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NCBC National Consortium of Breast Centers

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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).

The European Journal of Breast Health indexed in PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Embase, EBSCO, CINAHL, Scopus.

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The European Journal of Breast Health (Eur J Breast Health) is an international, open access, online-only periodical published in accordance with the principles of independent, unbiased, and double-blinded peer-review.

The journal is owned by Turkish Federation of Breast Diseases Societies and affiliated with Senologic International Society (SIS), and it is published quarterly on January, April, July, and October. The publication language of the journal is English. The target audience of the journal includes specialists and medical professionals in general surgery and breast diseases.

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Table 1. Limitations for each manuscript type

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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. All authors should be listed if an article has six or less authors; it should not be represented by "et al." in articles. Arabic numbers in parentheses. References published in PubMed should have a PMID: xxxxxx at the end of it, which should be stated in parenthesis. The reference styles for different types of publications are presented in the following examples.

Journal Article: Little FB, Koufman JA, Kohut RI, Marshall RB. Effect of gastric acid on the pathogenesis of subglottic stenosis. Ann Otol Rhinol Laryngol 1985; 94:516-519. (PMID: 4051410)

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

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

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

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

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

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

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

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

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

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option

may be cancelled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

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NCoBC 34TH ANNUAL INTERDISCIPLINARY BREAST CANCER CONFERENCE

Review

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Techniques for Retaining the Inframammary Fold in Implant-Based Reconstructive Breast Surgery

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ABSTRACT

Both reconstructive and aesthetic implant-based breast surgery are associated with the risk of damage or destruction of the inframammary fold (IMF). Such surgical complications lead to implant disposition and disruption of the natural shape of the breast. Various techniques are used to restore the IMF or prevent its damage, such as tissue rearrangement, sutures, capsular flaps, the use of biological matrices or synthetic meshes. In this review, all current methods of retaining the IMF and the frequency of complications reported over the past ten years are reviewed.

Keywords: Aesthetic plastic and reconstructive; breast reconstruction; implant; inframammary fold; review; surgery

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Key Points

- There are a number of methods for strengthening the inframammary fold in implant-based breast surgery, such as tissue rearrangement, sutures, capsular flaps, the use of biological matrices or synthetic meshes.
- All techniques can be highly effective, but the use of acellular dermal matrix is associated with slightly more complications.
- Not all synthetic or biological meshes/matrices are equally safe for the patients.

Introduction

The inframammary fold (IMF) is a critical structure in breast aesthetics, defining the lower pole of the breast and forming the acute angle with the chest wall (1, 2). To achieve a good and stable result in breast surgery, it is preferable to preserve the IMF. The ideal IMF has a semi-elliptical shape, which may become attenuated with age and may descend after some surgical procedures, such as implant-based breast surgery changing the position of the IMF or creating a new one (3).

Since the first description of the reconstruction of the IMF by Pennisi (4) and Ryan (5) using local tissue remodeling, new methods have emerged, based on suture techniques, and the use of biological or synthetic matrices. At the same time, these methods have gradually begun to be used not only in reconstructive surgery, but also in aesthetic breast surgery.

In this review, we would like to summarize the evidence of the past ten years publications for retaining or restoring the IMF in reconstructive and aesthetic breast surgery, and also try to identify the optimal methodology of achieving more predictable and durable outcomes with fewer complications.

Anatomy

The study of the anatomical structure of the IMF has been going on for about 200 years and there is still no clearly accepted optimal concept. In 1845, Cooper (6) suggested that the IMF was formed by turning the mammary gland under itself. Thus, something similar to a folded edge would be obtained. However, we now understand that the anatomy of the IMF is much more complex and includes a connective tissue component.

At the end of the 20th century, a theory was put forward about the formation of the IMF being due to the presence of a true ligament. The work of Bayati and Seckel (7) hypothesized for the first time a true ligament in regard of the IMF. According to their description, the ligament arises as a thickening of the fascia of the external oblique and serratus anterior muscles laterally and the fascia of the rectus abdominis muscle medially. The medial part of the inframammary ligament originates from the periosteum of the fifth rib, and the lateral part originates from the fascia between the fifth and sixth ribs, and then it grows into the deep layer of the dermis in the area of the IMF.

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However, these authors, having carried out studies on cadaveric bodies and with the help of histological studies, did not find the ligament (8-10). According to their research, the IMF was formed by dermal collagen fibers that are fixed to the thoracic fascia. Thus, the concept of the fascial origin of the IMF was formed. This concept was further generalized and supplemented by clinical observations (11). It was proposed that the formation of the IMF occurs due to the fusion of the sheets of the superficial fascial system (SFS) of the mammary gland. The entire thickness of the subcutaneous tissue of the human body is penetrated by collagen trabeculae that connect the skin to the deep fascia, this fascial network was called the SFS. The subcutaneous tissue is divided by the fascia of Scarpa into a stroma-rich, superficial, and deep layer. The superficial tissue layer has many strong transverse connective tissue fibers, between which small lobules of subcutaneous fat are enclosed. The surface layer is firmly connected to the skin, together with which it forms a cover for the rest of the mammary gland tissues. Deeper fascial fibers are less common, oriented radially, corresponding to the ductal-lobular structure. This fascial part is Cooper's ligaments system, which is involved in the formation and maintenance of the cone-shaped breast. Between the gland and the deep fascia, in the retromammary space, there are many fewer connective tissue fibers. As a result of the loose arrangement of the fibers, there are large lobules of fat between them, which ensures the sliding of the gland along the chest wall. Thinning of the deep fat layer occurs in the IMF area, as a result of which the superficial layer with the adjacent skin is fixed directly to the deep fascia. In fact, the skin grows into the fascia of the underlying muscle, which looks like a longitudinal groove. The latest study confirmed the IMF's fascial origin, and presents it not as a single membrane like Cooper's ligaments or other fascia, but as a multilayer structure formed by the gradual accretion of thin fascia and their interweaving into the dorsal fascia of the mammary gland and the superficial fascia above the rectus abdominis muscle (12).

Materials and Methods

A comprehensive search was performed in PubMed, Embase.com and the Cochrane Library from 2013 till 2024. Search terms included controlled terms (MesH in PubMed, Emtree in Embase), as well as free text terms. The reference lists of all identified publications were checked to retrieve other relevant publications. The search was limited to articles published in English. Search terms "inframammary fold" AND "implant" were used. The initial list included 154 articles. Based on the title and abstract, 115 articles were excluded. The exclusion criteria were: articles not related to implant-based mammoplasty and/or IMF surgery and articles not in English. In addition, 10 articles were excluded due to the impossibility of interpreting the results (a significant part of the data regarding the number of patients, surgical methods, and postoperative results were missing). However, the reference lists of eligible articles were analyzed, which led to the inclusion of seven more articles. A total of 36 articles were selected on the topic of strengthening the IMF in implant-based mammoplasty (Figure 1).

Results

General information about the studies, the methods used, and the number of complications is presented in Table 1.

Local Tissue Rearrangement

The patient can benefit from cost-effective methods of strengthening the IMF using their own tissues, such as dermis flaps or breast parenchyma, as "supportive structures". The composition of these flaps depends on the type of surgery, whether aesthetic or reconstructive.

De Vita et al. (13) studied the results of primary bilateral augmentation-mastopexy using an inferior dermoglandular flap in 182 patients. The technique involved isolating a parenchyma flap of the lower pole of the breast and creating a "balcony" with sutured edges to the pectoralis major muscle. Over four years, minor complications were identified, and six patients required revision surgery for hematoma, capsular contracture, or "bottoming out". The majority of patients rated their results as "good" and there were no dissatisfied patients. This technique allows surgeons to stabilize the implant in the projection of the IMF and from the medial and lateral sides, and protects the implant from exposure in case of suture failure. AboShaban and Abdelaty (14) shared their results on revision bilateral augmentation-mastopexy in 53 patients, covering the implant in two layers: the pectoralis major muscle and dermoglandular flap, the NAC-flap on top, and breast pillars on the bottom. No serious complications were identified, indicating that this technique allows surgeons to stabilize the IMF and implant position.

A study by Han et al. (15) reported on 170 primary and 14 secondary augmentations using the adipofascial flap. They partially dissected the pectoralis major muscle fascia with retromammary fat, covered the implant's lower slope, and sutured it to the mammary gland tissues or the lower edge of the muscle. This technique strengthened the IMF with dense, vascularized tissue. A cadaver study showed a flap thickness of 3–4 mm. However, doubts remain about the possibility of fixing the flap to the gland tissue and its cutting, and there was no information on reoperations with similar complications.

In oncological breast reconstruction, surgeons often cannot use glandular tissue for the lower covering flap, but the dermis can be used. A technique by Ellabban et al. (16) used a de-epithelialized skin "hammock" for immediate implant-based breast reconstruction, suitable for patients with severe breast ptosis undergoing skin-reducing mastectomy. In 42 cases, the skin flap was de-epithelialized, forming two upper edges and sutured to the lower pectoralis major muscle. This method is an alternative to the dermoglandular flap but has a risk of flap necrosis if excessively thinned.

Capsular Flap

Capsule formation around the implant is a natural delimiting reaction of the body against any foreign object. Replacing implants, surgeons used to remove the capsule to prevent further capsular contracture. In 2002, a technique using the capsule to strengthen the IMF and stabilize the position of new implant was first described (17).

In 2013, Bogdanov-Berezovsky et al. (18) published two clinical cases using a capsular flap. The first patient had an implant rupture and underwent bilateral implant replacement. They performed a partial capsulotomy on both sides and created a pocket with bipedical capsular flaps from the posterior segment of the peri-implant capsule. The second patient underwent augmentation mammoplasty after previously installed and removed implants. The lower distal edge of the capsule was raised in the form of a flap with an upper base from the chest wall to the calculated level of the newly created pocket. The postoperative period proceeded without complications.

In the same year, Persichetti et al. (19) published a study of 30 patients who underwent revision mammoplasty to correct IMF. The surgical

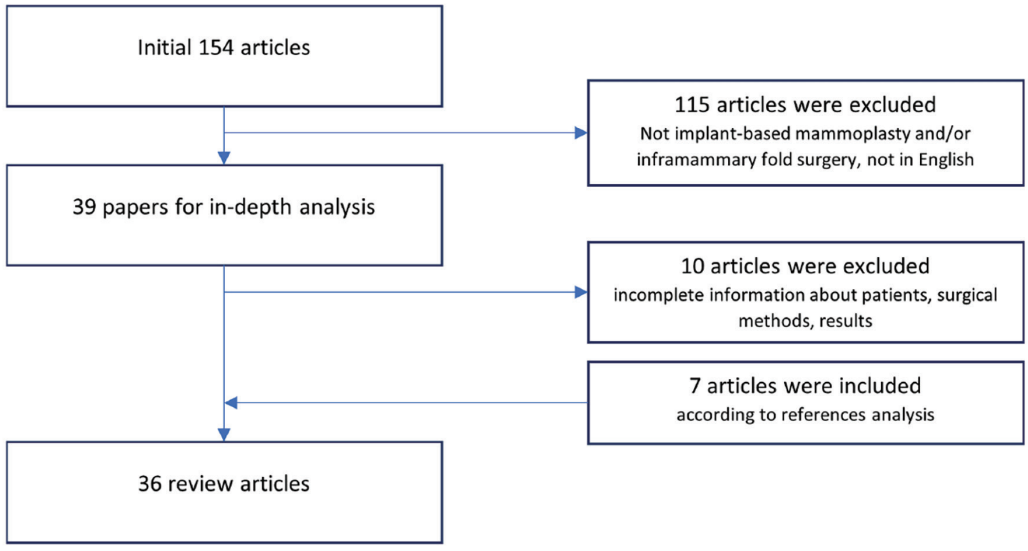


Figure 1. Diagram depicting the process of searching and selecting articles for review

Table 1. The table briefly describes all the articles included in this review

Author, y.	Surgical intervention	Methods	Number of patients	Number of complications (major and minor)	Follow-up period
Local tissue rearrangement					
de Vita et al. (13), 2017	Augmentation-mastopexy	"Balcony" technique	182 (*n* = 364 breasts)	Major: 6 Minor: 20	4 years
Han et al. (15) 2018	Augmentation mammoplasty	Adipofascial flap	184 (*n* = 368 breasts)	Major: 0 Minor: 21	21 mo
Ellabban et al. (16), 2020	Implant-based breast reconstruction	"Hammock" dermal flap	42 (*n* = 52 breasts)	Major: 4 Minor: 6	13 mo
AboShaban MS, Abdelaty (14) 2022	Revision bilateral augmentation-mastopexy	Dermoglandular flap	53 (*n* = 106 breasts)	Major: 0 Minor: 9	3.6 years
Capsular flap					
Bogdanov-Berezovsky et al. (18), 2013	Implant replacement/ augmentation mammoplasty	Capsular flap	2 (*n* = 4 breasts)	0	0/2 years
Persichetti et al. (19), 2013	Revision mammoplasty	"Slingshot" Capsular flap	30*	Major: 0 Minor: 5	0.5–3 years
Mayer et al. (20), 2014	Revision mammoplasty	Capsular flap/graft	21 (*n* = 23 breasts)	Major: 2 Minor: 5	16 mo
Wessels et al. (21), 2014	IMF reconstruction	"Hammock" Capsular flap	12 (*n* = 21 breasts)	0	N/A
Ismagilov et al. (22), 2017	Expander-based breast reconstruction	Posterior sheet of the expander capsule	321*	Major: 0 Minor: 42	5–6 years
Cogliandro et al. (23), 2018	Expander-based breast reconstruction + mastopexy	Dermo-capsular flap	20 (*n* = 40 breasts)	Major: 0 Minor: 2	12 mo

Table 1. Continued

Author, y.	Surgical intervention	Methods	Number of patients	Number of complications (major and minor)	Follow-up period
Sutures					
Mohmand and Ahmad (24) 2013	Augmentation mammoplasty	3 sutures	32 (*n* = 32 breasts)	Major: 0 Minor: 3	N/A
Hirsch et al. (25), 2014	Expander-based breast reconstruction	Barbed sutures	45*	Major: 0 Minor: 2	N/A
Terao et al. (26), 2015	Implant-based breast reconstruction	Drawstring method	95 (*n* = 95 breasts)	Major: 0 Minor: 10	N/A
Nakajima et al. (27), 2018	Implant-based breast reconstruction	Vertical pendulum suture	9 (*n* = 9 breasts)	Major: 0 Minor: 0	11 mo
Goddard et al. (28), 2022	Various mammalogical surgeries	Hemostatic net	24 (*n* = 48 breasts)	Major: 0 Minor: 2	12.9 mo
ADM					
Hanna et al. (30), 2013	Expander-based breast reconstruction	ADM/submuscular procedure	31 (*n* = 40 breasts)/44 (*n* = 62 breasts)	Major: 7 patients Minor: 6 patients/Major: 4 patients Minor: 13 patients	N/A
Avashia et al. (31), 2013	Immediate or delayed implant-based breast reconstruction	ADM + additional antibiotic prophylaxis	96 (*n* = 138 breasts)	Major: 14 Minor: 21	6.5 mo
Kornstein (39), 2013	Augmentation mammoplasty	PADM	3 (*n* = 6 breasts)	Major: 0 Minor: 0	18 mo
Spear et al. (32), 2014	Revision mammoplasty	ADM	118 (*n* = 154 breasts)	Major: 2 Minor: 6	N/A
Ibrahim et al. (33), 2015	Expander-based breast reconstruction	ADM/non-ADM	18 (*n* = 32 breasts)/20 (*n* = 32 breasts)	Major: 0 Minor: 9/Major: 0 Minor: 6	19 mo
Roh et al. (34), 2017	Expander-based breast reconstruction	ADM	25 (*n* = 50 breasts)	Major: 0 Minor: 7	≈12 mo
Brichacek et al. (35), 2017	DTI breast reconstruction	ADM	19 (*n* = 35 breasts)	Major: 0 Minor: 25	6 mo
Tsay et al. (36), 2018	Expander or implant-based breast reconstruction	ADM/non-ADM	23 breasts/16 breasts	Major: 0 Minor: 3/Major: 0 Minor: 2	6-9 mo
Kim et al. (37), 2020	Implant-based breast reconstruction	ADM (IMF incision/ Rd incision)	19 (*n* = 22 breasts)/69 (*n* = 75 breasts)	Major: 1 Minor: 0/Major: 9 Minor: 11	9.5 mo/7.9 mo
Luan et al. (38), 2021	Expander-based breast reconstruction	ADM	62 (n = 108 breasts)	Major: 16 Minor: 16	18 mo
Gao et al. (40), 2020	Implant-based breast reconstruction	SIS matrix/non-SIS matrix	79 (*n* = 79 breasts)/76 (*n* = 77 breasts)	Major: 5 Minor: 9/Major: 3 Minor: 5	≥12 mo

Table 1. Continued

Author, y.	Surgical intervention	Methods	Number of patients	Number of complications (major and minor)	Follow-up period
ADM					
Gao et al. (41), 2021	Implant-based breast reconstruction/ expander-based breast reconstruction	SIS matrix/non-SIS matrix	79 (*n* = 79 breasts)/45 (*n* = 46 breasts)	Major: 5 Minor: 9/Major: 3 Minor: 0	≥12 mo
Synthetic meshes					
Becker et al. (43), 2013	Various mammalogical surgeries	TIGR® matrix	62 (*n* = 112 breasts)	Major: 17 Minor: 6	16.5 mo
Hansson et al. (45), 2021	Expander-based breast reconstruction	TIGR® matrix/bovine pericardium matrix	48 (*n* = 24 breasts/*n* = 24 breasts)	Major: 2 Minor: 5/Major: 5 Minor: 15	16.4 mo
Dieterich et al. (47), 2013	Immediate or delayed implant-based breast reconstruction	Titanium-coated polypropylene mesh	207 (*n* = 231 breasts)	Major: 31 Minor: 36	14 mo
Haynes and Kreithen (46), 2014	Expander-based breast reconstruction	Vicryl mesh	38 (*n* = 46 breasts)	Major: 4 Minor: 3	43 mo
Dieterich et al. (48), 2015	Immediate or delayed implant-based breast reconstruction	Titanium-coated polypropylene mesh/non mesh	48 (*n* = 51 breasts)/42 (*n* = 47 breasts)	Major: 6 Minor: 1/Major: 10 Minor: 2	18 mo
Baldelli et al. (50), 2016	Immediate or delayed expander-based breast reconstruction	Polyester mesh/non mesh	63 (*n* = 70 breasts)/133 (*n* = 136 breasts)	Major: 10 Minor: 18/ Major: 17 Minor: 31	N/A
Hallberg et al. (44), 2018	Immediate or delayed implant-based breast reconstruction	TIGR® matrix	49 (*n* = 65 breasts)	Major: 4 Minor: 11	12–24 mo
Schüler et al. (51), 2021	Implant-based breast reconstruction	PADM/ polypropylene + polyglycolic acid mesh/ titanium-coated polypropylene mesh	34 (*n* = 40 breasts)/48 (*n* = 54 breasts)/75 (*n* = 94 breasts)	Major: 11 Minor: 11/ Major: 6 Minor: 7/Major: 14 Minor: 9	11.7 mo
Patzelt et al., 2022[54]	Implant-based breast reconstruction	Dermal flap/ polyglycolic acid mesh	32 (*n* = 64 breasts)/32 (*n* = 64 breasts)	Major: 0 Minor: 12/ Major: 1 Minor: 5	17.7 mo

*: No data about the number of breasts; IMF: Inframammary fold; ADM: Acellular dermal matrix; PADM: Porcine ADM

technique consisted of cutting the implant capsule at the level of its transition to the chest wall, advancing the anterior edge cranially along the chest wall in the form of a "Slingshot" and then fixing it to the posterior leaf of the capsule and costal periosteum. During postoperative follow-up, two patients had a slight recurrence of breast ptosis and three had hypodefinition of the IMF.

Mayer and Loustau (20) published a study involving a small group of patients who underwent immediate prosthetic breast reconstruction using capsular grafts and flaps. Capsular grafts were used in small strips to imitate anatomical structures supporting the implant's lower edge - the lateral tape was sutured distally to the serratus anterior muscle and to the lateral edge of the pectoralis major muscle, the lower tape was sutured between the lower edge of the pectoralis major muscle and the IMF. With a large implant size or a high IMF position the distal part of the capsular flap was sutured to the free edge of the pectoralis major muscle. The flap's length was created with an aspect ratio of 1:2/1:3 to maintain its viability. Two patients experienced complications, while others experienced

superficial epidermolysis, rippling, seroma, and mild contractures after irradiation (20).

The reverse method to the Persichetti method was published by Wessels et al. (21) Instead of dissection of the capsule at the level of the chest, the capsulotomy was performed in front of the implant and then dissection was carried out downwards with the formation of a "hammock". The length of the upper part of the capsular pocket was corrected for the size of the implant, taking into account the IMF. Thus, 12 patients were operated on, and, according to the authors, none of them had any complications.

Ismagilov et al. (22) demonstrated a new method of using the capsular flap in 321 patients. They supplemented the capsular flap technique with local tissue rearrangement, replacing the expander with an implant, cutting off the lower capsule horizontally in front and behind, dissecting it along the chest wall, and lifting tissues to the neo-IMF level. The lower capsule was then sutured to the upper capsule. It was reported that 42 patients had minor aesthetic defects, some of which resolved spontaneously.

Cogliandro et al. (23) developed a dermo-capsular flap for breast reconstruction and mastopexy in patients with severe weight loss. They performed bilateral or unilateral breast reconstruction with contralateral mastopexy on 20 patients. The flap, formed from the lower capsule and de-epithelized skin with fiber, was expected to increase the volume of the lower breast due to its thickness, but would be more dependent on blood supply.

Sutures

The simplest technique for strengthening the IMF, in our opinion, is suturing the bottom of the implant pocket. So, in 2013 Mohmand and Ahmad (24) shared their experience of primary periareolar augmentation mammoplasty in 32 women with three sutures under the implant in the IMF projection. During the study, only two cases of a slightly stretched scar and one case of a high implant position were noted.

Hirsch et al. (25) also strengthened the IMF using sutures, but they used barbed sutures. Forty-five patients had previously undergone a skin-sparing mastectomy and had tissue expanders placed. After capsulotomy at the IMF level, barbed sutures were applied, connecting the dermis and fascia of the rectus abdominis muscle, periosteum, or other tissues. Only two patients experienced asymmetry recurrence, leading to reoperation. The advantage of such sutures lies in controlled tension and the IMF level control.

Barbered suture was also used by Terao et al. (26) in 102 reconstruction patients. A distinctive feature of this method was the use of an epidural needle as a navigator and to control the complete passage of the thread through the entire dermis in the IMF projection. The authors noted the possibility of adjusting the IMF after implant placement by changing the tension of the barbered sutures. In 10 patients after reconstruction with implants, sagging of the sutures and a decrease in the definition of IMF were observed.

As the study of Nakajima et al. (27) has shown, the seam does not have to be internal. So, nine patients underwent unilateral breast reconstruction using implants. To recreate the IMF, the authors used several external vertical pendulum sutures with stitching of the chest wall. It has been shown that a scalloped IMF acquires a normal smooth structure after three months and the results do not differ from other methods. The advantage of this method is its simplicity and the absence of necessary control of seams, but this is associated with an increased risk of pneumothorax or infection.

