cancer; breast conserving surgery; pyoderma gangrenosum

Cite this article as: Costa G, İlgün S, Pisani D, Agius J. A Rare Complication Following Breast Conserving Surgery: Pyoderma Gangrenosum. Eur J Breast Health 2023; 19(4): 331-334

Key Points

- Early diagnosis of pyoderma gangrenosum (PG) is critical to avoid unnecessary treatment and aggravation of the surgical wound.
- PG of the breast although rare has been reported in the literature.
- However its onset following breast conserving surgery is very rare and may be difficult to diagnose due to its wound infection-mimicking nature.
- This case report should raise awareness about PG following breast conserving surgery as well as guide the clinician in making an appropriate and timely diagnosis to start targeted treatment.

Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis with multiple and differing clinical presentations and associated comorbidities (1). PG is often associated with systemic diseases, such as inflammatory bowel disease, rheumatoid arthritis or haematological malignancies (2). The pathophysiology is poorly understood and is thought to involve adaptive and innate immune system dysregulation, abnormalities of neutrophil function such as chemotaxis, adhesion and trafficking, abnormal phagocytosis and genetics (3).

PG typically presents with painful lesions in different locations and with non-specific histology. This poses a clinical challenge and diagnosis is often delayed. In the classic ulcerative variant, characterized by ulcers with inflammatory undermined borders, a broad differential diagnosis of malignancy, infection, and vasculitis needs to be considered, making PG a diagnosis of exclusion (4).

Breast PG is uncommon, with only 87 cases documented in the literature. It is most commonly associated with breast reduction surgery (38 cases, 44%) followed by augmentation mammoplasty and mastectomy with free deep inferior epigastric perforator flap (5). We present a very rare case of unilateral breast PG following breast conserving surgery in a 60-year-old woman which, to the best of our knowledge, is the first such case reported in the literature.

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The following case is presented in accordance with the CARE reporting checklist.

Case Report

A 60-year-old female patient with no previous co-morbidities underwent breast conserving surgery and sentinel lymph node biopsy for invasive breast carcinoma. The patient did not have any co-morbidities, either before or after the surgery. Her cancer was no special type, grade 3 (pT1c, N0). She presented to the emergency department on postoperative day 9 with increasing erythema and serosanguinous discharge in the lower outer quadrant of the right breast, at the site of tumour excision. A breast ultrasound carried out at the emergency department was suggestive of a seroma. A wound swab was taken and the patient was discharged on oral antibiotics (Ciprofloxacin and Clindamycin) with planned follow-up.

She presented one week later with recurrent febrile episodes (37.8 °C), severe tenderness and a rapidly evolving, cutaneous ulcer at the lower outer quadrant of the right breast, sparing the nipple and areola (Figure 1).

The patient was admitted for further investigations and treatment. She was noted to be febrile (Temp 38.5 °C) and tachycardic with a heart rate of 98 bpm. Blood tests revealed an inflammatory picture with leucocytosis (0.9 x 10^9/L), neutrophilia (37.8 x 10^9/L) and elevated C-reactive protein levels (136 µg/mL). Despite antibiotic treatment with high dose Tazocin and Metronidazole, the intermittent episodes of fever persisted and the breast ulcer continued to expand at a rate of 1-2 cm a day (Figure 2).

Microbiology and blood culture results were all negative. On the fifth day of admission the patient underwent surgical debridement to rule out necrotising soft tissue infection (Figure 3). Intraoperatively it was noted that only skin was affected and the underlying breast tissue was spared infection or necrosis.

Despite the debridement and antibiotics, the ulceration continued to progress and blood results did not improve. This led us to consider PG as part of the differential diagnosis.

A skin biopsy obtained during surgical debridement was reported as diffuse epidermal ulceration with associated gangrenous necrosis of the superficial dermis. A dense transdermal acute inflammatory infiltrate, comprised almost exclusively of neutrophil polymorphs, was evident. Associated luekocytoclastic vasculitis was also identified in places. There was no evidence of malignancy. No micro-organisms were identified histologically. These findings were supportive of the possible diagnosis of PG (Figures 4, 5).

The case was discussed with dermatology and the patient was started on oral prednisolone 60 mg daily for one week (tailed down by 10 mg every following week) and Cyclosporin 100 mg twice daily. A rapid response was noted with the steroid treatment. The patient reported reduced symptoms of pain and was no longer febrile within a matter of days. During the three-month follow-up period, a good healing process with significant improvement was evident (Figure 6).