In addition to the previous study, one can also consider the use of a hemostatic net as in the study of Goddard et al. (28). This is only a preliminary report, but the authors have already highlighted several key aspects of using such external sutures. Various bilateral implant-based mammoplasties (also one using a latissimus dorsi flap) were performed in 24 patients and good stable results with minimal complications were obtained. The authors concluded that skin redraping with a hemostatic net cannot be considered as an alternative to mastopexy, but in conjunction with the application of internal supporting sutures, a hemostatic net reduces the risk of their rupture.

Acellular Dermal Matrix

The use of acellular dermal matrix (ADM) was first described in 2005 by Breuing and Warren (29), whose research goals were to shorten the reconstructive process, improve results, and provide additional options for women seeking mastectomy. Biologic matrices provide the ability to create a pocket for an implant or tissue expander without using local tissues, such as serratus anterior or rectus abdominis muscles. Currently, most dermal matrices used for breast reconstruction include human, porcine or bovine matrix. Despite the widespread use of ADM, it is also associated with various complications, particularly seromas and infections.

A study by Hanna et al. (30) examined 75 patients who underwent two-stage breast reconstruction using tissue expanders. Of these, 44 patients underwent submuscular reconstruction, and 31 patients had reconstruction with ADM (AlloDerm, LifeCell Corp). If the IMF was violated during mastectomy, it was reconstructed with a 3–0 absorbable monofilament suture. The ADM was sutured to the pectoralis major muscle medially and to the serratus anterior muscle laterally, thus forming a new pocket for the expander. As a result, the ADM group included more major complications but fewer minor complications. The use of ADM allowed for intraoperative filling of expanders, reducing the reconstruction period by an average of a week.

A retrospective study by Avashia et al. (31) examined 96 patients who underwent expander-based breast reconstruction using ADM (AlloDerm, LifeCell Corp). The authors argued that ADM increased the risk of infectious complications during breast reconstruction, suggesting the use of additional antibiotic therapy for over 48 hours after surgery. The study involved 84 patients who received postoperative cephalosporins, vancomycin, clindamycin, or ciprofloxacin for ≥48 hours, depending on their allergic reactions. Twelve patients were prescribed antibiotic therapy not exceeding 24 hours. The study found that infectious complications leading to implant removal were detected in 6.7% of cases in the first group and 31.6% in the second group. The authors suggest that additional antibiotic prophylaxis reduced the risk of postoperative infectious complications when using ADM.

Spear et al. (32) studied in depth the issue of using ADM to control IMF in 118 patients. All patients underwent revision breast reconstruction. The authors identified five indications for ADM use: capsular contracture (Baker class III/IV), inferior fold malposition, inferior pole support, medial fold support or symmastia and rippling/palpability. The authors also considered the presence of a capsule around the implant during revision. They used an additional ADM

at the site of the inferior capsulorrhaphy for additional implant support and considered lowering the IMF. They performed all manipulations with the ADM without an implant installed to reduce the risk of damage. One patient developed complications leading to implant removal, including cellulitis and lack of IMF support. Other complications included capsular contractures in five patients and rippling in one patient.

The use of ADM is associated with improved aesthetic performance compared to non-ADM techniques. So, assessment by independent experts in the study of Ibrahim et al. (33), reported that the group of patients with ADM had significantly better assessments of the breast contour, the projection of the lower pole and the position of the implant than in the group of patients without ADM. Both groups experienced similar minor complications typical for two-stage breast reconstruction.

Expander-based breast reconstructions often require radiation therapy, and experienced surgeons aim to predict changes in the breast after radiation. So, for example, Roh et al. (34) deliberately created asymmetry for its further compensation during the passage of irradiation. ADM was used to strengthen the lower pole of both breasts in 25 patients, while on the side of the planned irradiation, the inferior edge of the ADM was not fixed to the chest wall, creating a "bottoming-out" effect. After radiation therapy, upward migration of the skin was noted, approaching the level of the contralateral breast. Thus, when replacing expanders with implants, six patients required a slight reduction in IMF, and one patient required an increase in IMF. This technique better predicted the position of the IMF in patients with planned radiation and improve the final aesthetic result.

Another feature of the use of ADM is that it allows reduction of surgical aggression on the pectoralis major muscle by increasing the area of implant coverage with matrix. In a study by Brichacek et al. (35), the pectoralis major covered only a few centimeters of the implant, with most being covered with ADM. This technique reduced the risk of animation deformities but increased operation costs, despite encountering some complications treated conservatively or in the outpatient clinic.

Most studies of the use of ADM or other methods, are based on the subjective opinions of the authors, a few involve independent experts, and even fewer question the patients themselves. In 2018, an attempt was made to objectify the results of ADM implantation and compare with techniques without ADM. Tsay et al. (36) enrolled 24 patients in the study and eventually performed ADM reconstruction on 23 breasts and 16 without ADM. Three-dimensional imaging and mammometrics were used to evaluate the difference between these two methods. The results reported a significantly better reconstruction with ADM compared to without ADM. Breasts reconstructed with ADM had a higher point of maximum projection and mean lower pole curvature, but this difference was clinically and aesthetically insignificant.

Based on the studies described above, it can be concluded that ADM is a viable option for breast reconstruction, but further research should focus on specific surgical techniques to establish the gold standard. In particular, it is necessary to determine the most effective surgical approach. Kim et al. (37) compared implant-based reconstruction through an IMF incision and through a radial incision and found that a radial incision increased infection and necrosis risks. Moreover, patients reported greater satisfaction with the IMF incision, as indicated by the Breast-Q questionnaire.

Another study, aimed at improving the technique of breast reconstruction, was described by Luan et al. (38) for expander-based reconstruction. Tissue expanders have tabs in their structure for attachment to surrounding tissues. The authors proposed a technique in which perforations were created in the ADM, through which these tabs were threaded and sutured with the matrix. Thus, the ADM and expander were implanted as a single unit, resulting in a single implant unit improving aesthetic prognosis and IMF position.

Both human and porcine ADM (PADM; Strattice, LifeCell Corp) are available for reconstructive surgery. So in 2013, Kornstein (39) described a series of clinical cases of PADM use in women with poor mammary soft-tissue quality with primary cosmetic breast augmentation. Three patients, two had a history of pregnancies and the third had a history of 10% weight loss. In all three patients, PADM was sutured along the IMF and pulled to the breast parenchyma and/or the caudal edge of the pectoralis major muscle. The matrix and implant pockets were flushed with antibiotic solution, and all patients received antibiotic therapy for seven days to prevent biofilms and colonize the chest pocket. The patients and physician were satisfied with the results of the operation, and it was also noted that the use of PADM with radial plication could replace the mastopexy step in patients with breast ptosis.

Another material that can be considered within the framework of this subsection is porcine small intestine submucosa (SIS). Gao et al. (40) conducted two retrospective analyses using this matrix for lower pole implant coverage and IMF reinforcement. SIS was compared with the standard technique of implant coverage with the pectoralis major muscle and with the technique of two-stage breast reconstruction. In general, the technique using SIS was associated with a higher number of complications (both major and minor), however, according to the results of the Breast-Q 2.0 questionnaire, breast satisfaction in both studies was higher in the SIS groups. Based on the data from these two analyses, it can be assumed that the use of SIS increases the risk of complications, but improves the aesthetic result of reconstruction (41, 42).

Synthetic Meshes

ADM is gradually being replaced by synthetic meshes, although the first attempts to use them were made at the same time as ADM. In 2002, Amanti et al. (42) published pilot results using a polypropylene mesh to create a subpectoral pocket for an implant. At the moment, there is no consensus on the use of biological or synthetic matrices, and the situation is complicated by the fact that today there are already a large number of synthetic analogues.

Becker and Lind (43) conducted research on the use of resorbable synthetic mesh TIGR® Matrix in various breast surgeries. A total of 62 patients took part in the study. The following surgeries were performed: primary reconstruction, reconstruction revision, augmentation/mastopexy revision, augmentation/augmentation mastopexy, mastopexy. TIGR® Matrix is a macroporous network consisting of two types of biodegradable fibers-fast-degradable (copolymer of glycolide and trimethylene carbonate) and slow-degradable (copolymer of lactide and trimethylene carbonate) and completely biodegrades within about three years. Due to the fact that the study did not provide for strict criteria for selecting patients (including 9 patients

who had previously undergone radiation therapy), 23 operated breasts had some complications, of which 17 required surgical intervention. However, in other cases, good aesthetic results were obtained. During repeated operations, the initial resorption of the surgical mesh, initial invasion by connective tissues was revealed. In a later study, Hallberg et al. (44) showed slightly better results - out of 65 immediate breast reconstructions with TIGR® mesh, minor complications occurred in 11 cases and major complications in 4 cases. The authors did not identify any specific risk factors with the use of this mesh.

A unique and valuable study was conducted by Hansson et al. (45), comparing the TIGR® mesh with a biological mesh made of bovine pericardium. Twenty-four patients underwent bilateral two-stage breast reconstruction, with a synthetic mesh used on one side and a biological mesh on the other. In addition to the results showing a higher number of seromas and, as a result, infectious complications in the biological matrix group, it was also shown that this study design yielded unsatisfactory aesthetic results due to asymmetry.

Haynes and Kreithen (46) used Vicryl mesh to support the lower pole of the implant in breast reconstruction in 38 patients. All meshes were used at the stage of tissue expanders implantation, and by the time the expander was replaced with an implant, the mesh was completely biodegraded. Three infectious complications were noted, two of which were in patients who underwent radiotherapy. Moreover, the expander was lost in a patient from the radiotherapy group. The study found that Vicryl mesh was more than 20 times cheaper than ADM, allowing more patients to receive high-quality breast reconstruction.

Separately, we can highlight the methods of strengthening the lower pole of the implant and IMF with non-bioabsorbable meshes, such as titanium coated polypropylene or polyester. In terms of surgical technique, there are no differences from the use of any other meshes or matrices, but their features may manifest in the long term. Titanium-coated meshes have been used in Europe since 2008 for breast reconstruction. They are cheaper than acellular matrices and have proven their safety. However, based on the results of the largest studies, in a lack of subcutaneous tissue or radiotherapy, it is possible to palpate the mesh. It is also worth noting that it cannot be determined with complete certainty whether the use of this mesh has a negative or positive effect on breast satisfaction due to insufficient data (47-49). Similar results were obtained with a polyester mesh, but due to the short observation period, late surgical complications were not taken into account (50).

Few studies have directly compared biological and synthetic meshes. Schüler et al. (51) found that synthetic meshes SERAGYN® (polypropylene + polyglycolic acid) and TiLOOP® led to a lower but not significant number of complications and implant loss than the use of PADM. The authors also note a correlation between radiation therapy and complications. We can also refer to the results of Eichler et al. (52). In their study, they compared SERAGYN® and TiLOOP® with ADM, finding similar complication rates and slight differences. However, a patient survey using the BREAST-Q method showed no significant difference between satisfaction and the mesh material, indicating a need for further research (53).

Patzelt et al. (54) compared the techniques of strengthening the IMF with a de-epithelialized skin flap and SERAGYN® mesh in 64 patients divided equally into two groups. In the first group, the skin flap covered the lower pole of the implant and was sutured to the edge of the pectoralis major muscle. In the second group, a synthetic mesh played the role of a "hammock". The first group had 12 complications treated conservatively, while the second group had five minor complications and one full necrosis of NAC. The authors believe that the synthetic mesh is more reliable in terms of strengthening the IMF and implant position, however, the results of the Breast-Q questionnaire did not show a significant difference between the two groups.

Discussion and Conclusion

Strengthening the IMF is important not only for reconstructive surgeries, but also for aesthetic ones. Unlike implants with a polyurethane foam, microtextured and especially smooth ones stretch the lower pole of the breast in the postoperative period, further lowering the position of the IMF. This effect also depends on the elasticity of the patient's breast tissue - the higher the elasticity, the lower the implant will drop (55). Thus, additional support of the implant and IMF can help to prevent excessive lower pole expansion.

In this review, we have summarized modern methods of strengthening the IMF and stabilizing the implant in reconstructive and aesthetic breast surgeries. It can be cautiously stated that some of the described methods are associated with lower risks of complications (such as suture techniques and local tissue rearrangement), while the use of biological and synthetic matrices not only increases the risk of complications, but also the cost of the operation, and, as a consequence, the cost of an error.

It can also be cautiously noted that the results of some studies may differ greatly from those in similar studies. This may suggest that sometimes the authors may unintentionally give preference to the investigated or more proven techniques.

Most studies do not present data from surveys of patients themselves and independent specialists. We understand that these assessments are subjective, but it is necessary to remember that we perform all operations, regardless of the indications, for our patients. We can endlessly admire our results, while our patients may be dissatisfied.

In plastic surgery, as in any other branch of surgery, the essential point is the surgeon's experience. The choice of the optimal and effective method of strengthening the IMF during breast reconstruction also depends on many factors and can be extremely individual, which makes it difficult to form identical groups of patients for study. For a more evidence-based analysis of the effectiveness of various techniques, a clear study design, randomization, a large sample of patients, and a long study time are required.

Footnotes

Authorship Contributions

Concept: A.M., A.K.; Design: A.M.; Data Collection or Processing: A.M., A.K., V.O.; Analysis or Interpretation: A.M., A.K., I.G.; Literature Search: A.M., A.K., V.O., I.G.; Writing: A.M., A.K.

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Original Article

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What Changes are Mandatory in Breast Surgery Training? An International Survey and Recommendations of the French Academy of Surgery and the Senologic International Society

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ABSTRACT

Objective: Breast cancer management has significantly evolved, particularly in surgical techniques, but breast surgery training remains unstandardized worldwide. This study, promoted by the Senologic International Society (SIS) and the French National Academy of Surgery (FNAS) aimed to evaluate training variability in the world and to provide ten recommendations to improve breast surgery training.

Materials and Methods: A 32-question electronic survey was sent between July-August 2023 to the SIS and FNAS network, covering personal experience, training practices, accreditation programs, and fellowship requirements.

Results: A total of 121 breast specialists from 42 countries participated, including mainly general surgeons (56%) and gynecologists (23%). Most respondents (66%) had over 15 years of experience, and 75% were male. While 50% reported that breast surgery fellowships were not mandatory, countries with requirements often stipulated a one or two-year experience and a minimum cases number. Multidisciplinary training was often lacking, with only half of countries requiring rotations in radiology, oncology, or pathology. Disparities in training quality and accreditation were evident, particularly in regions without formal breast surgery programs.

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Conclusion: High-volume centers and specialized surgeons consistently demonstrated improved outcomes, including lower mortality and recurrence rates for patients treated for breast cancer. Rising breast cancer incidence, combined with advances in surgical and multidisciplinary care, highlights the urgency for standardized training. Evidence shows that structured programs with volume thresholds, multidisciplinary approach, and modern surgical techniques improve patient survival and satisfaction. The survey underscores the need for international guidelines to ensure equitable, high-quality care. SIS and FNAS recommend a standardized breast surgery education framework with ten actionable proposals to address disparities, optimize training, and enhance global care quality.

Keywords: Breast surgery training; multidisciplinary approach; standardization

Key Points

- This study highlights the differences in breast surgery training worldwide and emphasizes the need for standardization in this field.
- Gaps in training, such as the lack of multidisciplinary approaches and specialized programs, create challenges in providing high-quality care.
- Senologic International Society and the French National Academy of Surgery present ten recommendations aimed at standardizing breast surgery education and improving global care quality.

Introduction

Breast cancer is the leading cancer in women, with 2,296,840 new cases worldwide in 2022, and the first cause of cancer-related death, with around 666,103 deaths annually (1). Breast cancer incidence and mortality constantly rise, with over three million new cases and more than a million deaths expected by 2040. In parallel with these epidemiological changes, the management of breast cancer has considerably changed over the last two decades. The evolutions have been numerous, including pre-operative diagnosis with extending screening, and developments in imaging modalities such as the use of magnetic resonance imaging (MRI), tomosynthesis, and positron emission tomography-MRIs; similarly, surgical modalities have evolved and include oncoplastic surgery, immediate reconstruction, skin-sparing mastectomies (SSM), nipple-sparing mastectomies, sentinel lymph node biopsy, and target axillary dissection. Treatments have also advanced with adjuvant and neo-adjuvant therapies (immunotherapy, CDK4/6 inhibitors) and new radiotherapy regimens (brachytherapy, hypo-fractionated radiotherapy) (Figure 1). Every patient, as the focal point of the healthcare system, should receive the appropriate diagnostic procedures, tailored surgeries, and personalized treatments at each stage of their care. These services should be delivered at the right time, by a skilled team, in the best possible setting. Over recent decades, as breast care has evolved globally, the focus on breast surgery as a specialized field has grown. Is there evidence suggesting that breast cancer treatment in high-volume centers by specialists leads to better survival rates and enhanced quality of care for patients? What would be the ideal education for future breast specialists? In light of these questions, the Senologic International Society (SIS) and the French National Academy of Surgery (FNAS) developed this survey with the goal of creating a global overview of surgical practices and training, as well as formulating tailored and optimal recommendations for a breast surgery educational program.

Materials and Methods

Members of the SIS and FNAS were invited to participate in an online survey with a Microsoft Forms questionnaire in English. Between July and August 2023, participants were invited to answer the questionnaire via email. The answers were directly recorded into an online database and only one response per participant was allowed. More than one response was authorized for each country.

The online survey consisted of 32 questions divided into four sections. Section 1 (10 questions) was discussing personal experiences and data concerning breast management. In section 2, 8 questions examined the training of breast surgery in different countries. Section 3 (10 questions) was about the accreditation and quality criteria of breast surgery centers. Finally, in section 4 (4 questions), the participants were asked for their recommendations about how to enhance breast surgery training and whether they think that breast surgery should be considered as a specialty. The questionnaire content is available in Tables 1, 2 and 3.

Results

Four hundred and sixty-six questionnaires (in English) were sent, based on SIS and FNAS mailing lists. A total of 121 breast specialists (26% response rate) completed the survey, composed of 103 surgeons and 18 physicians from non-surgical specialties. Among the respondents, 68 (56%) general and oncologic surgeons, 28 (23%) gynecologists, 3 plastic surgeons, 2 (2%) gastrointestinal surgeons, and 2 (2%) thoracic surgeons responded to the survey. Medical oncologists, radiation oncologists, and breast radiologists constituted 18 non-surgical specialties (Table 1).

The average time taken to complete the questionnaire was 24 minutes and 17 seconds.

Of the respondents, 92 (76%) were male and 29 (24%) were female. Thirty-nine (32%) were over 60 years old, 24 (20%) were between 30–40 years old, 23 (19%) were between 40–50 years old, 23 (19%) were between 50–60 years old, and 10 (7%) were under 30 years old (Table 1). The survey included participants from 42 countries: Algeria, Argentina, Azerbaijan, Benin, Bolivia, Brazil, Cameroon, Canada, Chile, China, Colombia, the Dominican Republic, Ecuador, El Salvador, France, Germany, Greece, Guatemala, Italy, Israël, Japan, Lithuania, Mali, Morocco, Nigeria, Peru, Poland, Portugal, Puerto Rico, Qatar, Russia, Rwanda, Saudi Arabia, Senegal, South Africa, Sudan, Sweden, Tunisia, Türkiye, the United Arab Emirates, Ukraine, and the United States (Figure 2).

Among the respondents, 48 (40%) identified as presidents of national professional societies or organizations. Sixty-six (55%) had been practicing breast surgery for over 15 years, while 28 (23%) had been doing so for 5 to 15 years. Regarding the types of cases treated, breast surgery made up more than 50% of daily practice for 78 (64%)

respondents. Thirty-two percent worked in university hospitals, 20% in private hospitals, 25% in public hospitals, and 18% in regional centers; some professionals worked across multiple sites (Table 1). On average, each surgeon performed 190 breast cancer surgeries annually, with a standard deviation of 88. In terms of fellowship or specific training requirements, responders from 10 countries (USA, Canada, Colombia, Ecuador, Peru, Chile, Russia, Lithuania, Bolivia, and Azerbaijan) reported a requirement for such training. While Brazil does not offer a fellowship program, it has a specialization in mastology, which has been available since 1978 with certification (2).

Among the countries requiring fellowship training, 32% required a minimum number of surgeries during fellowship training, with an average of 50 surgeries per year. In over 45% of respondents, rotations at non-surgical specialties, such as pathology, breast imaging, nuclear medicine, radiotherapy, and oncology were mandatory (Table 2).

Regarding quality control and accreditation, only 33 respondents (27%) indicated that it was necessary to obtain national accreditation to perform breast surgery with an average of accreditation duration of 4 to 5 years. Concerning international accreditation, 36 respondents (30%) worked in centers accredited internationally (with a minimum threshold of 70 to 150 surgeries by year and 3 surgeons by center) (Table 3).