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

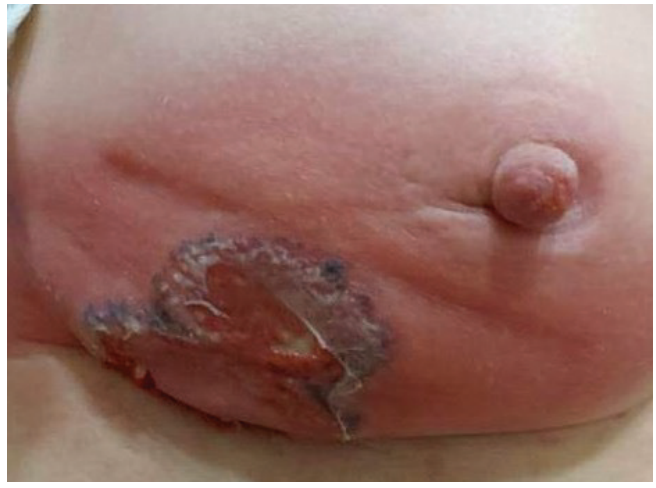

Figure 1. Ulcerated area with surrounding erythema on presentation

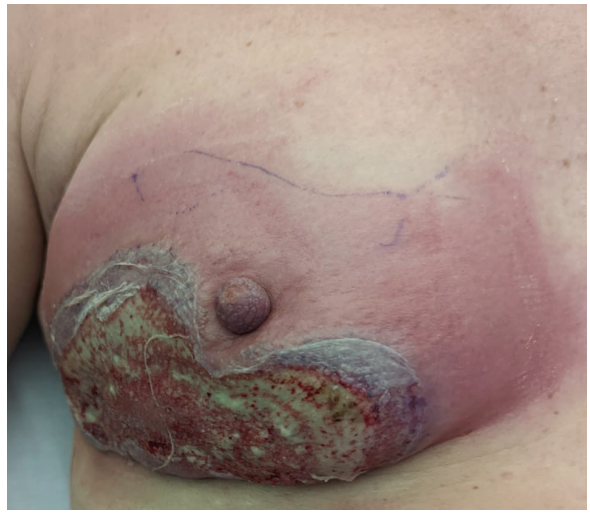

Figure 2. Evolution of ulcerated area and surrounding erythema

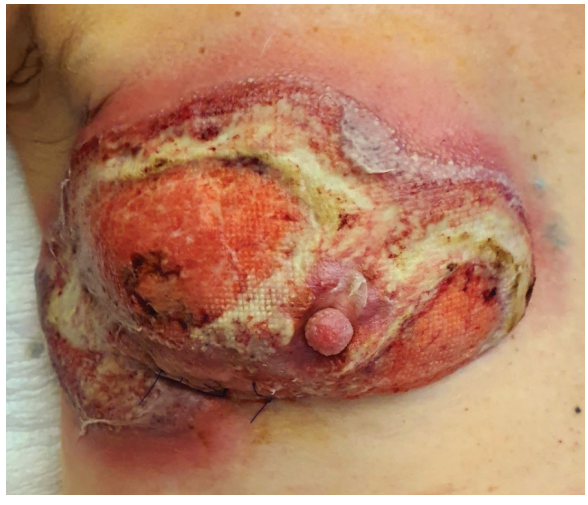

Figure 3. Two days following surgical debridement of non-viable skin

Discussion and Conclusion

PG is a reactive, non-infectious, inflammatory dermatosis, which falls within the spectrum of the neutrophilic dermatoses. These constitute a broad spectrum of diseases of uncertain and complex pathophysiology,