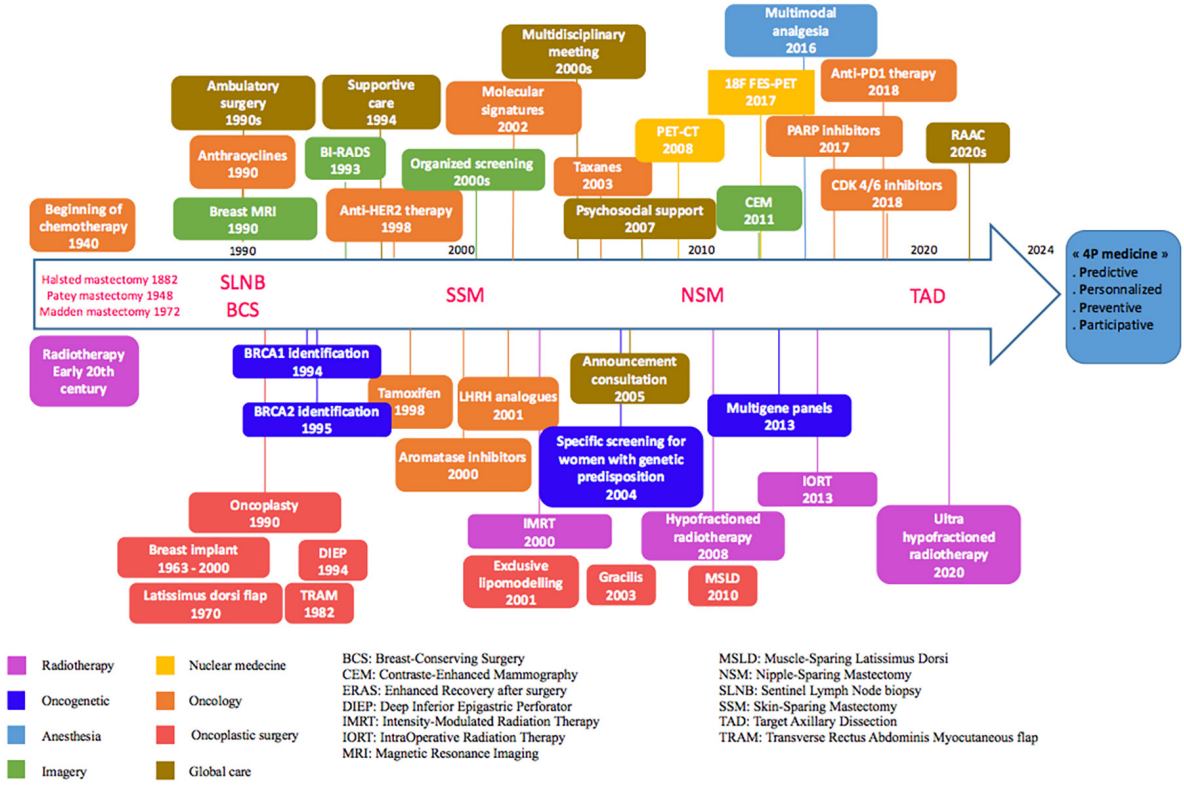


Figure 1. Multidisciplinary developments in breast cancer care

Table 1. Survey, variability in breast surgery training worldwide, first section: Personal surgical practice

Questions	Propositions (answers, n)
Your name (optional)	(90 answers)
Age group	• <30 years (10) • 30-40 years (24) • 40-50 years (23) • 50-60 years (23) • >60 years (39)
Gender	• Woman (29) • Man (92) • Non-binary • Prefer not to say

Table 1. Continued

Questions	Propositions (answers, n)
Country and region (i.e. France, Paris)	• (119 answers, 42 countries: Algeria, Argentina, Azerbaijan, Benin, Bolivia, Brazil, Cameroun, Canada, Chile, China, Colombia, Dominican Republic, Ecuador, El Salvador, France, Germany, Greece, Guatemala, Israel, Italy, Japan, Lithuania, Mali, Morocco, Nigeria, Peru, Poland, Portugal, Puerto Rico, Qatar, Russia, Rwanda, Saudi Arabia, Senegal, South Africa, Sudan, Sweden, Tunisia, Türkiye, United Arab Emirates, Ukraine and United States of America)
Number of years of experience of performing breast cancer surgery as a consultant/fully trained surgeon/attending surgeon?	• 0–5 years (21) • 5–10 years (18) • 10–15 years (10) • 15–20 years (15) • >20 years (51)
During your routine surgical activities, how much do the breast cases represent?	• <25% (17) • 25–50% (22) • 50–75% (20) • 75–100% (29) • 100% (29)
What is your primary specialist discipline?	• General surgery (68) • Obstetrics and gynecology (28) • Digestive surgery (2) • Plastic surgery (3) • Thoracic surgery (2) • Other (18)
How many cases of breast cancer did you (as surgeon) perform annually?	• (Average rate of 190±88 surgeries)
How many cases of breast cancer did your center perform annually?	(111 answers: from 200 to 1200)
Type of hospital where you practice:	• Public hospital (30) • University hospital (39) • Regional cancer center (22) • Private hospital (32) • Other

Table 2. Survey, variability in breast surgery training worldwide, second section: Training pattern in your country

Questions	Propositions (answers, n)
How many surgical specialties do you have in your country?	(111 answers)
What are the surgical specialties through which it is possible to perform breast cancer surgery?	• General surgery (98) • Obstetrics and gynecology (60) • Digestive surgery (12) • Plastic surgery (54) • Thoracic surgery (11) • Other (19)
Is breast surgery fellowship (or post graduate training) required to perform breast cancer surgery?	• Yes (59) • No (56)
If yes, what is the duration of breast surgery fellowship (or post graduate training)?	1 to 2 years
What is the minimal number of breast cancer surgeries required annually during your fellowship?	(Average of 50 surgeries per year)

Table 2. Continued

Questions	Propositions (answers, n)
Is there any mandatory rotation during your fellowship?	• Yes (55) • No (46)
What are the mandatory rotations during your fellowship?	• Pathology (45) • Radiology (40) • Medical oncology (57) • Radiotherapy (38) • Plastic surgery (48) • Other (1)

Table 3. Survey, variability in breast surgery training worldwide, third and fourth section: Accreditation, quality and recommendations for enhancing breast surgery training programs

Questions	Propositions (answers, n)
Is multidisciplinary team discussion of breast cancer cases mandatory in your center?	• Yes (104) • No (7)
Is it necessary in your country to obtain national accreditation for the breast center before treating patients?	• Yes (33) • No (84)
How long is the validity of your accreditation?	(33 answers: 4 to 5 years)
What type of accreditation do you have in your center?	• Local or national (30) • International (13)
What are the domains that should be investigated during the accreditation process?	• Pre-operative core biopsy (120) • Multidisciplinary meetings before treatment (80) • Multidisciplinary meetings after surgery (120) • Nuclear medicine (for sentinel lymph node and positron emission tomography-scanners) (104) • Complete breast imaging possibilities (110) • Genetic testing (90) • Pathology with immunohistochemistry (120) • Other (60)
Is a minimal number of breast cancer surgeries (per year) required for the center accreditation?	• Yes (18) • No (15)
If yes, how many in your center?	(33 answers: 70 to 150 surgeries by year)
Is a minimal number of breast surgeons required for the center accreditation?	• Yes (11) • No (22)
If yes, how many in your center?	(33 answers: minimum of 3 surgeons by center)
What types of surgery should be practiced for the center accreditation?	• Surgery for benign diseases (60) • Surgery for breast cancer (86) • Oncoplastic and reconstructive surgery (52) • Other (6)
Do you think that breast surgery should be a specialty?	• Yes (70) • No (31) • Maybe (16)

Table 3. Continued

Questions	Propositions (answers, n)
What are your suggestions for the development of breast surgery training programs?	• Training programs must become mandatory for junior surgeons who want to perform breast surgery • The modalities of specialized training in breast surgery must include training in breast imaging, pathology, oncology, radiotherapy, and nuclear medicine • Specialized training in breast surgery should be accessible to different surgical disciplines • The duration of specialized training should be one to two years • Continuing education programs for breast surgeons should be mandatory
If you are a member of SIS, would you want to participate in this project as co-author?	• Yes (74) • No (33)
If yes, please write your mail	

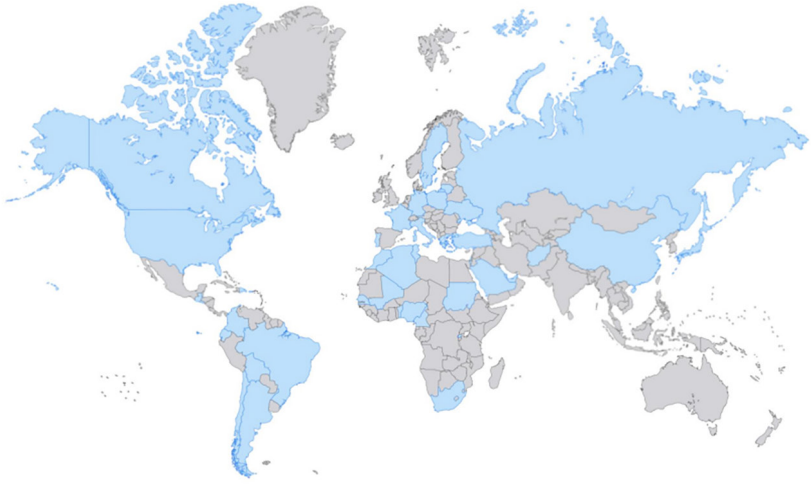


Figure 2. Countries that took part in the survey are indicated in blue

Discussion and Conclusion

This SIS and FNAS survey has some strengths. First, taking all countries that there were responses from, our survey represents a worldwide population of 3.29 billion people. However, some African countries did not contribute since they do not have official breast academic or scientific societies. Secondly, specialists who answered our survey had significant experience, being in charge of more than 150 new breast cancer patients each year and majority of the responders performing breast cancer treatment for more than 20 years for the majority of them.

Do the Surgeon's Experience and Volume of Activity Influence Patient Mortality?

We investigated whether a minimum number of breast surgeries should be encouraged for the training of breast surgeons during their fellowship, then, in their practice and in the care structures in which they practice. Most of the surgeons were in favor of a high surgical threshold, ranging from 20 to 150. Indeed, it has been shown that the volume of activity performed by a breast surgeon and a breast unit has an impact on patient mortality. International publications demonstrated improved surgical safety and mortality when the volume of activity, for both facilities and surgeons, increases. For example, in 1995 Sainsbury et al. (3) conducted a retrospective study of 12,861 patients treated for breast cancer in Yorkshire, UK, between 1979 and 1988, and highlighted that patients managed by surgeons operating on at least 30 cases of breast cancer per year had a significantly higher survival rate [risk ratio = 0.85, 95% confidence interval (CI) 0.77–0.93], compared with patients managed by surgeons operating on fewer cases of breast cancer per year (3).

In 1996 in Scotland, Gillis and Hole (4) conducted a retrospective study of 3786 female patients aged under 75 years old, with histologically verified breast cancer operated between 1980 and 1988 (before breast screening began). Patients were identified from the cancer registry and from pathology records of all hospitals in the urban west of Scotland. The follow-up was up to 13 years. The five-year survival rate was 9% higher and the 10-year survival 8% higher for patients treated by specialist surgeons. A reduction in risk of dying of 17% (95% CI 0.74–0.92) was found after adjustment for age, tumor size, socioeconomic status, and nodal involvement. The benefit of specialist care was apparent for all age groups, for small and large tumors, and

for tumors that did and did not involve the nodes and was consistent across all socioeconomic categories.

In 2003, Skinner et al. (5) conducted an insightful study using data from the Cancer Surveillance Program database in Los Angeles, covering the years 1990 to 1998. The study included 29,666 breast cancer cases, along with detailed information on surgeons, hospitals, and staging. Patients were stratified based on surgeon and hospital specialization, as well as by age, race, stage, surgical procedure, surgeon and hospital case volume. Survival analysis with its dependence on these factors was performed. Results showed that being a surgical oncologist (defined by being a member of the Society of Surgical Oncology requiring among other factors to treat at least 50 oncological cases per year) was an independent predictor of survival (risk ratio = 0.77, 95% CI 0.67–0.88), as were both hospital and surgeon case volume. Treatment by a surgical oncologist resulted in a 33% reduction in the risk of death at 5 years.

In 2003, Stefoski Mikeljevic et al. (6) examined 11,329 breast cancer patients diagnosed between 1989 and 1994 in Yorkshire, UK. The study found that patients treated by high-workload surgeons had better overall survival rates. The 5-year survival rate was 68% for those managed by surgeons handling more than 50 patients per year, 64% and 66% for those managed by surgeons with 10–29 and 30–49 patients per year, respectively, and 60% for those treated by surgeons with fewer than 10 patients annually. The relative risk of death increased by 15% (risk ratio = 1.15, 95% CI 1.03–1.28) for patients treated by surgeons with workloads under 10 cases per year, and by 10% (risk ratio = 1.10, 95% CI 1.02–1.18) for those managed by surgeons with 10–29 cases, compared to patients treated by surgeons with workloads over 50 cases annually.

A French study (7) conducted by the *Assurance Maladie* (French public health insurance) and published in 2019 also highlighted the impact of facility characteristics on breast cancer mortality. Between 2012 and 2014, about one-third of centers in France performed fewer than 30 breast cancer surgeries per year. Analyzing data from 43,274 breast cancer patients, the study found that the mortality rate in the year following surgery was 1.41%. Facilities with fewer than 30 surgeries per year had a mortality rate of 2.52%, which was twice as high as those with over 100 surgeries annually (1.21%). Mortality was also 20 to 30% higher in centers with intermediate activity levels (30–100 surgeries). Furthermore, mortality in the first year was more than twice as high in facilities that were not authorized to treat breast cancer patients. This difference persisted beyond the first year of follow-up. This study was carried out prior to the introduction of thresholds for authorization to perform breast surgery in France. In 2018, Greenup et al. (8) analyzed patients aged 18 to 90 with stages 0 to III unilateral breast cancer, diagnosed between 2004 and 2012, using data from the American College of Surgeons National Cancer Data Base. Over one million patients met the inclusion criteria. Hospitals were categorized into three groups based on volume: low-volume (<148 cases/year), moderate-volume (148 to 298 cases/year), and high-volume (>298 cases/year). Treatment at high-volume centers was linked to an 11% reduction in overall mortality (risk ratio = 0.89, 95% CI 0.84–0.96), with the greatest benefit observed in patients with stage 0–I, estrogen receptors (ER)+/progesterone receptors (PR)+ or ER+/PR- breast cancers.

In the UK, Kingsmore et al. (9) conducted a comparative study involving 2,146 women with breast cancer treated in specialized versus non-specialized units. Patients in specialized units had a significantly lower risk of inadequate treatment for breast tumors (24% *vs.* 47%, $p<0.001$), inadequate axillary staging (8% *vs.* 40%, $p<0.001$), and inadequate definitive axillary treatment (4% *vs.* 38%, $p<0.001$). Local recurrence rates were 57% lower (13% *vs.* 23% at eight years, $p<0.001$), and the risk of death from breast cancer was 20% lower for women treated in specialized units.

Do the Surgeon's Experience and Volume of Activity Influence Quality of Life?

In 2007, Waljee et al. (10) conducted a meta-analysis and found that patients were more satisfied with the decision-making process and their relationship with a highly qualified breast surgeon (defined as a surgeon who dedicates over 60% of their practice to breast disease). Patients also reported greater satisfaction with breast cosmetic outcomes and physical well-being when treated by a highly qualified breast surgeon (11).

A French study published in March 2017 by IRDES (*Institut de Recherche et Documentation en* Économie *de la Santé*) examined variations in surgical practices for breast cancer treatment (12). The study revealed that surgical management had improved due to advances in diagnostic and therapeutic techniques, as well as the reorganization of breast cancer centers. It also showed that surgical practices varied by center, particularly in terms of their volume of activity. For instance, women treated at centers performing over 110 breast cancer surgeries per year were twice as likely to undergo immediate breast reconstruction or sentinel lymph node biopsies compared to those treated at centers performing between 50 and 110 surgeries annually.

Over the past two decades, oncoplastic surgery has gained popularity, either to avoid mastectomy in cases of large tumors or for cosmetic purposes, such as breast reduction or ptosis correction, alongside oncological surgery. To perform such procedures, it is important to have experienced surgeons skilled in both oncologic and plastic surgery, which can be a challenge for centers with fewer breast cancer surgeries.

In 2018, Peiris et al. (13) compared breast surgery practices in Canada and the UK using the classification of oncoplastic breast surgery. The study showed that specialized breast surgeons, who had more focused fellowship training in both aesthetic and oncologic surgery, were more likely to offer immediate breast reconstruction or oncoplastic surgery. Their research demonstrated that such training programs improved long-term quality of life for Canadian breast cancer patients (13). In France, an analysis of real-life data published by the French National Cancer Institute (INCa) in 2021 showed that only 14% of breast cancer patients received immediate reconstructive surgery, while only 28% had delayed reconstructive surgery (14). These rates are considered too low, and in the absence of contraindications (such as comorbidities, old age, or patient preference), women should have the option to choose reconstructive or oncoplastic breast surgery (15). Ryan et al. (16) recommended in 2023 that modern breast surgeons should: 1) perform a moderate to high volume of breast surgeries; 2) be knowledgeable in oncoplastic techniques; 3) participate in continuous education and additional training opportunities; and 4) remain members of relevant scientific societies (16).

Is There a Standardization of Initial Training, Continuing Education and Certification of Breast Surgeons in the World?

In our survey, we explored whether there should be a minimum number of breast surgeries required for the training of breast surgeons during

their fellowship, in their regular practice, and in the care facilities where they work. In France, the minimum threshold for breast centers is set at 70 surgeries, while in the UK it is 100, in Belgium 125, and in many European countries (such as Germany, Italy, and Spain) the threshold is 150, in line with EUSOMA (European Society of Breast Cancer Specialists) recommendations. In England, the advanced breast surgery fellowship requires a minimum of 30 conservative surgeries, 25 total mastectomies (including simple and SSM), and 30 axillary procedures (17).

Currently, there is a lack of standardization in breast cancer surgery training across Europe. The ESSO-EUSOMA survey aimed to assess the current state of breast cancer surgery training in Europe. General surgeons, surgical oncologists, gynecologists, and plastic surgeons were invited to complete a custom survey with eighteen questions, distributed to 3,000 surgical oncologists across Europe. A total of 671 physicians responded (23% response rate), with 468 dedicating between 50% and 100% of their work to breast cancer treatment. Forty-four percent of respondents worked in community or university hospitals with dedicated Breast Units. However, additional breast surgery training was not universal: 20% had completed an accredited breast fellowship, 30% had worked as trainees in Breast Units, 21% had pursued additional courses, master's programs, or diplomas, and 8% had not received any extra training. The majority (61%) worked in units treating over 150 breast cancer cases annually, while 26% treated over 120 new primary cases per year, and 23% treated fewer than 50 new cases. Multivariate analysis showed that breast surgeons working in a Breast Unit and treating more than 50 cases per year were significantly more likely to perform oncoplastic procedures. This study highlighted the significant variation in breast cancer surgery training across Europe, and the authors argued that it is crucial to develop standardized, high-quality training to ensure consistent and certified surgical management across the continent (18). The differences in outcomes and access to the latest surgical techniques across Europe may partly stem from these training variations. Training in breast cancer surgery differs not only in its foundational discipline (general surgery, gynecology, or plastic surgery) but also in the duration of training and whether specialized training is required. Wyld et al. (19) stressed the urgent need for specialist training standards that should be adopted by all European member states. Excellent training models from the USA, the UK, Australia, and New Zealand can serve as a foundation for improving breast surgery training across Europe.

Accredited breast surgery fellowships were first established in the UK and USA in 2002 and 2003, respectively. In the USA, organizations, such as the Society of Breast Surgical Oncology (SSO) and the American Society of Breast Surgeons offer certification after a dedicated 12-month fellowship. This fellowship includes significant training in breast and plastic surgery, as well as exposure to other departments, like breast imaging, medical oncology, radiotherapy, and pathology. At the end of the fellowship, trainees must demonstrate their competency in a range of surgical and non-surgical procedures to earn certification (20, 21).

Wilson et al. (22) conducted a study to evaluate breast surgery education in USA general surgery residency programs. The survey, conducted in 2009 with applicants to the Roswell Park Cancer Institute surgical oncology fellowship program, assessed training types, breast surgery exposure, and applicants' comfort levels with breast cancer cases. Of the 29 respondents, 83% were chief residents, and they reported feeling comfortable with breast-related cases, although their comfort level dropped below 8/10 for modified radical mastectomies and axillary lymph node dissections. General surgery residents felt less comfortable operating in the axilla compared to the breast. The study emphasized the need for adequate breast surgery education in residency training, and noted that 25% of chief residents felt that a 5-year residency did not fully prepare them for transitioning into faculty roles, with 73% of graduates pursuing fellowships after residency (23, 24).

The first formal breast surgical oncology fellowship was established at Baylor University Medical Center in 1982, and since then, the number of such fellowship programs in the USA has grown to around 60. These programs now focus on training in breast surgery, as well as medical oncology, radiation oncology, pathology, breast imaging, and plastic surgery (25). Some fellowship programs have additional prerequisites, such as achieving a minimum score on a multiple-choice exam or meeting publication requirements to qualify for an interview. In 2023, a survey by Hedges et al. (26) showed that factors such as clinical rotation experience, research time, and the quality of interviews and recommendation letters were critical in determining an applicant's chances of being accepted into a fellowship program. To complete the SSO breast surgical oncology fellowship, trainees must perform a specified number of procedures, including partial mastectomies, total mastectomies, axillary lymph node biopsies, and axillary lymph node dissections (20).

In the UK, trainees can begin specializing in breast surgery during the last two years of their general surgery residency. Although it is not mandatory to practice breast surgery, trainees are encouraged to complete the 12-month fellowship from the Royal College of Surgeons, specializing in breast surgery (17). In Japan, the surgical training system is organized by the Japan Surgery Society as the first step for general surgeon and the Japanese Breast Cancer Society as the second step for breast surgery. In Israel, there is a one-year fellowship program since 2023 with a multidisciplinary training program that includes two months in oncology, one month in breast imaging, one month in pathology, and two months in plastic surgery. The fellow must participate at least to 100 surgeries according to a special list.

Beitsch and Whitworth (27) proposed in 2016 the importance of an adapted curriculum for specialists treating breast cancer, recognizing that the disease requires expertise across multiple disciplines. The idea of a "breast specialist" could lead to optimal diagnosis and treatment for both benign and malignant breast conditions, including risk assessment, image-guided biopsies, targeted and prophylactic treatments, as well as recurrence and survivorship monitoring (27, 28).

In Pakistan, a PubMed search from 1990 to 2021 revealed a significant increase in breast cancer research publications, from almost none before 1990 to 615 articles between 2012 and 2021. This surge can be attributed to the introduction of fellowship programs in breast surgery and related fields. In 2019, Pakistan's College of Physicians and Surgeons (CPSP) accredited a two-year breast surgery fellowship program. This program, combined with the rising incidence of breast cancer, has led to more General Surgery graduates pursuing specialized training (29).

There are different surgical specialties around the world (13 in France, for example), and some surgical specialties exist only in certain countries, such as carcinological surgery, which exists in the Maghreb and includes breast cancer surgery. In countries where this specialty does not exist, breast surgery is performed by gynecologists (France, Germany...), general, visceral or endocrine surgeons (USA, Türkiye)

and increasingly by plastic surgeons, in response to patient demand for immediate breast reconstruction.

For this reason, fellowships should be open to several specialties, as is the case in England with a joint program for plastic and general surgery. In other countries, such as Brazil, there is a specialty dedicated to the management of breast pathologies: mastology. These differences can be explained by the demographic, epidemiological and morphological diversity of patients around the world, resulting in a heterogeneity of resources.

Should Breast Surgeon Training Take Place in an Establishment With Specific Authorization for the Activity "Cancer Treatment"?

In certain countries, healthcare facilities are required to obtain specific authorization based on regulatory requirements to ensure the quality and safety of care nationwide. This authorization system, developed through a multi-professional collaboration, is grounded in three key principles: Cross-cutting quality standards, approval criteria established by scientific societies, and minimum activity thresholds for each facility. Among the quality measures, it is emphasized that every patient diagnosed with breast cancer must receive a clear diagnosis, that therapeutic decisions are made in multidisciplinary meetings adhering to best practice guidelines, that a personalized care plan is developed, and that access to necessary support care, innovative treatments, and clinical trials are provided when required.

There are variations in the quality of breast cancer care across different regions and hospitals, which negatively impacts women's health. A study by Taban et al. (30) in 2019 retrospectively analyzed patients treated for invasive breast cancer in Geneva's private sector from 2000 to 2009. The study concluded that the relationship between post-treatment mortality and surgeon experience was partially linked to adherence to quality-of-care indicators. Experienced surgeons were more likely to comply with the quality standards set by EUSOMA, including performing histological analysis before surgery, conducting selective sentinel lymph node biopsies when appropriate, ensuring axillary clearance with an adequate number of lymph nodes, and referring patients for adjuvant radiotherapy when necessary (30).

In 2021, Maes-Carballo et al. (31) found that over half of the countries in Europe and America had not implemented clinical pathways or integrated care processes for breast cancer, and that quality indicators were inconsistent. However, four quality indicators were more commonly implemented: preoperative breast and axilla radiology and physical examination, preoperative histology confirming malignancy, preoperative and postoperative case discussions in multidisciplinary teams, and image-guided axillary staging.

In France, the INCa has worked with the Haute Autorité de Santé and clinical experts from various scientific societies to develop Indicators of Quality and Safety of Care specific to breast cancer. These benchmarks, which aim to enhance care practices and quality, include ten key indicators, focusing mainly on diagnosis, treatment timelines, follow-up, and treatment (32).

Feminization of Surgical Professions and Consequences for Breast Surgery

Looking at our results, a quarter of responders were female. Regarding this, there are many concerns about the minority of female breast surgeons worldwide, with a rapidly inversing trend, with for example 58% of medical doctors being women in France in 2022 according to the *Direction de la Recherche, des Etudes, de l'évaluation et des Statistiques* data (33). The female representation at the American Society of breast surgeons annual meeting from 2009 to 2019 significantly increased in committee members (3.2% per year, $p = 0.01$) and chairs (6.0% per year, $p = 0.03$). Women represented the majority of speakership positions and the meeting-related publication rate with female senior authorship was higher that with male (41.0% *vs.* 36.3%, $p = 0.04$) (34). Interestingly, a retrospective cohort published in August 2023, including 1,765,711 patients who underwent 1 of 25 common surgeries in various specialties, has suggested that patients treated by female surgeons have lower rates of adverse postoperative outcomes including death at 90 days and 1 year after surgery compared with those treated by male surgeons (35). A comparative study including 2236 patients showed that satisfaction with information differed, as patients of female surgeons reported greater satisfaction ($p = 0.018$) (36). Moreover, a retrospective study conducted in the USA in 2021 with a cohort of 167 patients who underwent mastectomy with a reconstruction rate of 35%, female breast surgeons had 3.7 times greater odds of treating patients who had reconstruction than male breast surgeons (95% CI 1.20–11.42) (37). According to an observational study using the Surveillance, Epidemiology, and End Results-Medicare database, women who underwent breast conserving surgery were more likely to have female surgeons (odds ratio = 1.40; 95% CI 1.25–1.55) (38). However, studies on this topic are scarce and should be interpreted with caution.

Proposal for an Initial and Ongoing Training Program

According to the results of our study and the findings of a review of the international literature concerning the diversity of management of patients with breast cancer and the training of breast surgeons, it seems imperative to propose standardized training for breast surgeons to standardize practices and offer optimal patient management. This could take the form of one to two years' initial training, whatever the initial surgical specialty. During these years of training, in addition to breast surgical oncology period, several rotations should be organized in the various departments involving breast pathology, including medical oncology, breast imaging, radiotherapy, pathology, genetics, and plastic surgery. The aim is to master all aspects of breast pathology, from breast embryology to functional pathologies, benign pathologies and breast cancers, with a view to promoting overall breast health. By developing a general view of the breast, the surgeon can avoid over-treatment and help to improve women's quality of life. Similarly, it is important to develop training for communication skills, to help patients understand, without affecting their capacity for resilience following the announcement of the disease. In addition, in view of the constant and rapid evolution of scientific data, it seems necessary to set up ongoing training for professionals practicing breast surgery. Ten Recommendations have been established by the FNAS and the SIS concerning breast surgery training (Table 4).

Table 4. Breast surgery training: 10 recommendations of the French National Academy of Surgery and the Senologic International Society

1. Training programs must take account of expected trends in breast cancer incidence and mortality in each country worldwide.
2. Training programs must take account of changes in breast cancer management in the recent decade.
3. Training programs must become mandatory for junior surgeons who want to perform breast surgery.
4. Breast surgery must be performed in a specialized multidisciplinary breast cancer unit with a minimal threshold of breast surgeries per year (to be defined in each country).
5. The modalities of specialized training in breast surgery must include training in breast imaging, pathology, oncology, genetics, radiotherapy, and nuclear medicine.
6. Specialized training in breast surgery should be accessible to numerous surgical disciplines (gynecology, plastic and reconstructive, oncologic, general, digestive, endocrine and thoracic surgeries).
7. The duration of specialized training should be one or two years (to be defined in each country), without slowing down the surgical training curriculum specific to each country.
8. Continuing education programs for breast surgeons should be encouraged throughout their professional careers.
9. Clinical and translational research and innovations should be encouraged in breast surgery.
10. For Europeans countries, the educational program is committed to complying with European directives on the right to better health for those suffering from breast cancer.

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Original Article

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Breast Myofibroblastoma: A Single Institutional Case Series

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ABSTRACT

Objective: Breast myofibroblastoma (BM) is a rare, benign mesenchymal tumor primarily affecting older men and postmenopausal women. This study analyzed the clinicopathologic features, immunohistochemical profiles, and treatment outcomes of five BM cases diagnosed at a single institution over a period of 20 years.

Materials and Methods: A retrospective review was conducted for five patients diagnosed with BM between 1998 and 2024. Data included age, clinical presentation, tumor size, histopathologic findings, immunohistochemical profiles, treatment approaches, and follow-up outcomes.

Results: The median age at diagnosis was 68 years, with a mean tumor size of 5.06 cm. Clinical presentation included palpable, painless masses in two patients and an incidental finding in one, while data were unavailable for two cases. Histopathology showed well-circumscribed, unencapsulated tumors composed of spindle cells with admixed adipose tissue and collagen bundles. Immunohistochemically, all tumors were positive for desmin and CD34, with variable smooth muscle actin expression and negative S100 staining. No cases exhibited nuclear beta-catenin staining or 13q14 deletions. All patients underwent surgical excision, with one requiring re-excision due to tumor abutting margins. No recurrences were observed during follow-up (2–18 months).

Conclusion: BM is a benign tumor with favorable outcomes following surgical excision. This study underscores the variability in immunohistochemical staining and the importance of distinguishing BM from other spindle cell tumors. Increased numbers of published cases and refining diagnostic markers may be important to improve clinical management and reduce diagnostic uncertainty.

Keywords: Breast; myofibroblastoma; RB1 deletion; spindle cell tumor

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Key Points

- Breast myofibroblastoma is a rare, benign mesenchymal spindle-cell tumor.
- Imaging characteristics vary; biopsy is required for definitive diagnosis.
- Histologically, tumors are well-circumscribed, unencapsulated, with myofibroblastic differentiation, mostly positive for CD34 and desmin.
- Must be distinguished from other spindle cell tumors.
- Limited numbers of reported cases highlight the need for further study.

Introduction

Breast myofibroblastoma (BM) is a rare benign mesenchymal tumor predominantly seen in older men and postmenopausal women (1). Clinically, it presents as a painless, mobile mass, typically measuring 1–4 cm in size (2). Mammographically, BM often appears as a sharply circumscribed, round or ovoid, non-calcified mass (3). However, there is considerable variability in mammographic appearance, and image-guided biopsy is needed to establish a diagnosis. Histologically, these tumors are well-circumscribed and unencapsulated with myofibroblastic differentiation within a myxoid stroma; notably there is minimal atypia (Figure 1) (2). The diagnosis is confirmed via histopathology, revealing unencapsulated spindle cells with fibroblastic and myoblastic differentiation. This study examined five cases of BM from 1998 to 2024, with a focus on clinicopathologic features, immunohistochemical staining patterns, and treatment outcomes.

An important aspect of diagnosing benign spindle cell lesions in the breast is recognizing the overlap between myofibroblastoma and other entities, such as simple leiomyomas. Both tumors can demonstrate spindle cell morphology and express markers, such as desmin and smooth muscle actin (SMA); however, CD34 expression

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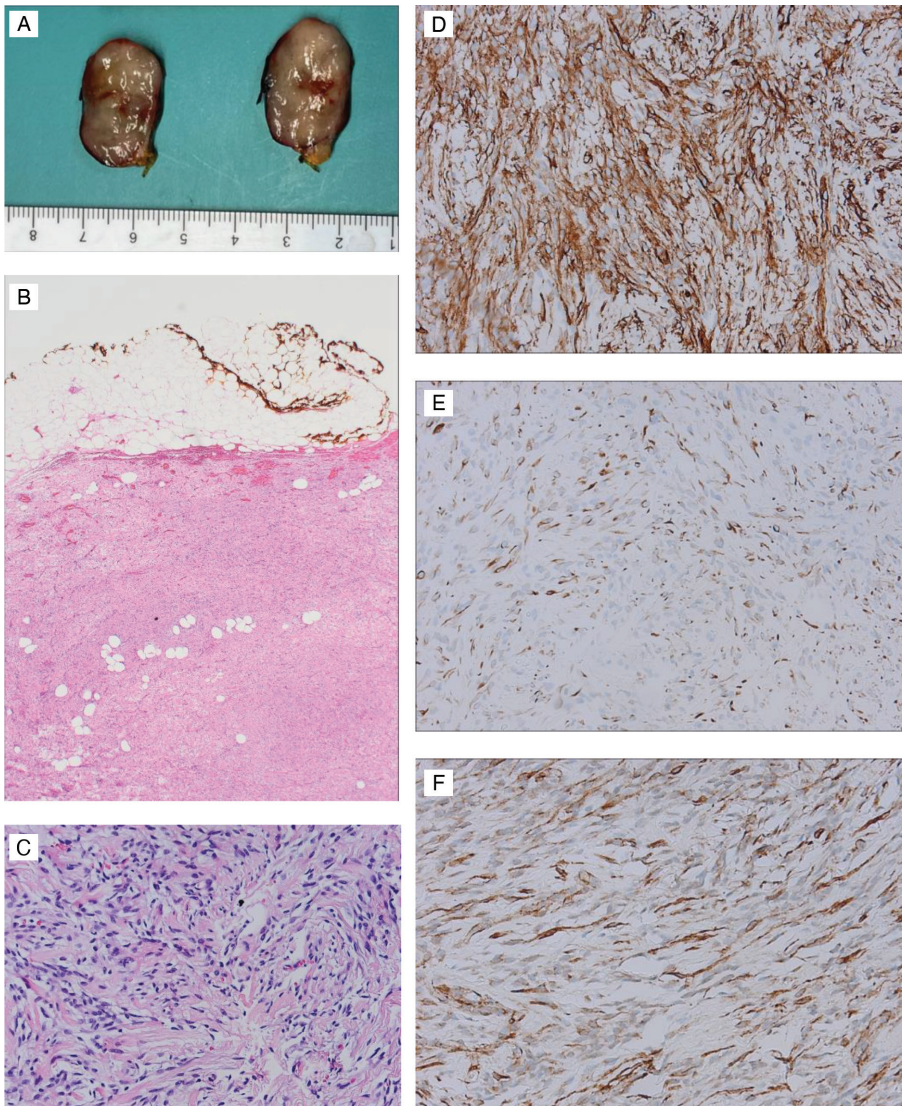


Figure 1. Gross and microscopic pathology of breast myofibroblastoma

A. Well-circumscribed homogeneous tan colored mass lesion. B. Low power photomicrograph highlights a well circumscribed spindle cell lesion containing fat, C. Higher power image highlighting bland appearing spindle cells with blunt ends arranged in fascicles, hematoxylin & eosin stain, 600x. The lesional cells are positive for CD34 (D), desmin (E) and smooth muscle actin (F) by immunohistochemistry, 600x

is a key differentiator, as myofibroblastomas typically express CD34 while leiomyomas do not (4-6). Nonetheless, there are documented exceptions where leiomyomas can express CD34, complicating the differential diagnosis (6). This overlap reflects the broader diagnostic challenge posed by the spectrum of myofibroblastic and smooth muscle differentiation in breast lesions.

The Armed Forces Institute of Pathology (AFIP) classification supports the concept of a spectrum of benign spindle cell lesions with overlapping myofibroblastic differentiation, underscoring the difficulty in drawing clear histological boundaries in many cases (7). These diagnostic challenges are further compounded by the embryologic origin of breast stromal components, which include both myoepithelial and smooth muscle lineages (8). Consequently, some tumors may exhibit hybrid features that defy precise classification, leading to potentially clinically irrelevant subclassifications.

Considering these diagnostic ambiguities, it is essential to approach such cases with a broader perspective that prioritizes clinical management and prognostic relevance over rigid histological labels. The use of ancillary studies such as fluorescent *in situ* hybridization (FISH) for 13q14 deletions, immunostains for retinoblastoma (Rb) protein, and STAT6 expression can aid in narrowing the diagnosis, but do not always resolve the ambiguity fully (5, 7, 9). Our case series, consistent with the AFIP perspective, supports an inclusive approach to categorizing benign spindle cell tumors of the breast as part of a morphologic and immunophenotypic continuum.

Materials and Methods

The medical records of five patients diagnosed with BM between 1998 and 2024 were retrieved from our hospital database and we ascertained the age at diagnosis, presenting symptoms, mode of detection, tumor size and location, radiographic characteristics, surgical treatment, histopathologic features and follow-up outcomes.

Results

There were five cases during the period of the study. The median age was 68 years with a mean of 65.2 years. All patients underwent primary resection without adjuvant therapies, and no recurrences were noted during a follow-up period ranging from 2–18 months. Two patients presented with a painless palpable mass, one presented with an incidental finding on a computed tomography scan, and mode of presentation was not documented for two cases. Tumor sizes ranged from 0.9 cm to 12.5 cm, with a mean size of 5.06 cm and a median size of 2.8 cm (Table 1). All lesions were well circumscribed and composed of fascicles of spindle cells with admixed adipose tissue. The spindle cells were cytologically bland with blunt ends, intersected by bundles of collagen. No significant nuclear atypia, mitoses or necrosis were seen in any of the cases. The majority of the tumors were positive for desmin and CD34 and negative for S100 (Table 2). Two tumors stained positive for SMA, two were negative, one unknown. No evidence of nuclear beta-catenin staining was seen. None of the five cases tested positive for 13q14 deletion. Following primary resection, one patient had tumor abutting resection margins and underwent re-excision of the lumpectomy cavity. No recurrences were noted during the variable follow-up periods. None of the patients received adjuvant radiation or systemic treatments.

Discussion and Conclusion

BM is a rare, benign, mesenchymal tumor originating from stromal cells and accounting for less than 1% of all breast tumors (10). It predominantly affects middle-aged to elderly individuals, with a slight male predominance (11). Libbrecht et al. (11) report that these lesions most commonly occur in individuals in their fifth and sixth decades of life. Typically, the tumor presents as a painless, well-circumscribed, mobile mass in the breast, often discovered incidentally during self-examination or routine mammography (10). Our physical exam mirrors what is seen in earlier publications about BM, where patients presented with a painless lump identified during self-examination.

Table 1. Clinical features of five cases of breast myofibroblastoma

Case number	Age	Laterality	Tumor size (cm)
1	51	Right	2.8x2.5x1.8
2	76	Left	1.1x1x0.7
3	61	Right	8.0x7.0x2.5
4	70	Right	12.5x11.8x5.7
5	68	Right	0.9x0.8x0.3

Table 2. Immunophenotype of five cases of breast myofibroblastoma

Case number	CD34	SMA	Desmin	S100
1	+	+	+	Unknown
2	+	+	+	-
3	Unknown	Unknown	Unknown	Unknown
4	+	-	+	-
5	+	-	-	-

SMA: Smooth muscle actin

The pathogenesis of BM is thought to involve several mechanisms. Chromosomal abnormalities, particularly deletions and rearrangements involving chromosomes 13q14 and 17, play a central role in tumor formation (4). Deletions within the 13q14 chromosomal region, including genes such as *RB1* and *FOXO1A*, disrupt cell cycle regulation and apoptosis, contributing to tumor growth (9, 12). Loss of heterozygosity at 13q14 and reduced Rb protein expression are critical features in the disease's progression (13). These genetic abnormalities are also seen in related tumors, such as spindle cell lipomas and cellular angiofibromas, suggesting a shared histogenetic origin (9). Advanced diagnostic tools, such as FISH and immunohistochemical analysis for Rb protein assist in identifying these alterations and distinguishing myofibroblastomas from other spindle cell tumors of the breast (4, 5, 14).

Histologically, BMs consist of randomly arranged fascicles of spindle-shaped cells mixed with adipocytes in a collagenous and myxoid background, consistent with our findings (6). Immunohistochemical studies typically show positivity for CD34, desmin, and SMA, and negativity for S100 and beta-catenin (1). However, certain variants may not display CD34 and desmin expression, which can complicate the diagnostic process (5). The expression of these markers helps distinguish myofibroblastoma from other spindle cell tumors, like schwannomas, malignant peripheral nerve sheath tumors, and synovial sarcomas (7). Among our five cases, three tumors were positive for desmin, one was negative (Patient 5), and one result was unavailable (Patient 3). CD34 was positive in four cases; the result for Patient 3 was unknown. SMA was positive in two cases, negative in two, with Patient 3 again being unknown.

The distinction between myofibroblastoma and leiomyoma remains particularly challenging. Leiomyomas, while typically negative for CD34, may exhibit focal positivity in rare instances, and show stronger and more diffuse desmin and SMA staining than myofibroblastomas. Yet, these immunophenotypic nuances may not always translate into clinical significance. Therefore, in cases where histologic and immunohistochemical features are equivocal, it may be more appropriate to emphasize the benign nature of the tumor and exclude malignancy, rather than overemphasize its precise nomenclature (4-7).

BMs are generally treated with wide local excision, without administration of radiotherapy or systemic therapy. In our series, the mean diameter of excision was 5.06 cm, consistent with what is reported in the literature. Imaging studies, such as mammography and ultrasound, are often used to help characterize these breast lesions but defining and distinguishing myofibroblastomas from other conditions remains challenging. Radiographic evaluations of myofibroblasotmas, including those by Magro et al. (9) often show benign features, with the tumors being incidentally found during examination for other symptoms (15).

Given its rarity, with less than 100 cases reported since its first description in 1987, each new case of BM significantly contributes to the understanding of this tumor. The importance of identifying additional cases of BM stems from the necessity to differentiate it from other breast lesions. Differential diagnosis of spindle cell lesions of the breast that diffusely express CD34 include myofibroblastoma, solitary fibrous tumor, pseudoangiomatous stromal hyperplasia (PASH) and dermatofibrosarcoma protruberans (DFSP). Solitary fibrous tumors share some morphologic features with myofibroblastoma with regards to spindle cell cytomorphology; in addition, they show prominent staghorn like vasculature, lack muscle markers and most importantly, express STAT6 by immunohistochemistry. PASH is a lesion of

myofibroblastic origin, and hence, will have immunophenotypic overlap with myofibroblastoma. However, PASH is morphologically distinct, forming slit like clefts in the stroma. DFSP is a cutaneous based, locally aggressive, spindle cell tumor with a storiform pattern of growth, poorly defined margins, lacks muscle marker expression, and is often positive for platelet-derived growth factor beta rearrangement, detectable by FISH. Therefore, expanding the pool of documented cases of BM will aid in establishing distinct diagnostic criteria and refining differential diagnoses to ensure appropriate clinical management. Our case series aims to enhance the differential diagnosis and reduce misdiagnosis.

In the context of breast cancer research, advanced genomic technologies, such as next-generation sequencing, hold significant potential for elucidating the molecular composition of BM. These approaches may offer valuable insights into its genetic aberrations, associated signaling pathways, and potential therapeutic targets. Prior studies have emphasized the impact of genetic predisposition on disease susceptibility, with *BRCA1* and *BRCA2* mutations being well-established risk factors for hereditary breast cancer. While BM is not typically associated with genetic predisposition or hereditary syndromes, exploring the genetic composition of this tumor could reveal novel genetic alterations or loci that contribute to its development. The collection of additional cases and further exploration of advanced techniques will be important to enhance diagnostic accuracy, optimize treatment strategies, and improve overall patient care.

Study Limitations

Our findings aligned with the existing but limited literature on BM, further demonstrating its benign nature and favorable prognosis following surgical excision. The variability in immunohistochemical staining highlighted the need for continued study to refine diagnostic markers. This study adds to the limited body of literature on BM, contributing to the differentiation of BM from other spindle cell tumors of the breast, such as phyllodes tumors and fibroadenomas, ensuring accurate diagnosis and appropriate treatment.

In conclusion, BM represents a unique entity among benign spindle cell tumors. Increased numbers of published cases, refining diagnostic markers and applying advanced molecular profiling techniques may aid in producing consensus diagnostic criteria and treatment guidelines, ultimately resulting in better care for individuals affected by this rare tumor.

Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Not necessary.

Footnotes

Authorship Contributions

Concept: A.N., I.J.; Design: A.N., I.J.; Data Collection or Processing: M.P., M.G.P., V.R., A.N.; Analysis or Interpretation: M.P., M.G.P., V.R., A.N., I.J.; Literature Search: M.P., M.G.P., V.R., A.N., I.J.; Writing: M.P., M.G.P., V.R., A.N., I.J.

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

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Original Article

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Unveiling the Diagnostic Potential of Platelet-to-Lymphocyte Ratio and HALP Score in Newly Diagnosed Breast Cancer: A Step Toward Early Detection

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ABSTRACT

Objective: Breast cancer (BC) is a global concern due to its high incidence worldwide. The alarming increase in BC cases highlights the need for careful management of the disease at multiple levels. This study investigated the diagnostic value of hemoglobin, albumin, lymphocyte and platelet counts (HALP score), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) in newly diagnosed BC patients.

Materials and Methods: A total of 84 individuals, including 42 healthy volunteers (group I) and 42 patients newly diagnosed with BC (group II), were included. Serum albumin levels were determined using spectrophotometry. The levels of tumor-markers carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA 15–3) in serum were analyzed by electrochemiluminescence immunoassay. Hemogram parameters were analyzed using fluorescence flow cytometry.

Results: The median PLR was significantly lower in group II than group I (p = 0.014). There were no statistical differences in HALP score, NLR, LMR, and prognostic nutrition index between the two groups (p = 0.133, p = 0.993, p = 0.591, and p = 0.294, respectively). The sensitivity and specificity of PLR in predicting BC were 61.90% and 64.29%, respectively, with an area under the curve of 0.665 (p = 0.009, 95% confidence interval: 0.5480 to 0.7819, cut-off value ≤124). PLR, CEA and CA 15–3 were independent risk factors for BC (p<0.05).

Conclusion: The findings suggest that PLR may serve as a potential biomarker for the early diagnosis of BC; however, further validation is required. Conversely, the HALP score and other parameters did not demonstrate a significant association with early BC diagnosis. These results warrant corroboration through regional and community-based studies.

Keywords: HALP score; breast cancer; diagnosis

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Key Points

- Breast cancer has a high global incidence, necessitating improved diagnostic and management strategies.
- The research focused on evaluating the diagnostic utility of hematological biomarkers, including the hemoglobin, albumin, lymphocyte and platelet count score, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, in newly diagnosed breast cancer patients.
- The PLR was significantly lower in breast cancer patients compared to healthy individuals (p = 0.014).
- PLR showed a sensitivity of 61.90% and specificity of 64.29% for predicting breast cancer.
- PLR may have potential as a diagnostic biomarker for breast cancer, but further validation through larger studies is necessary.

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Introduction

Breast cancer (BC), which has a high global prevalence, continues to be a major health concern. The rising number of cases highlights the urgent need for effective management strategies across various levels. Understanding the underlying pathogenetic mechanisms is important for the rapid development and implementation of effective diagnostic and therapeutic approaches for BC (1). Carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA 15–3) as tumor markers are currently among the key biomarkers used for BC (2), primarily in diagnosis and for follow-up. However, their effectiveness in diagnosing early-stage BC remains questionable because of low sensitivity and specificity, leading to ongoing research efforts aimed at discovering more reliable biomarkers for early detection (3). Studies have also reported the use of these markers for monitoring recurrence and treatment rather than for early diagnosis (4, 5). Moreover, the limited sensitivity and specificity of tumor markers are compounded by analysis availability, as these tests may not directly be performed in all healthcare settings, such as public health laboratories and small county state hospitals. This underscores the need for accessible, minimally invasive, reliable, and cost-effective biomarkers in routine assessments (3, 6, 7).

While identifying new prognostic and predictive biomarkers is essential for early detection (8), recent studies indicate that inflammation significantly influences tumor development, progression, proliferation, invasion, and metastasis (9). Blood cells such as lymphocytes and monocytes contribute to these processes by releasing cytokines that drive inflammatory responses (10, 11). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and prognostic nutrition index (PNI) have been evaluated to predict prognostic outcomes, such as the risk of recurrence, poor disease-free survival, distant metastasis and cancer staging in different cancers (12-15).