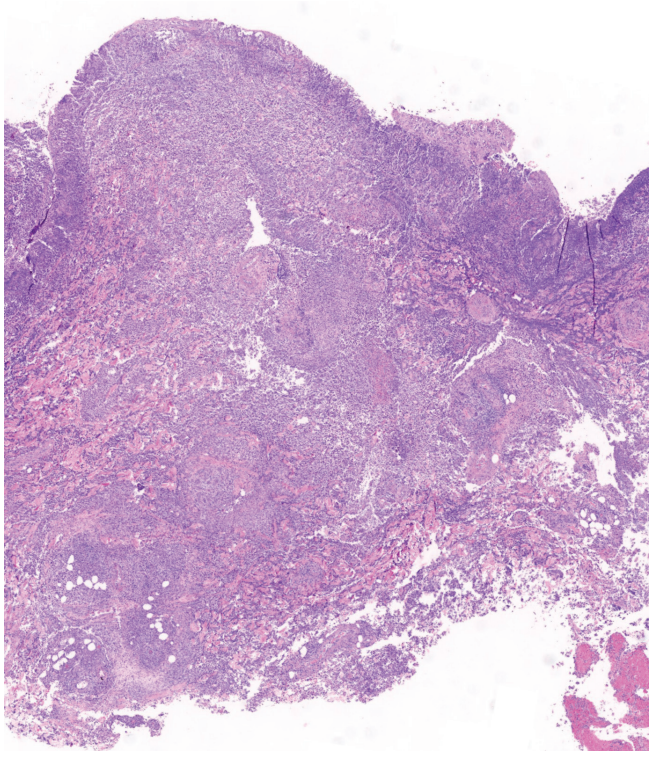

Figure 4. Skin biopsy showing diffuse epidermal ulceration with gangrenous necrosis of the superficial dermis and a dense transdermal inflammatory infiltrate (H&E, x20)

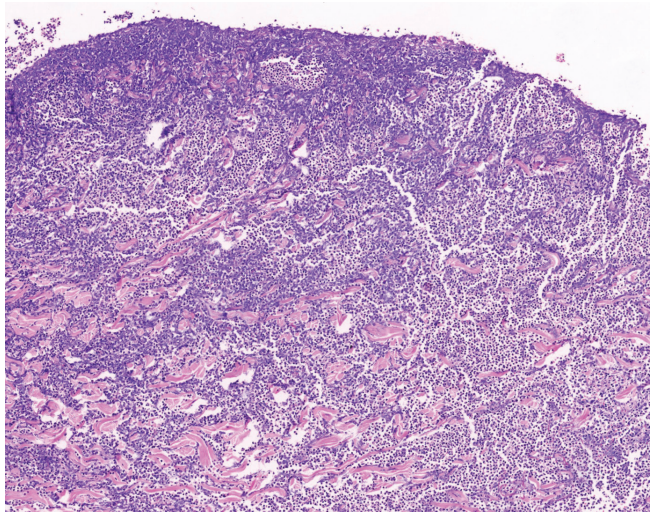

Figure 5. Diffuse epidermal ulceration with gangrenous necrosis of the upper dermis is evident. The inflammatory infiltrate is comprised almost exclusively of polymorphonuclear leukocytes. Micro-abscess formation is evident

which also includes Sweet's syndrome, neutrophilic dermatosis of the dorsal hand, neutrophilic eccrine hidradenitis and Behcet's disease. Classical PG is the most common form (85% of cases) and usually presents as an extremely painful erythematous lesion, which rapidly progresses to a blistered or necrotic ulcer. The lower legs are most frequently affected, although PG can present at anybody site (6).

Minor trauma to skin can result in exaggerated skin injury, a phenomenon known as pathergy (7). PG lesions can be easily misdiagnosed as simple non-healing ulcers and patients usually undergo debridement, resulting in a rapid deterioration of the condition through a pathergic response.