Combining these indices often offers a more accurate prognosis than any single marker, and they can be derived from routine laboratory tests (10, 16). The hemoglobin, albumin, lymphocyte and platelet count (HALP score), combining hemoglobin, albumin, lymphocytes, and platelets, reflects nutritional status and systemic inflammation, serving as a significant prognostic biomarker in certain cancers (17, 18). The HALP score, which provides simple and rapid results, may be an important predictor of patients' pathological stages and indirectly predict disease survival (19). The evaluation of these hematological parameters in patients with BC appears to mainly focus on the prognosis of the disease in the current literature and the number of studies on their utility in diagnosis of BC was limited. Therefore, we investigated the diagnostic value of HALP score in newly diagnosed BC patients and aimed to support the results with analysis of other biomarkers including NLR, PLR, and PNI, which are hematological parameters frequently encountered in the literature.

Materials and Methods

Establishing Working Groups

This retrospective study included a total of 84 female participants aged between 18 and 75 years, comprising 42 patients with newly diagnosed BC (group II) who visited the Department of Medical Oncology at Nigde Omer Halisdemir University Training and Research Hospital, and 42 age-matched healthy volunteers (group I). The participants' data, including albumin and hemogram test results, age, and any co-existing conditions, were gathered from the hospital's information system based on records from the time of initial BC diagnosis.

Inclusion and Exclusion Criteria

Patients were excluded if they had a history of surgery within the past six months, chronic diseases such as liver or kidney failure in addition to cancer, a concurrent diagnosis of another cancer in addition to BC, hematological comorbidities (e.g., anemia of chronic disease, thalassemia, thrombocytopenia), immunological diseases, or recent use of antibiotics. The control group consisted of healthy volunteers who met these criteria.

Blood Sample Protocol and Measurement Methods

Blood samples were collected using specific protocols to ensure consistent measurement methods:

• For albumin testing, blood was drawn into 5 mL biochemistry gel-separated tubes (BD, Becton Dickinson). The sera were obtained by centrifuging at 4.000 rpm for 10 minutes, and serum albumin levels were determined using a spectrophotometric approach on a Roche Cobas c701 spectrophotometer (Mannheim, Germany).

• The levels of CEA and CA 15–3 in serumwere analyzed by electrochemiluminescence immunoassay using a Roche Cobas e801 analyzer (Mannheim, Germany). Blood for these tests was drawn into 5 mL tubes without anticoagulants and the serum was separated as described above (BD, Becton Dickinson).

• Hemogram parameters were analyzed using fluorescence flow cytometry on a Sysmex XN-1000 devices (Kobe, Japan) from blood samples taken into tubes containing ethylenediaminetetraacetic acid.

Calculation of Scores and Ratios

• The HALP score = [hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)] / platelets (/L).

• NLR = neutrophil/lymphocyte count.

• PLR = platelet count/lymphocyte count.

• LMR = lymphocytes/monocytes.

• PNI was calculated using the formula: PNI = 0.005 × lymphocytes/mm^3 + 10 × albumin (g/L).

Ethical Statement

Ethical approval was granted by the Nigde Omer Halisdemir University Faculty of Medicine Non-Interventional Ethics Committee (protocol number: 2023/81, date: 10.11.2023).

Statistical Analysis

SPSS, version 22.0 (IBM Inc., Armonk, NY, USA)) and GraphPad Prism 9.5.0 program (Boston, MA, USA) were used for statistical analysis. Descriptive statistics are given as mean, standard deviation, median and interquartile range. Normality was checked using the Shapiro-Wilk test, histograms, skewness, and kurtosis. Categorical variables were compared using the chi-square test. For comparing two group means, an independent samples t-test was used if parametric assumptions were met; otherwise, the Mann-Whitney U test was applied. Variance homogeneity was assessed using Levene's test; if

variances were unequal, the Welch test was applied, and if equal, the Student's t-test was performed. Correlation analysis was conducted using Spearman's test. GraphPad Prism was used to perform receiver operating characteristics (ROC) curve analysis to determine the sensitivity and specificity of HALP, NLR, PLR, LMR, and PNI. Logistic regression analysis was used to identify independent risk factors for BC.

Establishing Working Groups

G*Power version 3.1.9.4), the sample size was decided as 80 participants (patients + controls) to achieve 95% (1- ß = 0.95) power at α = 0.05. According to reference article (20), the HALP score was taken as a reference parameter.

Results

Study Results

The study included age-matched groups, with both group I and group II having a mean age of 55.30±12.5 years. Upon examination of the parameters, CEA, CA 15–3, C-reactive protein, mean corpuscular volum, and basophil count in group II were significantly higher than in group I (p = 0.016, p = 0.001, p = 0.001, p = 0.001, and p = 0.001, respectively). Conversely, platelet and PLR values in group II were significantly lower than in group I (p = 0.020 and p = 0.014, respectively). No significant difference was observed between the groups with respect to other parameters (p>0.05). Detailed analysis data for other tests are presented in Table 1.

Correlation results are shown in Table 2. In group I there was a weak negative correlation between HALP score and NLR (r = -0.392, p<0.001) and a strong negative correlation between PLR and HALP score (r = -0.851, p<0.001). A weak positive correlation was found between LMR *vs.* HALP score (r = 0.440, p = 0.0041). A strong negative correlation was found between NLR *vs.* PLR (r = -0.632, p<0.001). There was no correlation between NLR *vs.* LMR, NLR *vs.* PNI and PLR *vs.* LMR (r = 0.260, p = 0.453, r = -0.161, p = 0.382, r = -0.285, p = 0.661, respectively).

In group II, a strong negative correlation was found between HALP score and NLR and HALP score and PLR (r = -0.603, p<0.001, r = -0.956, p<0.001, respectively), a weak positive correlation was found between LMR and HALP score (r = 0.317, p = 0.041). While there was a strong positive correlation between NLR and PLR (r = 0.584,

Table 1. Comparison of age and clinical variables between healthy controls (group I) and women with early diagnosed breast cancer (group II)

Parameters	Group I (n = 42) mean ± SD or median (IQR)	Group II (n = 42) mean ± SD or median (IQR)	p-value
Age, years	55.30±12.5	55.30±12.5	0.844
CEA, ng/mL	1.27 (0.96–1.70)	1.97 (1.29–3.12)	**0.016**
CA 15–3, ng/mL	12.20 (9.77–16.20)	19.5 (14.9–24.4)	**0.001**
Albumin, g/L	44.00 (42.75–45.25)	44.00 (40.97–45.00)	0.327
C-reactive protein, mg/L	1.60 (0.95–2.90)	3.35 (1.95–5.90)	**0.001**
Leukocyte count, (10^3/μL)	6.34±0.19	6.74±0.38	0.602
Hemoglobin (g/dL)	13.85 (12.90–14.42)	13.20 (12.4–14.05)	0.080
Erythrocyte count (10^6/μL)	4.70 (4.57–4.92)	4.72 (4.26–4.90)	0.230
MCV (fL)	83.00 (80.92–85.67)	87.7 (83.4–91.12)	**0.001**
MCH (pg)	29.90 (27.70–29.62)	29.00 (27.77–30.60)	0.597
MPV (fL)	10.13±1.11	10.40±0.86	0.728
Platelet count (10^3/μL)	292.45±60.74	247.50±69.31	**0.020**
Neutrophil count (10^3/μL)	3.47 (2.90–4.00)	3.78 (2.35–4.50)	0.486
Lymphocyte count (10^3/μL)	1.95 (1.77–2.42)	2.20 (1.74–2.60)	0.563
Basophil count (10^3/μL)	0.02 (0.01–0.03)	0.04 (0.02–0.06)	**0.001**
Eosinophil count (10^3/μL)	0.10 (0.07–0.18)	0.13 (0.08–0.20)	0.322
Monocyte count (10^3/μL)	0.45 (0.34–0.58)	0.48 (0.34–0.59)	0.855
HALP score	4.57 (3.25–5.84)	5.27 (4.10–6.06)	0.133
NLR	1.60 (1.26–2.18)	1.63 (1.22–2.20)	0.993
PLR	134.30 (113.55–169.50)	111.26 (93.21–141.98)	**0.014**
LMR	4.93 (4.04–5.98)	4.81 (3.70–6.00)	0.591
PNI	54.22±2.23	53.20±4.18	0.294

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count score; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MPV: Mean platelet volume; SD: Standard deviation; IQR: Interquartile range

p<0.001), there was a strong negative correlation between NLR and LMR (r = -0.490, p<0.001). There was also a weak negative correlation between NLR and PNI (r = -0.357, p<0.001). There was a weak negative correlation between PLR and LMR (r = -0.312, p = 0.045) (Table 2).

In the ROC analysis PLR, CEA and CA 15–3 were significant predictors of early BC diagnosis (p = 0.009, p = 0.017, p<0.001, respectively). HALP score, LMR, NLR, and PNI were not significant predictors of early BC diagnosis (p>0.05) (Table 3 and Figure 1).

Logistics regression analysis was used to investigate whether CEA, CA 15–3 and PLR were independent risk factors for BC. CEA, CA 15–3 and PLR were shown to be independent risk factors for early BC in this study (Table 4).

There were no significant baseline differences between healthy participants in group I and group II in terms of NLR, LMR, PNI, and HALP score (p>0.05). However, the PLR value significantly decreased in group II compared to group I (p = 0.014). Comparative data and p-values for the differences between other parameters are displayed in Figure 2.

Discussion and Conclusion

The present study set out to investigate the diagnostic potential of hematological markers of inflammation, including NLR, PLR, LMR, PNI, and HALP score with classical routine markers, CEA and CA 15–3, in patients with newly diagnosed with BC. The key finding was that PLR was significantly decreased in the newly diagnosed BC group, a result not previously reported. To the best of our knowledge, no other study has assessed the diagnostic value of NLR, PLR, LMR, PNI, and HALP scores together in newly diagnosed BC patients, making this the first study to evaluate these hematological parameters at the time of diagnosis.

Biomarkers may help in the early detection and earlier initiation of treatment in BC, but no current tumor marker can precisely predict the diagnosis or onset of the disease due to various factors that influence their levels, thereby affecting their sensitivity and specificity (21). Therefore, research has focused on finding easily accessible, minimally invasive, and reliable markers to complement existing diagnostic markers (7).

In the past years, the HALP score has been identified as a novel prognostic biomarker for predicting survival outcomes in various

Table 2. Correlation analysis results

Parameters	Group I (healthy participants)		Group II (breast cancer patients)	
	r	*p*	*r*	*p*
HALP score *vs.* NLR	-0.392	<0.001	-0.603	<0.001
HALP score *vs.* PLR	-0.851	<0.001	-0.956	<0.001
HALP score *vs.* LMR	0.440	0.004	0.317	0.041
NLR *vs.* PLR	-0.632	<0.001	0.584	<0.001
NLR *vs.* LMR	0.260	0.453	-0.490	<0.001
NLR *vs.* PNI	-0.161	0.382	-0.357	<0.001
PLR *vs.* LMR	-0.285	0.661	-0.312	0.045

HALP score: Hemoglobin, albumin, lymphocyte and platelet count score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index

Table 3. ROC analysis results for CEA, CA 15–3, PLR, NLR, HALP score, LMR and PNI

Parameters	AUC	Optimal cut-off point	*p*-value	95% confidence interval	Sensitivity (%)	Specificity (%)
CEA ng/mL	0.651	>1.38	0.017	0.5306 to 0.7710	66.67	64.29
CA 15–3 ng/mL	0.769	>15.60	<0.001	0.6673 to 0.8707	71.43	69.05
PLR	0.665	<124	0.009	0.5480 to 0.7819	61.90	64.29
NLR	0.510	>1.651	0.874	0.3853 to 0.6346	47.62	51.16
PNI	0.555	<54.12	0.381	0.4306 to 0.6805	50.00	52.38
HALP score	0.596	>5.079	0.131	0.4716 to 0.7200	59.52	61.90
LMR	0.545	<4.835	0.474	0.4208 to 0.6699	52.38	54.76

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count score; ROC: Receiver operating characteristic; AUC: Area under the curve

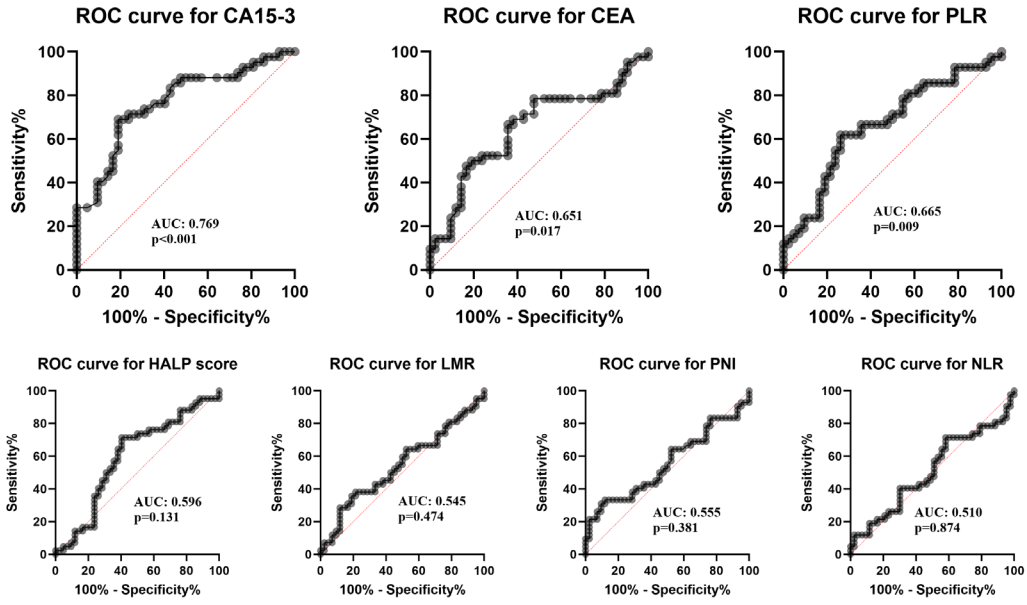


Figure 1. ROC curves of CEA, CA 15–3, PLR, NLR, HALP score LMR and PNI in detecting breast cancer

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count; ROC: Receiver operating characteristic curve

Table 4. Logistics regression analysis results for CEA, CA 15–3 and PLR

Parameters	Beta	OR	95% lower	95% upper	*p*-value
CEA ng/mL	0.424	1.529	1.090	2.137	0.006*
CA 15–3 ng/mL	0.160	1.174	1.085	1.290	<0.001*
PLR	-0.012	0.987	0.976	0.998	0.019*

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; PLR: Platelet-to-lymphocyte ratio; OR: Odds ratio

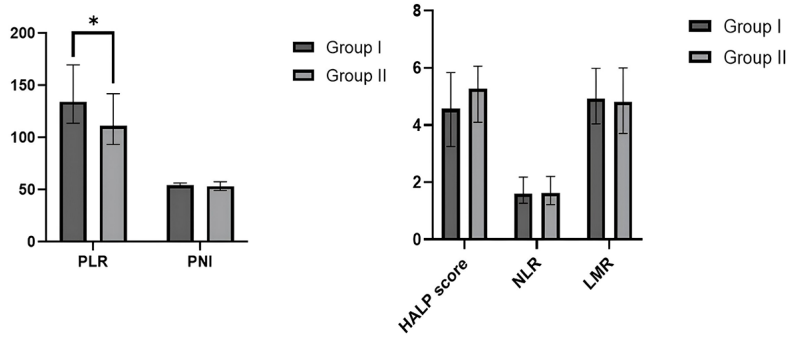


Figure 2. Comparative graphs of the results of all parameters (p<0.05)

*NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count; *: is represent p<0.05*

cancers (22, 23). These parameters provide a comprehensive view of a patient's immuno-nutritional status, which is very important for cancer patients due to increased metabolic demands and risks of chronic conditions such as cachexia (10, 22). Although the HALP score has gained recognition in the scientific literature, it has not yet been widely implemented in clinical settings.

A large meta-analysis showed that lower pre-treatment HALP scores were linked to poorer outcomes in cancer patients, suggesting its potential as a prognostic tool (22). Another meta-analysis indicated that decreased HALP scores were associated with poor survival outcomes, supporting its role as a prognostic biomarker in some cancers (24). Studies in patients with metastatic bladder and kidney cancers have shown that higher HALP scores are linked to better

survival, further highlighting its prognostic value (23, 25). In gastric adenocarcinoma, higher HALP scores correlated with improved survival (26), and in tongue squamous cell carcinoma, it was an independent predictor of prognosis (27). Similarly, it has been used as a prognostic marker in lung cancer patients (10).

While prognostic findings for other cancers align with these outcomes, studies in BC patients show that the HALP score serves as an independent prognostic indicator for early-stage BC and is linked to a lower recurrence-free survival rate. It has been suggested that this score can predict tumor recurrence or metastasis before and after surgery (28). Further studies noted that late-stage BC patients had significantly lower HALP scores compared to those with early-stage disease (29). Nevertheless, the study conducted by Alandağ et al. (30) showed that HALP score had no prognostic value in early-stage triple-negative BC subtype. In a diagnostic study involving prostate cancer, although the HALP score was not found to be diagnostic, it was noted that further validation is needed through multicenter studies (31).

For BC diagnosis, low HALP scores were correlated with aggressive tumor characteristics, including advanced tumor stage and axillary lymph node positivity, though the score by itself was not sufficient to accurately predict axillary lymph node involvement (32). The present study found that HALP scores were higher in newly diagnosed BC patients than in healthy controls, but this increase was not significant. In addition, we observed a strong negative correlation between PLR and HALP scores within the BC group, suggesting a need for further diagnostic validation of the HALP score in newly diagnosed BC patients. Furthermore, we found that PLR values were lower in newly diagnosed BC patients compared to healthy participants in our study. The results of a study reported that low PLR values in BC patients receiving neoadjuvant treatment were associated with high chemotherapy sensitivity (33). Platelets are rich in growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta, and platelet-derived endothelial cell growth factor. Cancer cells often produce these PDGFs in abundance, playing a significant role in promoting tumor growth and influencing cancer histology. Lymphocytes play a crucial role in mounting the immune response against tumors (34). The decrease in PLR values in newly diagnosed BC patients in the present study is quite interesting because studies generally emphasize that there is thrombocytosis at the beginning of cancer. However, thrombocytosis occurs variably in 10% to 57% of cancer patients (34).

Existing studies on PNI, PLR, NLR, and LMR in BC patients have primarily focused on prognosis (24-36). Research on these parameters in BC has highlighted PLR as a significant marker of systemic inflammation, with preoperative PLR levels potentially outperforming other inflammatory markers in predicting clinical outcomes (36). A retrospective study also indicated that PLR and NLR may be linked to age at BC diagnosis, though more research is needed to fully understand their prognostic implications (35). Further findings suggest that NLR and PLR increase with advancing tumor stage, while LMR decreases, emphasizing their potential utility in staging BC (19). A low LMR has been associated with poor prognosis in BC, while NLR and PLR were not predictors of disease-free survival, though elevated levels were related to tumor size, recurrence and metastasis (37). From a diagnostic perspective, these markers have shown potential in bladder cancer, where high NLR and PLR and low LMR and PNI were linked to invasive disease risk (38).

In the current study, the median values of HALP score, NLR, PNI, and LMR in group II did not differ significantly from those in group I, but PLR was significantly lower. ROC analysis showed significance for PLR and its sensitivity and specificity in detecting BC were moderate but better than the other biomarkers analyzed (except for CEA and CA15-3). At the same time, logistic regression analysis showed that PLR may be an independent risk factor for BC diagnosis. The significant difference between the groups and the fact that PLR has almost as good sensitivity and specificity as CEA and CA15–3 in the diagnosis of BC may suggest that PLR may be a potential biomarker in the diagnosis of BC. Despite the focus on prognostic evaluation in both BC and other cancers, the diagnostic relationship between the HALP score and systemic inflammatory markers, PNI, PLR, NLR, and LMR, remains unclear. This study is the first to assess these markers together in a diagnostic context, and we believe our findings may offer new insights not only for BC but also for other cancers.

Study Limitations

The current study has some limitations, including a small, region-specific population, which may limit the generalizability of our findings. Furthermore, as our study included newly diagnosed BC patients, we were unable to access certain pathological data (e.g., tumor size, grade, subtype), preventing a comprehensive evaluation of these prognostic markers.

HALP score may not be a viable diagnostic marker for BC, but decreased PLR levels may serve as a promising adjunct diagnostic marker for BC. Since PLR is derived from a simple, accessible, and inexpensive hemogram test, it offers significant advantages in BC diagnosis. However, PLR alone should not be used as a diagnostic tool for BC as changes in PLR and the cell numbers used to calculate may occur for many reasons, reducing its specificity. Therefore, further large-scale studies are needed to validate our findings.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Nigde Omer Halisdemir University Faculty of Medicine Non-Interventional Ethics Committee (protocol number: 2023/81, date: 10.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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Original Article

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The Effect of Aromatherapy on Pain and Anxiety Levels Before Breast Biopsy: A Randomized Controlled Trial

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ABSTRACT

Objective: Aromatherapy is widely used in the management of symptoms caused by interventional procedures. This randomized controlled trial evaluated the effectiveness of lavender and lavender-peppermint aromatherapy before breast biopsy for reducing women's pain and anxiety.

Materials and Methods: This trial was conducted in the breast outpatient clinic of a university hospital in İstanbul between July 2021 and March 2023. Patients were randomly assigned to one of two intervention groups; lavender or lavender-peppermint or the control group. Twenty minutes before the breast biopsy, a small pad impregnated with lavender or lavender-peppermint essential oil was attached to each patient at shoulder level, allowing for inhalation. The patients' anxiety and pain levels were assessed before and after the biopsy procedure using the state anxiety inventory and visual analogue scale, respectively.

Results: Study population was 135 patients, equally divided between lavender, lavender-peppermint or control groups (each n = 45). The mean age of the patients was 46.30±10.31 years, 76% were married, 65.9% were employed, and 64.4% underwent thick-needle biopsy. After the biopsy, reported anxiety and pain levels had decreased significantly more in the aromatherapy groups compared to the control group (p<0.05). However, no significant difference was found between the lavender and lavender-peppermint groups in terms of anxiety and pain reduction (p>0.05). Anxiety and pain levels were positively correlated (r = 0.406; p<0.001).

Conclusion: The use of lavender and lavender-peppermint essential oil via inhalation before breast biopsy was effective in reducing reported anxiety and pain levels. Implementing lavender and lavender-peppermint essential oil inhalation before interventional procedures may offer a simple and cost-effective approach to improving patient outcomes.

Keywords: Anxiety; aromatherapy; breast biopsy; breast cancer; pain management

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Key Points

- Aromatherapy with lavender and lavender-peppermint essential oil impregnated into an absorbent pad and worn on the shoulder for 20 minutes before breast biopsy reduced anxiety and pain levels in women.
- A positive correlation was found between pain and state anxiety levels, indicating that managing one may help alleviate the other.
- Aromatherapy provided a simple, cost-effective, and non-invasive nursing intervention that improved reported patient comfort before an interventional procedure.

Introduction

Breast cancer is the most common cancer in women, accounting for 30% of cases. According to GLOBOCAN 2020, its incidence was 47.8 per 100,000 women, representing 24.5% of all new cancer diagnoses (1). Early diagnosis significantly improves treatment outcomes (2), and breast biopsy is a key diagnostic method (3). However, this procedure can cause anxiety, stress, and pain, with fear of both the procedure and a potential cancer diagnosis contributing to emotional distress (4). Aromatherapy involves the use of essential oils extracted from plants for therapeutic purposes (5, 6). While the evidence on its benefits is mixed, no adverse effects have been reported (7, 8). Deng et al. (9) found that aromatherapy significantly reduced pain, anxiety, and interleukin-6 levels compared to standard care. In women with breast cancer, essential oils, including lavender, have been associated with reduced anxiety, stress (10, 11), pain (12), and other physical and psychological symptoms (13).

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In the literature, aromatherapy is frequently used in cancer and breast cancer patients for symptom management, particularly in alleviating anxiety and pain (6, 14). However, fewer studies have examined the effects of aromatherapy in individuals undergoing diagnostic procedures, such as breast biopsy. Some research has suggested that aromatherapy may be beneficial in reducing procedural anxiety and pain in similar interventional settings, such as diagnostic imaging or minimally invasive procedures. Expanding on this area of research, the present study was conducted during the breast cancer diagnostic process and compared different aromatherapy oils with a control group.

In addition, while lavender, rose, and orange essential oils are commonly studied for stress and anxiety in clinical settings (6), this study uniquely compared lavender-peppermint aromatherapy against lavender alone to explore potential differences in effectiveness. The rationale for choosing this combination was based on the complementary properties of the two oils. By combining peppermint with lavender, this study aimed to investigate whether a synergistic effect could be achieved in procedural anxiety and pain management, as is frequently applied in integrative aromatherapy practices. A peppermint-only group was not included, as its independent efficacy in reducing procedural anxiety and pain has not been consistently supported in prior research. The rationale for this study design was to obtain higher-quality evidence on the role of aromatherapy in procedural anxiety and pain management. Since anxiety and pain are closely interrelated, both parameters were assessed separately using validated measurement tools to ensure an objective evaluation.

Materials and Methods

Design and Aim

A randomized controlled trial was conducted to compare the effectiveness of lavender or lavender-peppermint aromatherapy in reducing anxiety and pain before breast biopsy. The study was registered in a clinical trial registry (NCT: 05276505) and complied with the CONSORT guidelines.

Research Hypotheses

H1: Applying lavender aromatherapy prior to breast biopsy reduces anxiety and pain.

H2: Applying lavender-peppermint aromatherapy prior to breast biopsy reduces anxiety and pain.

H3: There is a difference in the effectiveness of lavender and lavender-peppermint aromatherapy oils in reducing anxiety and pain before breast biopsy.

Population and Sample

The study was conducted in the breast outpatient clinic of a hospital in İstanbul between July 2021 and March 2023. Sample size was determined by performing power analysis in the G*Power (v3.1.9) program. Trambert et al. (11) calculated an effect size of d = 0.603. Based on this estimated effect size and an alpha level of 0.05, at least 45 patients in each group (total of 135 patients) were required to achieve 80% power (1-β).

Therefore, a total of 135 patients, two-thirds (n = 90) of whom were in the experimental group and the remining third (n = 45) in the control group, were included. Adult female patients >18 years and scheduled for breast biopsy (vacuum biopsy, thick-needle biopsy, magnetic resonance imaging-guided biopsy) were included in the study. Excludion factors included pregnancy or breastfeeding, lavender allergy, impaired sense of smell, difficulty breathing or active wheezing, history of asthma, epilepsy, or seizures, a diagnosed psychiatric disorder or migraines, and any cognitive, verbal, or hearing impairment that could affect communication. At the end of the study, the sample effect size was calculated. Post-hoc analysis showed effect sizes (Cohen's d) of 0.924 (98% power) between the lavender and control groups, 1.139 (99% power) between the lavender-peppermint and control groups, and 0.176 (12% power) between the two aromatherapy groups.

Randomization

Randomization was done using an online randomizer (https://www.randomlists.com/random-letters). Patients were randomly assigned to the experimental and control groups according to the number sequence generated by the program.

Data Collection Process

The breast clinic in which the study was conducted is staffed by three physicians and two nurses. Thick-needle and vacuum biopsy procedures are performed most often, with an average of two patients biopsied daily. The biopsy method may vary depending on institutional functioning, and patient and physician preferences. After the physician explains the steps of the biopsy procedure in the breast clinic, the patient's consent is obtained. Patients are taken to the waiting room while preparations are made. Biopsy procedures take approximately 15–20 minutes.

For all participants in the present study, pre-biopsy pain and anxiety were assessed in the waiting room, before starting the intervention in the aromatherapy groups. The control group received no intervention before the biopsy procedure. Assessments of post-biopsy pain and anxiety were performed immediately after procedure in the biopsy room. The study design is shown in Figure 1.

Lavender or lavender-peppermint aromatherapy absorbent pad intervention: Twenty minutes before the breast biopsy, a small (approximately 2.5×1.2 cm) rectangular absorbent pad impregnated with 2 mL of lavender or lavender-peppermint essential oil was attached to each patient at shoulder level. All patients wore the aromatherapy absorbent pads for exactly 20 minutes under the supervision of the researcher, and the pads were removed immediately before the breast biopsy procedure began. The exposure time was standardized for all participants to ensure consistency. After the procedure, the patients' anxiety and pain levels were reassessed. To prevent the aromas from mixing in the waiting room atmosphere, the procedures were performed in different biopsy rooms for the two groups. No patient reported any severe adverse events.

Lavender essential oil (Lavandulae aetheroleum): Lavender essential oil is reported to have antibacterial, antiviral, antifungal, and anti-inflammatory effects (15), as well as analgesic and anti-edema effects (16). It is used for pain relief and relaxation (17). The active ingredient in lavender oil that reduces pain is linalool. Lavender oil is also effective in regulating emotional responses, heart rate, blood pressure, and respiration (5).

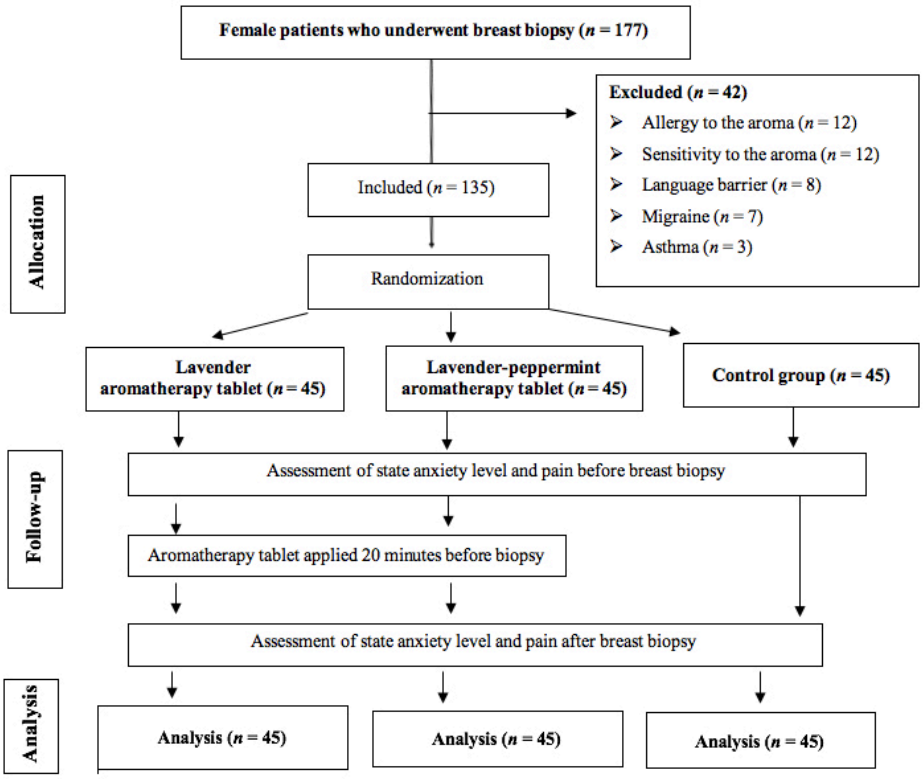


Figure 1. CONSORT flow chart

Peppermint essential oil (Menthae piperitae aetheroleum): The pharmacological effect of peppermint essential oil is due to the menthol it contains (18). It is reported to have antipruritic, astringent, and antiseptic effects. It is a powerful supporter of the digestive and respiratory systems. Peppermint essential oil is effective against physical and mental fatigue and increases physical and mental capacity (19).

Data Collection Tools

The study data were collected using a personal information form, the state anxiety inventory, and visual analog scale. The personal information form was created by the researchers and included questions about the participants' demographic characteristics, such as age, comorbity, and marriage status and their biopsy procedure, including details of biopsy type and biopsy history.

State anxiety inventory: The scale was developed by Spielberg et al. (21) in 1970 and adapted to Turkish by Öner and Le Compte (20). For each item, the patient selects "not at all" (1), "a little" (2), "somewhat" (3), or "very much" (4) according to how they feel at the present moment. Items expressing positive emotions (e.g., "I feel calm") are reverse-scored. The total score ranges from 20 to 80. A high scale score is directly proportional to a high anxiety level. A score of 20 points can be interpreted as no anxiety, 21–39 points as mild anxiety, 40–59 points as moderate anxiety, 60–79 points as severe anxiety, and 80 points as extreme anxiety, equivalent to panic (20, 21).

Visual analog scale: The patient rates their pain level on a 10-cm line marked at 1-cm intervals from 0 ("no pain") on one end to 10 ("worst pain") on the other. Scores of 1–2 describe slight pain, 3–4 describe mild pain, 5–6 describe moderate pain, and 7 or higher describe severe pain (22).

Ethical Considerations

Acıbadem University and Acıbadem Healthcare Organizations Medical Research Ethics Committee approved the study (decision number: 2021-14/18, date: 29.07.2021) and written informed consent from all participants were obtained. The study was supported by the Acıbadem University Scientific Research Projects Coordination Unit (project number: 2022/07-19).

Statistical Analysis

SPSS, version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses of the study data. For statistical analysis of continuous variables, the Kolmogorov-Smirnov test was used to test the normality of score distributions. In addition to descriptive statistical methods, comparisons of quantitative data between groups were made with one-way analysis of variance or its non-parametric equivalent, the Kruskal-Wallis H test, followed by post-hoc Bonferroni test. Qualitative comparisons between groups were made using Pearson or Fisher chi-square tests. Relationships between continuous variables were analyzed using Spearman's correlation test. Differences in repeated measures were evaluated using Friedman's test for within-group comparisons and Wilcoxon's test for comparisons between two groups. Results were evaluated within 95% confidence intervals and significance was accepted at $p<0.05$.

Results

A total of 135 female patients who underwent breast biopsy were recruited for the study. The mean age of the participants was 46.30±10.31 years; 76% were married, 70.4% had children, 65.9% were actively working, and 83.3% had a university degree or higher level of education. Ultrasound-guided, thick-needle biopsy was

performed in 64.4% of the patients, while the remaining 35.6% underwent vacuum-assisted biopsy. Additionally, 32.6% of the participants reported having at least one chronic comorbidity. The demographic and clinical characteristics of the patients are presented in Table 1. The only significant difference between the groups was observed in terms of biopsy type (p = 0.027).

There were no significant differences in pre-biopsy state anxiety scores among the groups (p>0.05). However, post-biopsy anxiety levels were significantly higher in the control group compared to the lavender-peppermint group, with no significant difference between the control and lavender groups (p = 0.039). Bonferroni-adjusted post-hoc analysis confirmed that this difference was between the lavender-peppermint group and the control group (p = 0.032; d = 0.527), while no significant difference was detected between the lavender and control groups (p>0.05). Effect size analysis indicated large effects for both aromatherapy interventions (Cohen's d = 1.098 for the lavender group and d = 1.302 for the lavender-peppermint group) and a moderate effect for the control group (d = 0.380). When comparing the amount of reduction in state anxiety scores between groups, both the lavender (p = 0.001, d = 0.924) and lavender-peppermint groups (p<0.001, d = 1.139) exhibited significantly greater decreases than the control group, with no statistically significant difference observed between the two aromatherapy groups (p>0.05) (Table 2).

Similarly, no significant difference was found in pain levels between the groups before the biopsy (p>0.05). Post-biopsy assessments, however, revealed a significant difference in pain scores among the groups (p = 0.034). The Bonferroni-adjusted post-hoc analysis showed that this difference was between the lavender-peppermint group and the control group (p = 0.028; d = 0.646), while no significant difference was noted between the lavender and control groups (p>0.05). Effect size analysis revealed large effects for both aromatherapy interventions (Cohen's d = 1.004 for the lavender group and d = 1.316 for the lavender-peppermint group) and a moderate effect for the control group (d=0.475). In terms of the amount of reduction in pain scores, both the lavender (p = 0.001, d = 0.823) and lavender-peppermint groups (p<0.001, d = 1.112) demonstrated significantly greater reductions compared to the control group, with no significant difference found between the two intervention groups (p>0.05) (Table 3).

Table 1. Distribution of the patients' demographic and descriptive characteristics

	Total (n = 135)	**Lavender group (n = 45)**	**Lavender-peppermint group (n = 45)**	**Control group (n = 45)**		
Variable	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**Test value**	***p*-value**
Age (year), mean ± SD	46.30±10.31	45.22±11.22	45.27±9.41	48.42±10.10	2.896[a]	0.235
Marital status					0.573[b]	0.751
Married	103 (76.3)	36 (80.0)	34 (75.6)	33 (73.3)		
Single	32 (23.7)	9 (20.0)	11 (24.4)	12 (26.7)		
Children					0.497[b]	0.780
Yes	95 (70.4)	33 (73.3)	30 (66.7)	32 (71.1)		
No	40 (29.6)	12 (26.7)	15 (33.3)	13 (28.9)		
Actively employed					0.857[b]	0.651
Yes	89 (65.9)	32 (71.1)	28 (62.2)	29 (64.4)		
No	46 (34.1)	13 (28.9)	17 (37.8)	16 (35.6)		
Education level					3.820[c]	0.437
Elementary school	6 (4.4)	3 (6.7)	1 (2.2)	2 (4.4)		
Middle school	17 (12.6)	6 (13.3)	3 (6.7)	8 (17.8)		
University or higher	112 (83.3)	36 (80.0)	41 (91.1)	35 (77.8)		
Biopsy type					7.565[b]	0.023*
Vacuum biopsy	48 (35.6)	11 (24.4)	14 (31.1)	23 (51.1)		
Thick-needle biopsy	87 (64.4)	34 (75.6)	31 (68.9)	22 (48.9)		
Chronic disease					0.067[b]	0.967
Yes	44 (32.6)	15 (33.3)	15 (33.3)	14 (31.1)		
No	91 (67.4)	30 (66.7)	30 (66.7)	31 (68.9)		
Biopsy history					0.084[b]	0.959
Yes	31 (23.0)	10 (22.2)	11 (24.4)	10 (22.2)		
No	104 (77.0)	35 (77.8)	34 (75.6)	35 (77.8)		

[a]: Mann-Whitney test; [b]: Pearson's chi-square test; [c]: Fisher's exact test; SD: Standard deviation

Table 2. Patients' state anxiety levels before and after biopsy

	State anxiety level					
	Pre-biopsy	Post-biopsy	Difference			
Research groups	**Mean ± SD**	**Mean ± SD**	**Mean (95% CI)**	**Test value**	***p*-value**	***d***
Lavender group 1	50.44±8.67	39.67±9.41	-10.78 (-13.73; -7.83)	-5.485[b]	<0.001*	1.098
Lavender-peppermint group 2	49.42±8.95	36.93±11.67	-12.49 (-15.37; -9.61)	-5.442[b]	<0.001*	1.302
Control group 3	46.04±10.84	43.27±12.36	-2.78 (-4.97; -0.58)	-2.882[b]	0.004*	0.380
Test value	4.343[a]	6.503[a]	26.006[a]			
***p*-value**	0.114	0.039*	<0.001*			
Subgroup	***p*-value/[d]**	***p*-value/[d]**	***p*-value/[d]**			
Group 1 *vs.* group 2	N/A	0.526[c]/0.258	0.682[c]/0.176			
Group 1 *vs.* group 3	N/A	0.698[c]/0.328	0.001[c*]/0.924			
Group 2 *vs.* group 3	N/A	0.032[c*]/0.527	<0.001[c*]/1.139			

*p<0.05; [a]: Kruskal-Wallis H test; [b]: Wilcoxon signed-rank test; [c]: Bonferroni test; SD: Standard deviation; CI: Confidence interval; N/A: Not available; [d]: Cohen's effect size

Table 3. Patients' pain levels before and after breast biopsy

	Pain level					
	Pre-biopsy	Post-biopsy	Difference			
Research groups	**Mean ± SD**	**Mean ± SD**	**Mean (95% CI)**	**Test value**	***p*-value**	***d***
Lavender group 1	6.09±1.87	3.71±2.13	-2.38 (-3.09; -1.67)	-5.349[b]	<0.001*	1.004
Lavender-peppermint group 2	6.00±1.75	3.20±1.89	-2.80 (-3.44; -2.16)	-5.535[b]	<0.001*	1.316
Control group 3	5.40±2.40	4.67±2.59	-0.73 (-1.20; -0.27)	-2.773[b]	0.006*	0.475
Test value	4.366[a]	6.789[a]	24.855[a]			
***p*-value**	0.113	0.034*	<0.001*			
Subgroup	***p*-value/[d]**	***p*-value/[d]**	***p*-value/[d]**			
Group 1 *vs.* group 2	N/A	0.768[c]/0.254	0.561[c]/0.188			
Group 1 *vs.* group 3	N/A	0.430[c]/0.403	0.001[c*]/0.823			
Group 2 *vs.* group 3	N/A	0.028[c*]/0.646	<0.001[c*]/1.112			

*p<0.05; [a]: Kruskal-Wallis H test; [b]: Wilcoxon signed-rank test; [c]: Bonferroni test; SD: Standard deviation; CI: Confidence interval; N/A: Not available; [d]: Cohen's effect size

Discussion and Conclusion

This study was conducted to determine the effect of two different aromatherapy essential oils before breast biopsy on patients' pain and anxiety levels. The results showed that anxiety decreased more in patients who received aromatherapy compared to those who received standard care, with a significant reduction seen with lavender-peppermint aromatherapy. We believe this combination might be more effective because of the mental relaxation induced by the active ingredient in peppermint essential oil in addition to lavender.

Undergoing a biopsy is a stressful experience, and all patients in our study had moderate anxiety before the procedure, which decreased afterward. The invasive nature of the biopsy and its role in cancer diagnosis may heighten anxiety, while completing the procedure may bring relief. Previous studies have shown that aromatherapy can reduce anxiety in various medical settings, including breast biopsy and imaging (11, 23). While a previous study found no significant effects of aromatherapy on perioperative anxiety and pain (24), our findings suggest that the use of some aromatherapy before interventional procedures may enhance the quality of care. This discrepancy may be due to differences in study design, the type and concentration of essential oils used as the only significant differences in this study were between the controls and the patients exposed to essential oils containing peppermint, the mode of administration, or variations in patient populations.

Biopsy procedures are also associated with pain. In this study, the participants reported moderate levels of pain before the biopsy. This may be related to increased pain sensitivity resulting from pre-biopsy

anxiety. However, considering that these patients were women at high risk for breast cancer and were in the process of diagnosis, their pain may also have been due to the presence of a mass, which is one of the symptoms of breast cancer. Participants in all three groups reported lower pain after the biopsy, but pain levels clinical and statistical decreased more in the aromatherapy groups with a significant difference again between the group exposed to peppermint and the controls. A similar study suggested that peppermint aromatherapy reduced pain and anxiety associated with intravenous catheterization (12). İlter et al. (25) also observed that orange, chamomile, and lavender inhaler aromatherapy reduced procedural pain and improved cooperation during port catheter insertion. In another study, bitter marjoram aromatherapy was reported to be an effective method of pain control (26).

There was a significant relationship between the anxiety and pain levels in this study. As suggested earlier, increased anxiety experienced by patients may increase their perception of pain. Previous studies have also demonstrated that anxiety and pain are positively associated in invasive procedures and that anxiety increases pain (27-29).

The use of aromatherapy absorbent pads prior invasive procedures offers a simple, cost-effective, and uncomplicated nursing intervention for reducing patient anxiety and pain. Although no statistically significant difference was found between the lavender and lavender-peppermint groups, clinical differences were observed. Our findings indicate that both lavender and lavender-peppermint essential oils may contribute to anxiety and pain reduction before breast biopsy but the only significant difference was observed for women exposed to peppermint essential oils compared to controls. Given the potential benefits, clinics may consider offering aromatherapy options to women based on their preferences if no contraindications exist.

Future studies should focus on conducting multicenter trials with larger and more diverse samples, including different patient groups. Furthermore, given the differences observed in the present study between lavender only or lavender plus peppermint essential oils, more research is needed to compare the effectiveness of various flavors of aromatherapy oils and the administration routes that result in optimal patient experiences. Finally, future studies should consider integrating qualitative patient experiences with fully quantitative findings.

Study Limitations

This randomized controlled study ensured comparable demographic variables across groups, with all interventions performed by the same researcher. Objective semi-quantitative methods were used for pre- and post-intervention assessments. However, the study's single-center design limits generalizability, and the high educational level of patients in a private health center may have influenced stress levels. In addition, anxiety and pain were measured based on patient self-perception. Furthermore, while the combination of lavender and peppermint oils was selected for their complementary properties, the absence of a peppermint-only group limits the ability to evaluate the independent effect of peppermint aromatherapy.

Ethics

Ethics Committee Approval: Acıbadem University and Acıbadem Healthcare Organizations Medical Research Ethics Committee approved the study (decision number: 2021-14/18, date: 29.07.2021).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

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

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

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Original Article

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Use of Three-Dimensional Surface Imaging to Measure Breast Volume in the Upright Position With Acceptable Accuracy

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ABSTRACT

Objective: The utility of three-dimensional surface imaging (3DSI) for measuring breast volume in the upright position has not been established.

Materials and Methods: First, the accuracy of 3DSI measurements was evaluated using plastic models with known breast volumes. Then, the breast volumes of 30 patients were measured using 3DSI in the upright position, computed tomography (CT) in the supine position, magnetic resonance imaging (MRI) in the prone position, and mammography (MMG) of the compressed breast. To determine the impact of 3DSI measurements, the correlation coefficients between 3DSI and CT, between MMG and CT, and between MRI and CT were calculated.

Results: The accuracy of 3DSI measurements was confirmed using plastic models. The correlation coefficients between 3DSI and CT, between MRI and CT, and between MMG and CT were 0.83, 0.997, and 0.84, respectively. Although the breast volume measured by 3DSI was closely associated with that measured by CT, this correlation was weaker than that between the MRI- and CT-measured volumes and comparable with that between the MMG- and CT-measured volumes.

Conclusion: 3DSI can be used to measure breast volume in the upright position with clinically acceptable accuracy for the evaluation of cosmetic surgical outcomes.

Keywords: Breast volume; three-dimensional surface imaging; magnetic resonance imaging; computed tomography; mammography

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Key Points

- Three-dimensional surface imaging (3DSI) can be used to measure breast volume in the upright position with clinically acceptable accuracy.
- The correlation coefficient between 3DSI-measured and computed tomography (CT)-measured breast volumes was 0.83.
- Breast volume measured by magnetic resonance imaging was 5% larger than that measured by CT.
- Mammography is a convenient tool to estimate breast volume.

Introduction

The increasing survival rates of breast cancer patients have shifted the focus of research toward the management and quality of life of survivors. While breast-conserving surgery (BCS) and breast reconstruction have minimal impact on survival outcomes, they play a vital role in subsequent patient satisfaction. Achieving optimal esthetic outcomes in these procedures improves the overall well-being of breast cancer survivors.

Breast volume is a critical factor influencing the esthetic results of both BCS and breast reconstruction. In BCS, the cosmetic outcome is largely determined by the ratio of tumor volume to the affected breast volume (1), with a ratio of 10% or lower being associated with favorable results (2). Similarly, in breast reconstruction, accurate breast volume measurement is essential for selecting the appropriate size of tissue expanders, prostheses, or donor tissue for autologous reconstruction (3).