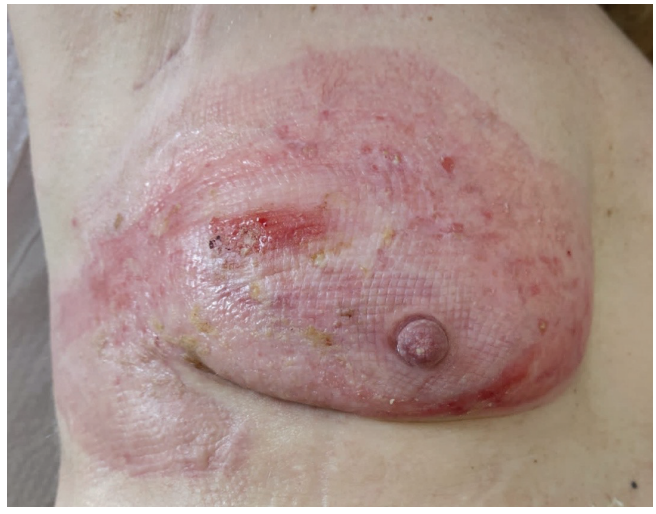

Figure 6. Significant clinical improvement noted after three months of treatment

PG has an extensive differential diagnosis because all other causes of cutaneous ulcers should be considered. These include arterial and venous disease, haematological/immunological causes (sickle cell disease, cryoglobulinemia, anti-phospholipid syndrome), vascular occlusion, vasculitis, infections, calciphylaxis, drug-induced ulceration, primary or metastatic tumours, hypertension (Martorell ulcer) and other inflammatory disorders including cutaneous Crohn's disease (6).

PG remains a clinical and sometimes challenging diagnosis and although histology of skin biopsies can be supportive, the main value of the skin biopsy is to exclude other causes of cutaneous ulceration and to allow specimens to be sent for bacterial, mycobacterial and fungal cultures. This makes PG a diagnosis of exclusion, based on ulcerative characteristics, negative microbiological results, supportive histological findings, resistance to antibiotic and surgical therapy and improvement after steroid treatment (8).

The severity of PG influences the mode of treatment. The aim of first-line treatment is to optimise local wound care. Potent topical corticosteroids and tacrolimus ointment applied to the ulcer surface are useful and intralesional injections of corticosteroid into the erythematous active border may be considered (9).

In more severe cases, such as the case presented above, systemic therapy is required. Oral corticosteroids are the mainstay of treatment and are used to gain rapid control. Cyclosporin can be used, either alone or in combination with corticosteroids, as a steroid-sparing agent in cases where prolonged treatment is required (10). In the present case, antibiotics were initially started based on signs of inflammation and probable infection. Since the microbiology and blood culture results were negative, a therapeutic approach with corticosteroids and cyclosporin was initiated and this provided effective treatment.

PG following breast-conserving surgery is rare and is not easily diagnosed. Early suspicion, careful macroscopic evaluation of disease progression and appropriate use of immunosuppressive therapy are important for the management of PG. Prompt initiation of immunosuppressive therapy may avoid unnecessary treatment and aggravation of the surgical wound.

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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Case Report

Eur J Breast Health 2023; 19(4): 335-337
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Primary Breast Pleomorphic Liposarcoma Evaluation With MRI and Pathology: A Rare Case

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Keywords: Breast; liposarcoma; pleomorphic; magnetic resonance imaging

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Key Points

- Magnetic resonance imaging makes an important contribution to demonstrating the fat content in the diagnosis of liposarcoma.
- When a spindle cell tumor is detected in the mammary gland which is an epithelial organ, it should be differentiated from metaplastic carcinoma and malignant phyllodes tumor by performing large tissue sampling and immunohistochemical studies for the diagnosis of sarcoma.

A 22-year-old female patient complained of a mass in the left breast. The patient had a first degree-family history of liposarcoma in the eye. Rapid enlargement of the breast was described in the anamnesis.

Dynamic contrast-enhanced breast magnetic resonance imaging (MRI) was performed for the patient who presented to another center with heterogeneous mass information on breast ultrasound. The mass showed heterogeneous fat intensity in T-1 weighted (T1W) examination (black arrowheads - Figure 1a) in the MRIs. In addition, signal reduction was observed with fat-suppressed T1W images with Spectral Attenuated Inversion Recovery sequence in areas where the mass contained macroscopic fat (asterisk - Figure 1b) and a spontaneous hyperintense area (arrowhead- Figure 1b) consistent with a focal hemorrhage. A curvilinear hypointense structure (black arrowhead- Figure 1c) shows a vascular feeder within the well-circumscribed mass. The high signal in the fat-suppressed Short Tau Inversion Recovery sequence of MRI examination reflected the high-water content of the lesion while reduced signal was observed in macroscopic fat areas within the lesion. In the first minutes following intravenous contrast administration, the tumor showed intense heterogeneous enhancement along with necrotic areas (black arrow - Figure 2a) in places where no enhancement was seen. Contrast washout was observed in the mass