There are several methods of measuring breast volume using preoperative diagnostic imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and mammography (MMG). However, the optimal method has not yet been determined. CT and MRI require the patient to be in the supine and prone positions, respectively, while MMG requires compression of the breast. As the cosmetic outcome of the breast is usually evaluated with the patients in the upright or sitting position, these methods likely do not reflect subjectively meaningful breast volume (4, 5).

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Desktop personal computers are now sufficiently powerful to allow the use of three-dimensional cameras and to easily process three-dimensional images. Hence, three-dimensional surface imaging (3DSI) may have a role in improving the esthetic outcomes of breast surgery. Some researchers have attempted to use three-dimensional cameras to evaluate the shape of the treated breast (6, 7).

In light of these studies, we attempted to clarify the impact of 3DSI on breast volume measurements using other methods. First, we evaluated and confirmed the accuracy of the 3DSI volume measurements using plastic models in which the breast volumes were measured by the water replacement method. Then, we measured the breast volumes of 30 women using 3DSI, CT, MMG, and MRI. We evaluated the relationship between 3DSI-measured breast volume and CT-measured breast volume, the latter of which is considered equivalent to the volume of a surgically resected specimen. The association of breast volume measured by 3DSI, MMG, or MRI and that measured by CT was evaluated. Using these data, the utility of 3DSI for breast volume measurement was assessed.

Materials and Methods

3DSI Measurement of Breast Volume and Its Validation Using Phantoms

The K3 3D camera system (Kiisya Corporation, Tokyo, Japan) was used in this study. This 3D camera produces three-dimensional images of the target object and this was used to measure breast volume according to the manufacturer's manual. When imaging the right breast, the camera is positioned 60 cm away from the patient and slightly to the patient's right from the front to scan the entire breast. Four points forming a quadrilateral that covers the entire breast were placed on the image (Figure 1a). The extracted breast image was then sectioned horizontally at 10 levels. The boundary of the breast was marked at each level (Figure 1b), and the posterior side was closed with a straight line. The areas of the enclosed figures were summed to calculate the breast volume. The skin of the breast, as well as subcutaneous fat tissue, was included in the breast volume.

Before the study, we conducted a performance evaluation of the accuracy of the K3 camera. We created plastic breast models with volumes of approximately 300, 500, and 900 mL, respectively. The volumes of these three models were measured precisely based on Archimedes' principle (the volume is equivalent to the volume of displaced water). Measurements were repeated 10 times in each of these models and the resulting volumes were compared with the volume of displaced water.

Patients

Female breast cancer patients who are participating in an ongoing study in which we are investigating the usefulness of 3DSI for BCS were recruited to the present study. All participants in the present study underwent BCS. Three-dimensional imaging data for both breasts were obtained before the operation. In addition to these data, we obtained the demographic characteristics of the participants, clinical and pathological features of the breast cancer, and MMG, CT, and MRI images. This study was approved by Nihon University Itabashi Hospital Ethical Review Board (approval no.: RK-220208-4, date: 10.02.2025). Our study was performed in accordance with the principles of the Declaration of Helsinki. We obtained written informed consent from all participants.

CT Measurement of Breast Volume

CT was performed to examine the area from the neck to the pelvic organs for screening for metastatic lesions. For CT imaging, patients were placed in the supine position. In general, contrast medium was not used. Osirix® (Pixemo SARL, Switzerland) was used to measure the breast volume by CT according to the software manual. Briefly, the CT data were imported into this software, the margins of the sectioned breast image were traced in each slice (Figure 2), and the breast volume was calculated by summing the values of the traced area and multiplying by a section interval of 5 mm. The breast margin was defined as the breast skin surface and the outside lines of the muscle and bones of the thorax.

Fujii et al. (8) demonstrated that breast volume measured by CT is closely related to the volume determined from mastectomy specimens.

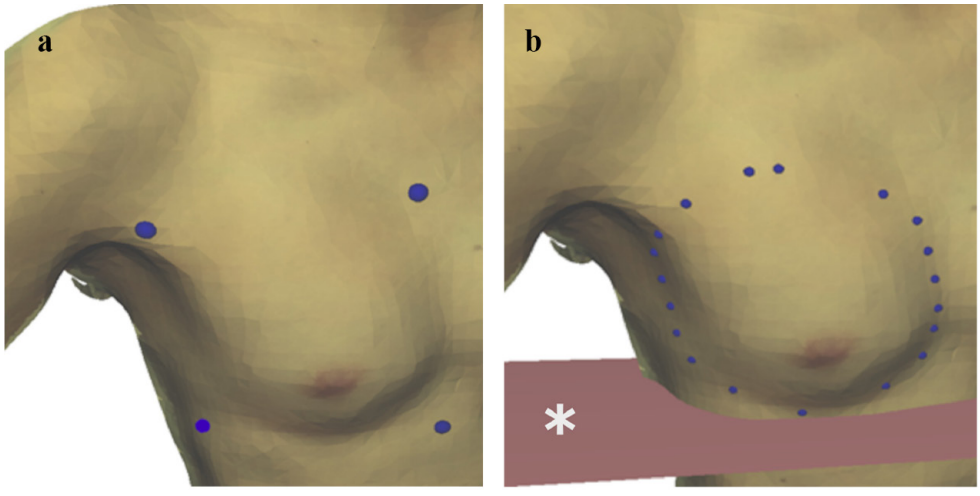


Figure 1. Measurement of the breast volume using 3DSI. Four points forming a quadrilateral covering the entire breast were placed on the image (Figure 1a). The extracted breast was then horizontally sectioned at 10 levels. The solid reddish-brown color with the symbol '*' indicates the section level (Figure 1b). The boundary of the breast was dotted at each level, and the posterior side was closed with a straight line. The areas of the enclosed figures were summed to calculate the breast volume

3DSI: Three-dimensional surface imaging

Based on this report, the CT volume was used as the benchmark in our study.

MRI Measurement of Breast Volume

MRI was performed to reveal the extent of the cancerous breast lesions and any unknown lesions. Patients were placed in the prone position. Contrast medium was used in all cases. The enhancement phase in MRI was not specified in the breast volume measurement. The procedure of breast volume measurement was the same as that for CT (Figure 3).

MMG Measurement of Breast Volume

The procedure for measuring breast volume by MMG was described by Cochrane et al. (2). Briefly, an MMG image is taken from the oblique lateral view shaped like a cone, denoting the breast (Figure 4). The distance from the upper to lower edges of the breast parenchyma is defined as the diameter of the cone base (2r). The distance from the nipple to the major pectoral muscle is regarded as the height of the cone (h). These values are used in the formula for calculating the volume of a cone to determine breast volume. The formula for the volume of a cone is volume = (1/3) $\pi r^2 h$.

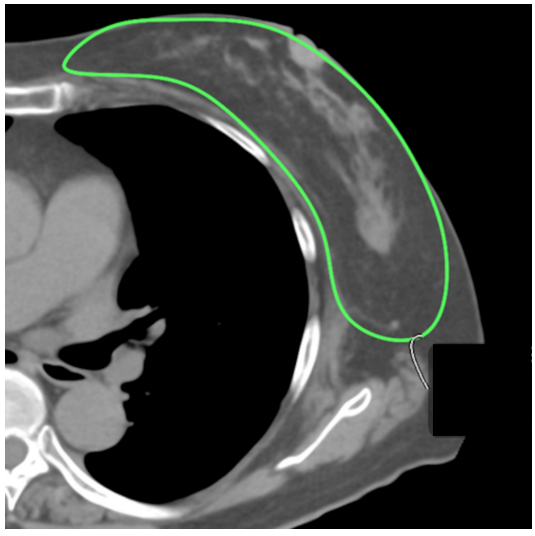


Figure 2. Measurement of the breast using CT. The margins of the sectioned breast image were traced in each slice (Figure 2), and the breast volume was calculated by summing the values of the traced area and multiplying by a section interval of 5 mm

CT: Computed tomography

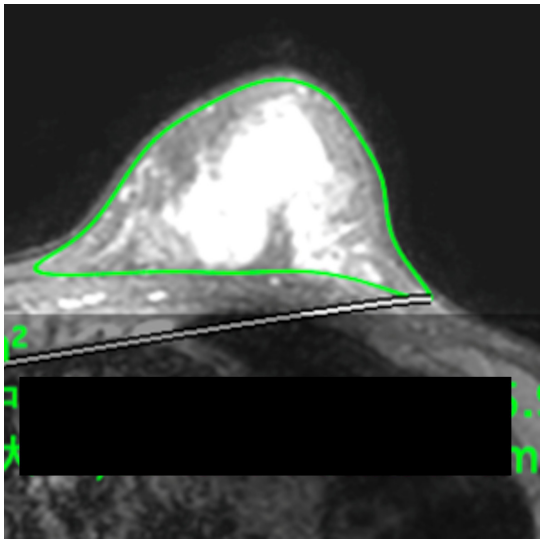


Figure 3. Measurement of breast volume using MRI. The margins of the sectioned breast images were traced in each slice (Figure 3). The measurement method using MRI is the same as that for CT. The MRI image is displayed upside down

MRI: Magnetic resonance imaging; CT: Computed tomography

Statistical Analysis

The relationship between two breast volume measurements was investigated using Pearson's correlation coefficients. Linear regression analysis was used to generate regression lines. The statistical package R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; http://www.R-project.org) was used for the statistical analyses. A $p<0.05$ was considered significant.

Results

Reliability of 3DSI

The breast volume measurements using the plastic models for 3DSI validation are summarized in Table 1 and Figure 5. The volumes of these models were also measured according to Archimedes' principle. Based on these results, the measurement obtained by 3DSI was considered reliable, and we adopted the measured volume without calibration.

Demographic Characteristics of Participants

The characteristics of the 30 patients enrolled in this study are summarized in Table 2. The mean age, height, weight, and body mass index were 56.5 years, 161.8 cm, 58.4 kg, and 22.3 kg/m^2, respectively. Most patients (83.4%) had stage 0 or I disease. The mean tumor largest diameter measured by ultrasonography was 16.9 (range: 7.0–29.0) mm.

Although 60 breast volumes were studied, one data point for the unaffected breast volume measured by 3DSI was missing. Furthermore, two breast volumes were not measured by CT and MRI due to a

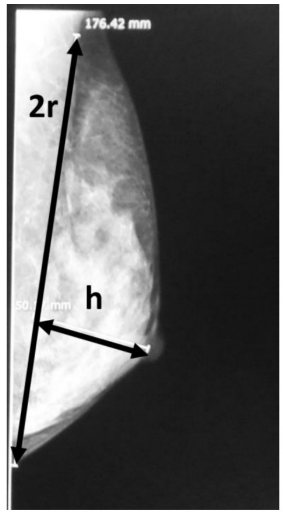


Figure 4. Measurement of breast volume by MMG from the oblique lateral view. The breast is regarded as a cone. The distance from the upper to lower edge of the breast parenchyma is defined as the diameter of the cone base (2r). The distance from the nipple to the major pectoral muscle is regarded as the height of the cone (h)

MMG: Mammography

history of breast surgery for the unaffected breast or elastic tape compression of the affected breast for post-biopsy hemostasis. Aside from these three cases, the breast shapes on both sides were comparable upon inspection. There were no cases of skin involvement or apparent skin retraction due to breast cancer.

Comparison of 3DSI, MRI, and MMG With CT for Breast Volume Measurement

The distributions of the breast volumes measured by CT, 3DSI, MRI, or MMG are summarized in Figure 6. The volume measured by MMG tended to be larger than the other measurements. Scatter diagrams of the breast volumes measured by 3DSI, MRI, and MMG versus CT are shown in Figure 7a, 7b, and 7c, respectively. Pearson's correlation coefficients for the breast volumes measured by 3DSI, MRI, or MMG versus CT were 0.83, 0.997, and 0.84, respectively (Table 3). Although the correlation coefficient for 3DSI versus CT was clinically acceptable, it was lower than that for MRI versus CT and comparable with that for MMG versus CT. When breast volume is estimated based on 3DSI measurements, the following formula should be used:

Estimated Breast Volume = (Breast Volume Obtained by 3DSI–128.7)/0.73

Notably, the breast volume measured by MRI was closely associated with that measured by CT (Figure 7b). In this comparison, the slope and y-intercept values were 1.05 and 8.5, respectively, indicating that the breast volume measured by MRI was 5% larger than that measured by CT.

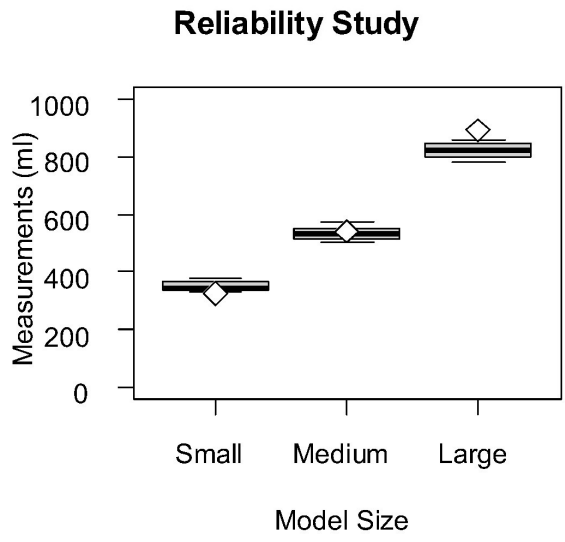


Figure 5. Measurements of three breast models using three-dimensional images. We created three plastic models of the breast with volumes of 300, 500, and 900 mL. We measured the volume of each breast model 10 times, and these results are summarized in box plots. The horizontal line in the box indicates the median size of the samples. The upper and lower ends of the box represent the 75th and 25th percentiles, respectively. The upper and lower ends of the whiskers represent the maximum and minimum values of the samples, respectively. The white diamond mark indicates the value measured based on Archimedes' principle

Table 1. Performance test of the K3 camera using models with three different breast volumes

	Median	Mean	Max	Min	SD	Archimedes method
300 mL size	346	351	382	328	18.8	326
500 mL size	532	534	576	504	21.0	541
900 mL size	823	820	859	779	27.8	892

Unit: mL; Min: Minimum; Max: Maximum; SD: Standard deviation

Table 2. Clinical characteristics of the 30 study patients

Characteristic		No. of cases or mean	Percentage or range
Mean age, years		56.5	(35–73)
Mean height, cm		161.8	(147.8–172.6)
Mean weight, kg		58.4	(44.6–82.9)
Mean body mass index		22.3	(17.7–31.4)
Laterality	Right	12	40%
	Left	18	60%
Stage	0	5	16.7%
	I	20	66.7%
	II	5	16.7%
Mean tumor size (range), mm[§1]		16.9	(7.0–29.0)

[§1]: The tumor size was measured by ultrasonography. One case was excluded because the lesion could not be measured by ultrasonography

Discussion and Conclusion

3DSI can be used to measure breast volume in the upright position with clinically acceptable accuracy. This conclusion is supported by the finding that the breast volumes measured by 3DSI and CT were moderately associated, with a correlation coefficient of 0.83, which was lower than that for MRI and comparable with that for MMG. The dorsal side of the breast on 3DSI consists of a flat plane, which is different from the true dorsal side of the breast. This is the probable reason why the correlation coefficient between the 3DSI- and CT-measured volumes was lower than that between the MRI- and CT-measured volumes.

3DSI may be used to measure breast volume in the upright or sitting position and thus enables evaluation of the visual cosmetic outcome (7). Therefore, 3DSI-determined breast volume may be useful as an indicator for esthetic purposes. Due to the moderate concordance between the 3DSI- and CT-measured volumes, 3DSI is useful for measuring breast volume, with clinically acceptable accuracy.

We used the breast volume measured by CT as a benchmark in this study for two reasons. First, CT clearly delineates the margin of the breast by revealing both the skin surface and dorsal margin of the breast. These clear margins lead to high reproducibility of the breast volume measurement. This high reproducibility is supported by the close association between the breast volume measured by CT and that measured by MRI, and these two techniques are similar in their measurement procedures except for the position of the patients. Second, a prior study reported that breast volume measured by CT is closely related to that determined from mastectomy specimens (8).

We found a close relationship between the breast volumes measured by MRI and CT. The regression line determined by Pearson's correlation analysis for the CT- and MRI-determined volumes had a slope of 1.05 and y-intercept of 8.5. Because this y-intercept value is significantly smaller than the whole breast volume, the volume measured by MRI is estimated to be 5% larger than the volume measured by CT. This

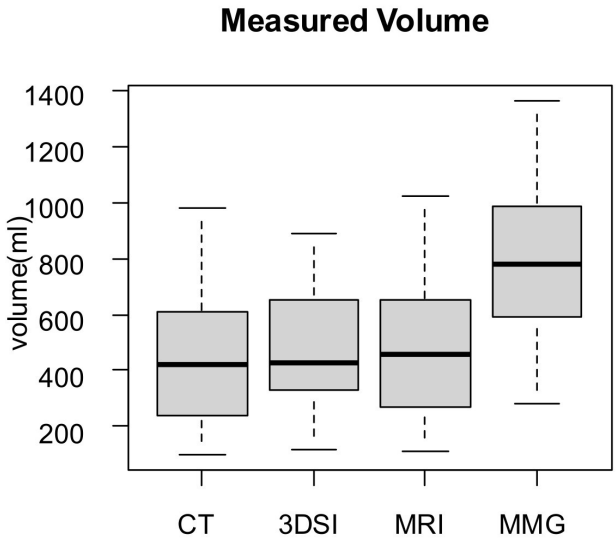


Figure 6. Boxplots showing the breast volumes measured by CT, 3DSI, MRI, and MMG

3DSI: Three-dimensional surface imaging; MRI: Magnetic resonance imaging; CT: Computed tomography; MMG: Mammography

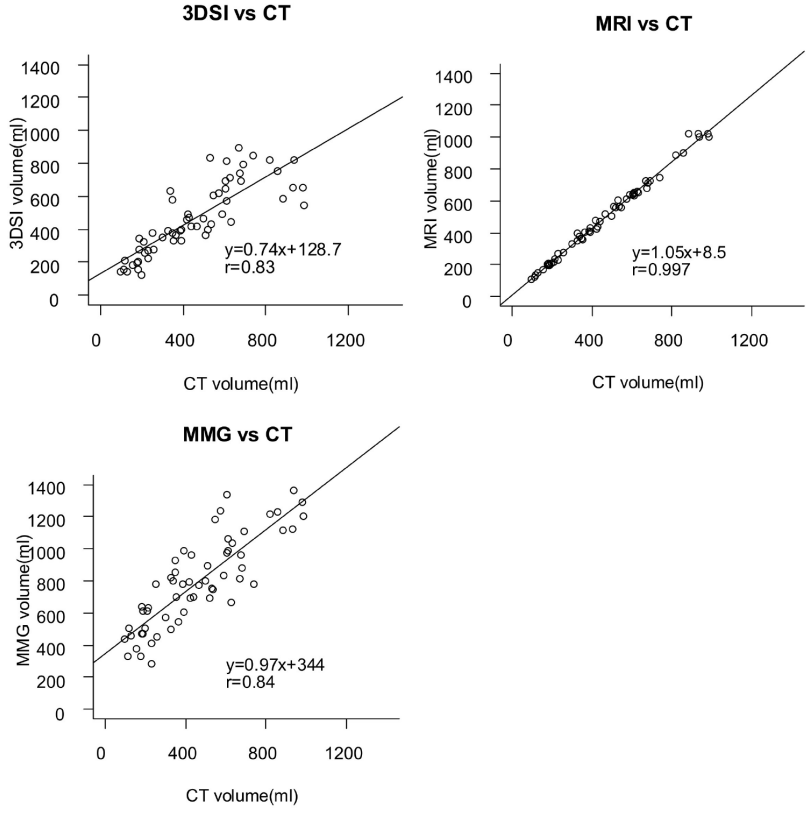


Figure 7. Scatter diagrams of breast volumes measured by 3DSI (Figure 7a), MRI (Figure 7b), and MMG (Figure 7c) *vs.* CT

3DSI: Three-dimensional surface imaging; MRI: Magnetic resonance imaging; CT: Computed tomography; MMG: Mammography

Table 3. Pearson's correlation coefficients for breast volume measured by 3DSI, MRI, or MMG *vs.* CT

Variables	Correlation coefficient	Slope	y-intercept	*p*-value
3DSI *vs.* CT	0.83	0.74	128.7	5.3×10^{-16}
MRI *vs.* CT	0.997	1.05	8.5	2.2×10^{-16}
MMG *vs.* CT	0.84	0.97	344.0	2.2×10^{-16}

3DSI: Three-dimensional surface imaging; MRI: Magnetic resonance imaging; CT: Computed tomography; MMG: Mammography

5% increase is attributable to the patient's posture during imaging; specifically, patients assume a supine position in CT studies and a prone position in MRI studies. A recent study has demonstrated that even arm positioning can affect breast volume (9). The only shortcoming of MRI and CT in this setting is that the measurements are time-consuming.

Our results suggest that breast volume measured by MMG is moderately different from that measured by CT or MRI. The correlation was weaker between the CT- and MMG-determined volumes than between the CT- and MRI-determined volumes. However, MMG is the most common and easy method of breast examination. We believe that the accuracy of breast volume measured by MMG is acceptable for daily practice (2).

Breast volume measurement is a promising area of study for the future. Beyond cosmetic evaluation in BCS or breast reconstruction, it is also used to predict oncologic factors, such as the likelihood of axillary lymph node metastasis (10) or the expression level of estrogen receptors (11). Furthermore, breast volume serves as an indicator for appropriate gender-affirming hormone therapy in transgender individuals (12).

Study Limitations

Our study has some limitations. All participants underwent BCS so there was no data on the volume of the whole breast specimen, which could be used as a benchmark for comparison. However, the lack of such data does not affect our conclusions because a previous study showed no difference in breast volume between CT measurements and mastectomy specimens (8). Thus, we used the breast volume measured by CT as the baseline volume in this study. Another limitation is that the range of the breast volume among our participants was 100–1,200 mL. Because some women have breast volumes of 2,000 mL or greater (2), our results may not apply to greater breast sizes. Further investigations are necessary.

3DSI can be used to measure breast volume in the upright position with clinically acceptable accuracy for evaluation of cosmetic surgical outcomes. 3DSI is a potential option for comparing breast volumes between the preoperative and postoperative breast for esthetic evaluation.

Ethics

Ethics Committee Approval: This study was approved by Nihon University Itabashi Hospital Ethical Review Board (approval no.: RK-220208-4, date: 10.02.2025).

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

Footnotes

Authorship Contributions

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

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

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Original Article

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Categorization of Breast Fine Needle Aspirates Using Yokohama Classification and Its Correlation With Histopathological Findings

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ABSTRACT

Objective: Breast cancer is the most prevalent cancer among women worldwide. In developing countries, fine needle aspiration cytology (FNAC) is commonly used for screening to reduce mortality rates. The International Academy of Cytology has established the Yokohama system to enhance diagnostic clarity and communication between pathologists and clinicians. A triple test approach, incorporating clinical evaluation, imaging, and FNAC, can further improve patient care for breast lesions and may enhance the Yokohama System's effectiveness.

Materials and Methods: A prospective study about breast FNAC was done over a period of one year, from October 2022 to September 2023. The study involved patients with breast lesion referred for FNAC in the department of Pathology. The FNAC results were further classified using the Yokohama system for reporting breast cytopathology, 2016. The cytological findings were correlated with available histopathological results.