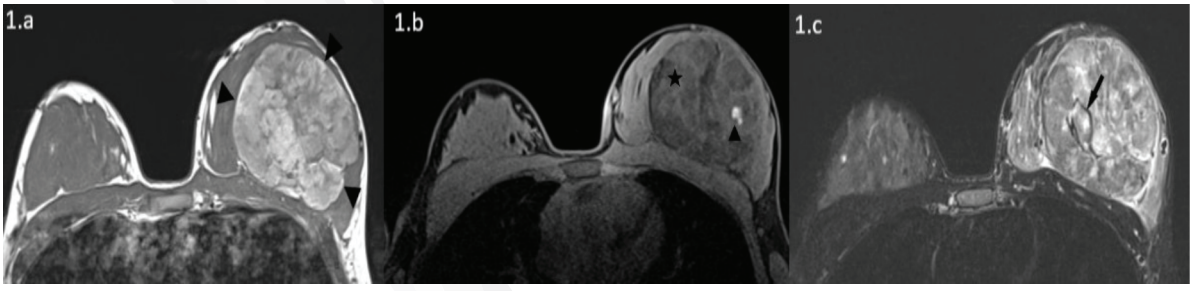

Figure 1. Turbo spin echo – T1 weighted **(1a)**, pre-contrast fast low angle shot T1 weighted **(1b)**, Short Tau Inversion Recovery (STIR) (**1c**) axial image of both breast magnetic resonance imaging examination. The mass that expands the left breast asymmetrically compared to the right showed heterogeneous fat intensity (black arrowheads - 1a), signal reduction with fat-suppressed T1W images with spectral attenuated inversion recovery in areas where the mass contained macroscopic fat (asterisk - 1b) and a spontaneous hyperintense area (arrowhead - 1b) consistent with a focal hemorrhage. STIR image shows high signal reflected the high-water content of the lesion, a vascular feeder as curvilinear hypointense structure (black arrowhead- 1c) within the well-circumscribed mass

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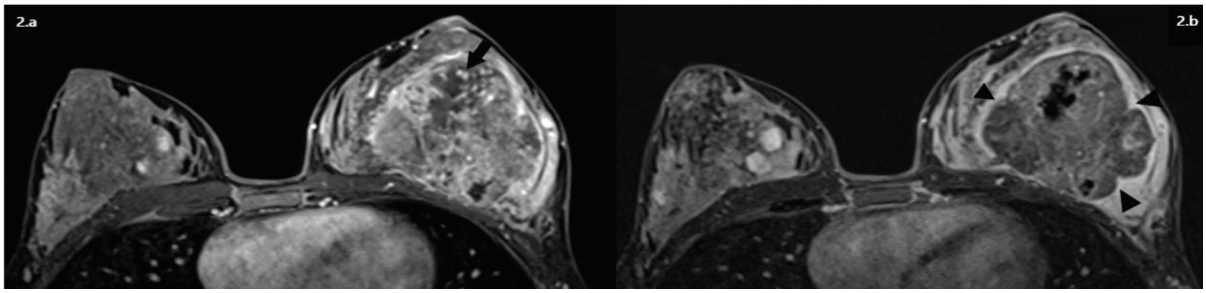

Figure 2. Subtraction images of dynamic contrast-enhanced T1W images. In early phase, the tumor showed intense heterogeneous enhancement along with necrotic areas (black arrow - **2a**) in places where no enhancement was seen. In the late phase, contrast washout was observed in the mass, in addition to the continuation of peripheral enhancement (black arrowheads - **2b**)

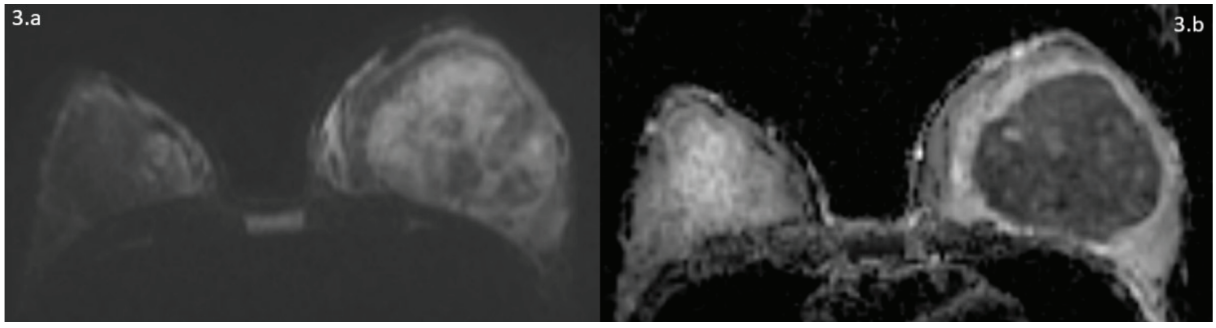

Figure 3. Diffusion weighted image (DWI; b value: 1000) (**3a**) and Apparent Diffusion Coefficient (ADC) map images (**3b**). The tumor was seen to have a high signal on DWI and low signal on the ADC map. The significant diffusion restriction suggested the presence of high cellularity and possibly high-grade tumor

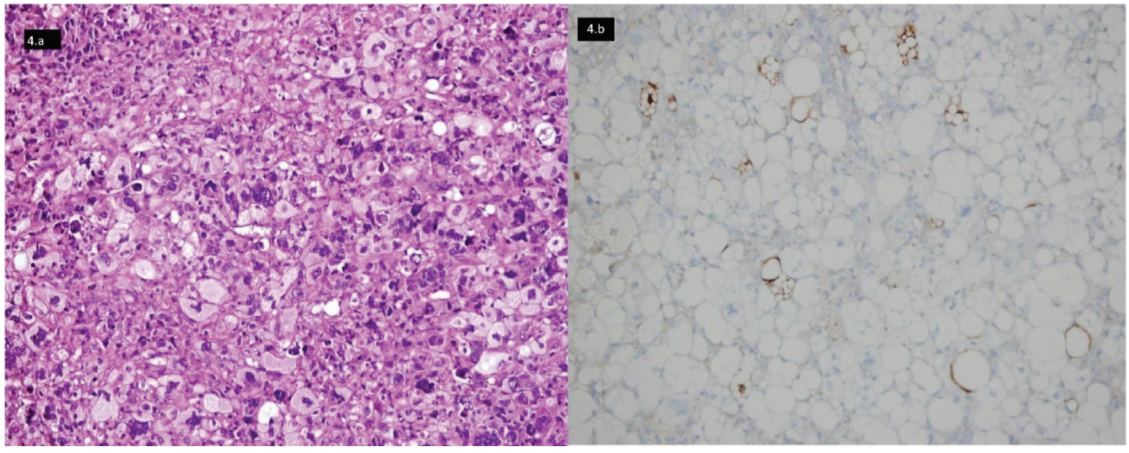

Figure 4a. The tumor was composed of high-grade cells with varying numbers of pleomorphic and atypical multinucleated tumor cells (H&E, X 200), **4b.** S100 positivity

in the late phase (sixth minute) dynamic image, in addition to the continuation of peripheral enhancement (black arrowheads - Figure 2b). The tumor was seen to have a high signal on diffusion-weighted image and low signal on the apparent diffusion coefficient map. The significant diffusion restriction suggested the presence of high cellularity and possibly high-grade tumor (Figures 3a, 3b). Tru-cut biopsy of the mass indicated the diagnosis of a sarcoma with possible pleomorphic liposarcoma. The patient underwent left mastectomy. The tumor was composed of high-grade cells with varying numbers of pleomorphic and atypical multinucleated tumor cells (H&E stain - Figure 4a) and S100 positivity in the tumor cells (Figure 4b). Although Vimentin and S100 positivity were observed by immunohistochemistry, the sections were negative for keratins and SOX-10. The tumor was diagnosed histologically as a pleomorphic liposarcoma (Fédération Nationale des Centres de Lutte Contre le Cancer grade 3). Since the patient also had a family history, *TP53* gene mutation was detected in the genetic research performed after the surgery, and Li Fraumeni syndrome was diagnosed. MRI made an important contribution in the current case, albeit with low specificity, by demonstrating the fat content in the diagnosis of liposarcoma (1). When a spindle cell tumor is detected in the mammary gland, which is an epithelial organ, it should be differentiated from metaplastic carcinoma and malignant phyllodes tumor by performing large tissue sampling and immunohistochemical studies for the diagnosis of sarcoma (2-4). Wide excision is important in the treatment and adjuvant chemotherapy-radiotherapy may be required.

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.G.C., A.B., R.Y.; Design: R.Y.; Analysis or Interpretation: R.G.C., A.B., R.Y.; Literature Search: R.G.C., A.B., R.Y.; Writing: R.G.C., A.B., R.Y.

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