Results: In the study of 104 cases, 60 (57.7%) of whom had available histopathology results, breast lesions were categorized using the Yokohama system as: 7.7% insufficient, 47.1% benign, 26.9% atypical, 2.9% suspicious of malignancy, and 15.4% malignant. The risk of malignancy varied by category: 0% for category 1, 3.2% for category 2, 47% for category 3, and 100% for categories 4 and 5. The maximum sensitivity was 94.7% when considering atypical, suspicious, and malignant cases as positive. The highest specificity was 97.56% for malignant cases alone, while the best diagnostic accuracy was 83.3% when both malignant and suspicious cases were counted as positive.

Conclusion: The Yokohama system effectively classified borderline lesions, facilitating early detection and improved management options. By integrating FNAC with standardized reporting, healthcare providers can make informed decisions, enhancing the diagnosis and treatment of breast lesions.

Keywords: Breast cancer; fine needle aspiration cytology; Yokohama system; risk of malignancy

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Key Points

- Breast cancer is the leading cancer among women worldwide.
- Fine needle aspiration cytology (FNAC) is preferred for breast lesions, particularly in experienced hands, and its turnaround time can be further reduced with rapid onsite evaluation.
- The newly proposed International Academy of Cytology Yokohama System for Reporting Breast Cytopathology presents a straightforward approach that enhances diagnostic precision, thereby facilitating improved communication between pathologists and treating clinicians.
- This study underscores the importance of using a standardized reporting systems for FNAC to improve diagnostic accuracy and patient care in breast lesions.

Introduction

Breast cancer is the most prevalent cancer among women worldwide and ranks second in overall cancer incidence after lung cancer. In 2022, there were an estimated 2.29 million new breast cancer cases, accounting for 11.5% of all cancer diagnoses. It is also the fourth leading cause of cancer-related deaths, with 666,103 fatalities (1).

In India, breast cancer is the most common cancer overall and among women, with 192,020 new cases reported in 2022, representing 13.6% of all new cancer cases. The total number of deaths due to breast cancer was 98,337, resulting in a mortality rate of 10.7%. Among females, breast cancer accounts for 26.6% of all new cancer cases (2).

All breast lesions are not malignant, and all the initially benign lesions do not progress to cancer; however, the accuracy of diagnosis can be

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increased by a combination of preoperative tests, such as physical examination, mammography, fine needle aspiration cytology (FNAC), and core needle biopsy (CNB) (3).

To enhance outcomes and survival rates for breast cancer, early detection is essential. The aim is to raise the percentage of breast cancers identified at an early stage, which facilitates more effective treatment and lowers the risk of mortality. Strategies for early detection involve screening and prompt diagnosis (4).

In the developing world, FNAC remains one of the most frequently performed procedures and is increasingly integrated into screening initiatives aimed at lowering breast cancer mortality rates. FNAC is commonly employed to evaluate breast lesions. This outpatient procedure involves extracting a small sample of breast tissue or fluid from a suspicious area to check for cancer cells. FNAC is a cost-effective method that can help avoid unnecessary surgeries (5).

FNAC is very effective at distinguishing between benign and malignant lesions. Both FNAC and CNB provide comparable pathological information, but FNAC has the added benefits of being more affordable, quicker, and offering rapid reassurance (6). FNAC is valued for its simplicity, cost-effectiveness, and quick results. However, CNB has become popular for its ability to assess histological grade and hormonal status. When FNAC is combined with clinical and radiological data, its sensitivity and specificity match those of CNB. At our tertiary facility, FNAC is particularly important due to the time and cost constraints associated with CNB. It is the preferred method for evaluating breast lesions, especially when conducted by skilled professionals, and its processing time can be shortened with rapid onsite evaluation. We primarily use FNAC and reserve CNB for cases with atypical or suspicious characteristics. Implementing standardized reporting systems improves consistency across institutions, enhances communication between clinicians and pathologists, and ultimately benefits patient care (7).

Recently the International Academy of Cytology (IAC) proposed a new reporting system for breast FNAC named the Yokohama System. It defines five categories for reporting breast cytology, each with a clear descriptive term for the category, a definition, a risk of malignancy (ROM) and a suggested management algorithm (8). The Yokohama System classifies cytologic diagnoses into five categories: (1) insufficient material, (2) benign, (3) atypical, (4) suspicious for malignancy, and (5) malignant. This system highlights the importance of FNAC smears and the expertise of well-trained cytopathologists for effective diagnostic breast FNA cytology. Current practices in breast FNAC have advanced with the greater use of ultrasound guidance and rapid onsite evaluation. Triple test of clinical, imaging and FNAC assessment will lead to improvements in the care of patients with breast lesions and possible modifications to the IAC Yokohama System (8).

In this study, we used the newly proposed IAC Yokohama classification system to analyse breast FNAC cases from our Pathology Department. We assessed the ROM for each category and evaluated the diagnostic effectiveness of this technique.

Materials and Methods

This cross-sectional study was conducted in Department of Pathology, Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan, Sonepat over one year from September 2022 to September 2023. The study was conducted with 104 cases with breast lesions. Patients with breast lesions presenting to the Surgery OPD at BPS GMC for Women, were selected and referred to the Pathology Department for FNAC. Cases were categorized based on the IAC Yokohama classification into different diagnostic groups. Imaging findings, classified according to the breast imaging-reporting and data system, were also correlated with FNAC results to enhance diagnostic accuracy. The FNAC results were correlated with the clinical and imaging findings of the lesion. If the lesion was benign on imaging findings, no further investigation was done. If suspicious on imaging/clinical, then CNB was performed. In atypical, Suspicious and malignant cases, CNB/excision biopsy was done. The FNAC findings were compared with histopathological results to assess the diagnostic accuracy, sensitivity, specificity, and predictive values of Yokohama System of FNAC in the evaluation of breast lumps. Out of the included cases that underwent FNAC, 60 (57%) proceeded to histopathological evaluation at our institute.

Consecutive sampling technique was used for collection of the study sample.

Ethical approval for the study was granted by the Institutional Ethics committee of Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan vide IEC registration number: BPSGMCW/RC/799/IEC/2022, dated 11/10/2022. Study participants had the purpose of the study explained to them and were also informed of absolute confidentiality and privacy of the data. The information sheet was read out to the study subjects in a language they could understand, and all the questions and queries raised by them were answered to their satisfaction. It was stressed that participation in the study was purely voluntary, and they were free to withdraw from the study at any point of time and there would be no administrative consequences for their withdrawal from the study. A well-informed written consent was taken from all participants.

Inclusion Criterion

All the patients having breast lesion who was referred for FNAC in department of Pathology.

Exclusion Criteria

1. Patients with ulcerative lesion or skin involvement.

2. Patients with history of chemotherapy and/or radiotherapy.

Statistical Analysis

Statistical analysis was executed using SPSS, ver. 20 (IBM INc., Armonk, NY, USA) Data was collected and stored on a Microsoft Excel Spreadsheet. The ROM was defined for each category as the number of confirmed malignant cases/total number of cases in the diagnostic category. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and accuracy ratios were calculated using the histologic diagnosis as the gold standard. The ratios were determined based on three categories. In category A only malignant cases were regarded as a positive test result. Both suspicious and malignant cases were included as positive tests in category B, and in category C atypical, suspicious, and malignant cases were all included. Chi-square test and other appropriate test were used to investigate association between categorical variables. A $p<0.05$ was considered statistically significant.

Results

A total of 104 cases were included, with the highest number of cases in the age group 21–30 years (31.7%), followed by 41–50 years (23.07%). The age of presentation ranged from 14 to 82 years in study with a mean age of 36.78±14.65 years. Breast lesions were more common in the left breast (54.8%) compared to the right (45.2%). The breast lesions were more common in females with female to male ratio of 52:1. The majority of breast lesions diagnosed on cytology were benign proliferative lesions (26%) followed by atypical proliferative breast lesions (21%). Sixteen lesions were categorised under category 5 suggestive of carcinoma of the breast (Table 1).

Diagnostic categorization of breast lesions using the Yokohama system resulted in the following:

1. Insufficient – 7.7%

2. Benign – 47.1%

3. Atypical – 26.9%

4. Suspicious of malignancy – 2.9%

5. Malignant – 15.4%

To enhance the understanding of the morphological features associated with each category of the Yokohama System of Reporting Breast Fine Needle Aspirates, representative images from actual cases are included. These images illustrate key cytological findings across the five diagnostic categories (Figure 1).

The histomorphological features of a few selected cases are depicted in the images below, highlighting the typical microscopic appearances of various benign and malignant breast lesions observed in the study (Figure 2).

The highest number of lesions were categorized under category 2 (benign) followed by category 3 (atypical) and category 5 (malignant) respectively. Histopathological diagnosis available in the 60 breast cases showed fibroadenoma (20%) and benign phyllodes (16.7%) as the most common diagnoses in the benign category and invasive ductal carcinoma (20%) as the most common diagnosis in the malignant category. Out of these 60 cases, the largest number were invasive ductal carcinoma n = 13 (21.7%) followed by fibroadenoma n = 12 (20%), and then n = 10 cases of benign phyllodes (16.7%). Four lesions were diagnosed as granulomatous and three cases each of borderline phyllodes and metaplastic carcinoma (Table 2). Table 3 shows histopathological spectrum of breast lesions and its correlation with the Yokohama system. Most cases were categorized under category 2 with 31 cases (51.7%) followed by category 3 with 17 cases (28.3%).

Sensitivity, specificity, PPV, NPV and accuracy of the Yokohama classification when only malignant lesions were considered positive were 47.37%, 97.56%, 90%, 80% and 81.67% respectively. When malignant and suspicious of malignancy lesions were combined and considered positive these same values were 52.63%, 97.56%, 90.91%, 81.63% and 83.33% respectively. Finally, when the categories malignant, suspicious of malignancy and atypical were combined and considered positive the sensitivity, specificity, PPV, NPV and accuracy were 94.74%, 75.61%, 64.29%, 96.87% and 81.67% respectively. The ROM for various categories in the present study was 0% for category 1, 3.2% for category 2, 47% for category 3, 100% for category 4, and 100% for category 5 (Table 4).

Table 1. Cytological diagnosis of breast lesions (n = 104)

Yokohama category	No. of cases	Cytological diagnosis
I (Insufficient)	8	
II (Benign)	49	Proliferative benign mammary lesion (27) Benign mammary lesion with cystic change (9) Granulomatous inflammation (2) Proliferative mammary lesion with lactational changes (1) Subareolar abscess (1) Inflammatory lesion (4) Duct ectasia (2) Fibrolipoma (1) Necrotic change (1) Lipomatous lesion (1)
III (Atypical)	28	Proliferative breast lesion with atypia (22) Fibroadenoma With epithelial hyperplasia (3) Atypical ductal hyperplasia (2) Papillary lesion (1)
IV (Suspicious of malignancy)	3	Suspicious of carcinoma (3)
V (Malignant)	16	Carcinoma breast (16)
Total cases	**104**	

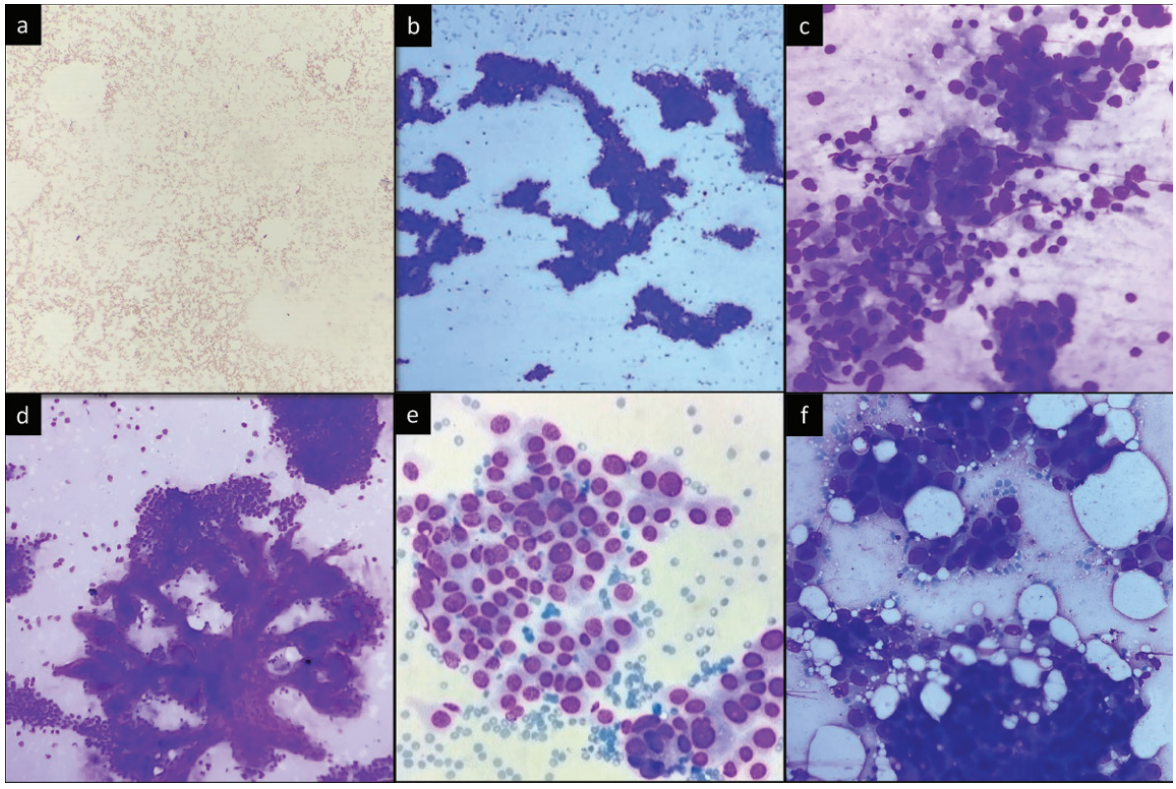


Figure 1. (a) Category I, Insufficient (MGG 40X), **(b)** Category II, Benign: Antler horn architecture in the background of numerous bare nuclei. (MGG 100X), **(c)** Category III, Atypial: Benign cluster with slight nuclear enlargement and pleomorphism (MGG 400X), **(d)** Category IV, Suspicious of Malignancy: Papillary architecture with mild nuclear pleomorphism and inconspicuous nucleoli. (MGG 100X), **(e,f)** Category V, Malignant: **(e)** Loose cohesive cluster of intermediate-sized cells with a high N:C ratio, moderately enlarged and pleomorphic nuclei with small nucleoli (MGG 100X), **(f)** Fat infilteration by neoplastic cells (MGG 100X)

Table 2. Histopathological diagnosis of breast lesions (*n* = 60)

Category	Histological diagnosis	No. of cases
Benign (41)	Fibroadenoma/fibroadenoma with epithelial hyperplasia	**12**
	Benign phyllodes tumor	**10**
	Granulomatous mastitis	**4**
	Borderline phyllodes tumor	**3**
	Duct ectasia	2
	Fat necrosis	2
	Fibroadenosis	1
	Complex fibroadenoma	1
	Lipoma	1
	Adenomyoepithiloma	1
	Pleomorphic adenoma of breast	1
	Lactational adenoma	1
	Intraductal papillomatosis	1
	Gynaecomastia	1
Malignant (19)	Infiltrating/invasive ductal carcinoma	13
	Metaplastic carcinoma	3
	Non-Hodgkin lymphoma	1
	Lobular carcinoma	1
	Invasive ductal carcinoma with medullary features	1
Total		60

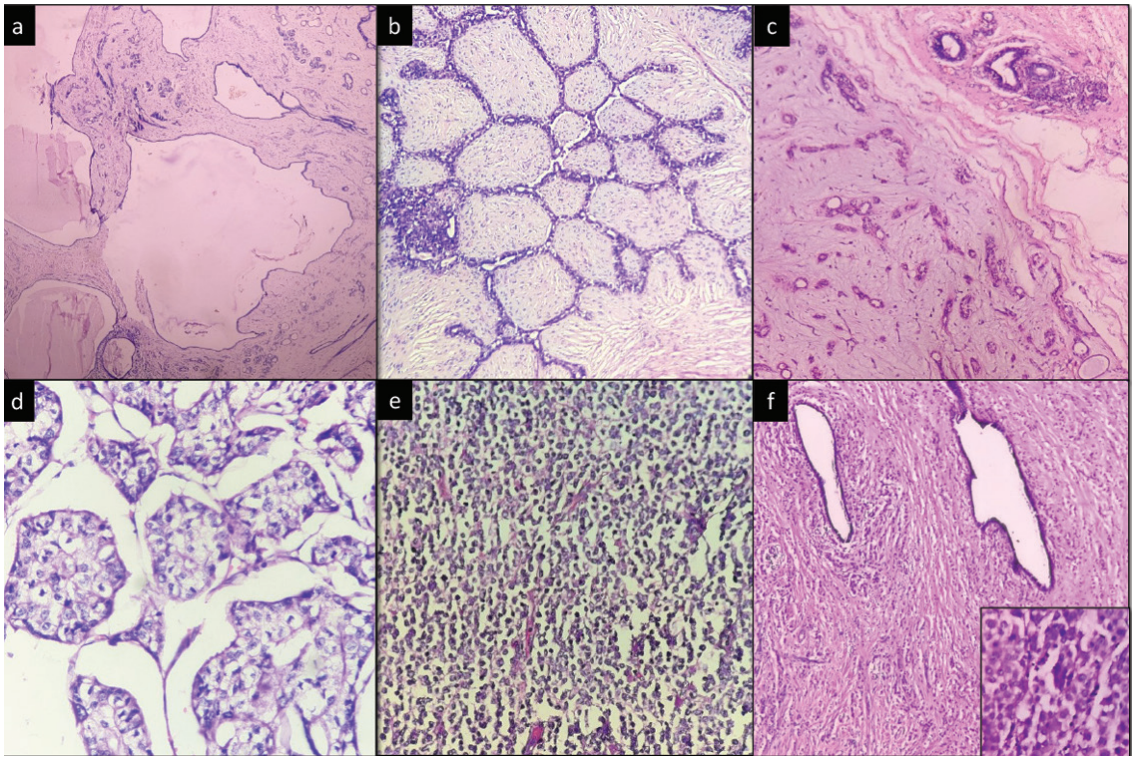


Figure 2. (a) Complex Fibroadenoma: Fibroadenoma showing multiple cystic changes (H&E, 100X). **(b)** Benign Phyllodes: leaf-like epithelial pattern with exaggerated intracanalicular pattern suggestive. (H&E, 100X). **(c)** Pleomorphic adenoma: well circumscribed lesion with characteristic epithelial and myoepithelial elements without atypia, embedded into a chondromyxoid stroma. (H&E, 100X). **(d)** Invasive ductal carcinoma: infiltrative back to back nests of tumour cells with moderately enlarged nuclei. (H&E, 100X). **(e)** Non Hodgkin Lymphoma: tumour cells arranged in sheets, small clusters and groups. The cells were large with irregular nuclear contour, vesicular chromatin and prominent nucleoli. (H&E, 100X). **(f)** Lobular Carcinoma: Section shows strands of tumour cell having abundant eosinophilic cytoplasm with slight pleomorphic nuclei. (H&E, 100X,400X)

H&E: Hematoxylin-eosin

Discussion and Conclusion

The study highlighted the potential of the Yokohama system to classify borderline lesions more accurately, aiding in early detection and management decisions. The atypical category included fibroadenomas, fibroadenomas with epithelial hyperplasia, or low-grade phyllodes, challenging to differentiate on cytomorphology. Misdiagnosis of malignant lesions as benign/atypical was the result of scant cellularity and deep-seated lesions. Discordant findings in the "triple test" parameters warrant further evaluation, such as an additional CNB. Indeterminate categories in the Yokohama system (atypical and suspicious) allow classification of borderline lesions with a greater ROM.

Overall, our study underscores the importance of FNAC with utilizing standardized reporting systems to improve diagnostic accuracy and patient care in breast lesions.

FNAC is valued for its simplicity, practicality, cost-effectiveness, and quick results, but CNB has become popular due to its ability to assess histological grade and hormonal status. However, when FNAC is combined with clinical and radiological findings, its sensitivity and specificity is increased (9). At our tertiary centre, FNAC plays a crucial role, especially considering limitations in time and cost for CNBs. FNAC is preferred for breast lesions, particularly in experienced hands, and its turnaround time can be further reduced with rapid onsite evaluation. We use FNAC primarily, resorting to CNB only for atypical or suspicious cases. Standardized reporting systems improve report consistency across institutions, enhancing communication between clinicians and pathologists and ultimately benefiting patient care.

The Yokohama system proposed by the IAC classifies FNAC results into five categories, aiding diagnosis and management.

The mean age of the patient was almost 37 years and the age ranged from 14 to 82 years. The findings are similar to a previous study by Sundar et al. (10) where mean age was 41.3 years and ranged from 14 to 83 years.

The greatest number of cases were categorized as Yokohama 2 (benign) followed by Yokohama 3 (atypical) fand thirdly Yokohama 5 (malignant). This distribution of Yokohama reporting system categories in the present study was similar to the results obtained by Apuroopa et al. (11) and Montezuma et al. (12) However, studies by De Rosa et al. (13), McHugh et al. (14), Wong et al. (15), Agrawal et al. (6), Kamatar et al. (16), and Ahuja and Malviya (9), reported the highest proportion of cases falling into category 2 (benign) followed by category 5 (malignant) followed by category 3 (atypical).

The ROM for various categories in the present study was 0% for category 1, 3.2% for category 2, 47% for category 3, 100% for category 4, and 100% for category 5. These results are similar to those reported by Kamatar et al. (16), Montezuma et al. (12) and Apuroopa

Table 3. Histopathological spectrum of breast lesions and its correlation with Yokohama categories (*n* = 60)

Histopathology diagnosis	Yokohama category					Total
	I	II	III	IV	V	
Benign phyllodes tumor	-	5	5	-	-	10
Fibroadenoma	-	8	1	-	-	9
Granulomatous mastitis	-	3	1	-	-	4
Fibroadenoma with epithelial hyperplasia	-	2	1	-	-	3
Borderline phyllodes tumor	-	2	1	-	-	3
Duct ectasia	-	2	-	-	-	2
Fat necrosis	-	2	-	-	-	2
Fibroadenosis	-	1	-	-	-	1
Complex fibroadenoma	-	1	-	-	-	1
Lipoma	1	-	-	-	-	1
Adenomyoepithiloma	-	1	-	-	-	1
Pleomorphic adenoma of breast	-	1	-	-	-	1
Lactational adenoma	-	-	1	-	-	1
Intraductal papillomatosis	-	1	-	-	-	1
Gynaecomastia	-	1	-	-	-	1
Infiltrating/invasive ductal carcinoma	-	1	5	1	6	13
Lobular carcinoma	-	-	-	-	1	1
Non-Hodgkin lymphoma	-	-	-	-	1	1
Metaplastic carcinoma	-	-	2	-	1	3
Invasive ductal carcinoma with medullary features	-	-	-	-	1	1
Total	**1**	**31**	**17**	**1**	**10**	**60**

Table 4. Distribution of IAC Yokohama system categories with cyto-histological correlation and risk of malignancy

	Insufficient	Benign	Atypical	Suspicious of malignancy	Malignant
Histological benign	1 (Lipoma)	30 (FA-8, benign PT-5, granulomatous mastitis-3, FA with epithelial hyperplasia-2, borderline PT-2, duct ectasia-2, fat necrosis-2, fibroadenosis-1, complex FA-1, adenomyoepithiloma-1, pleomorphic adenoma of breast-1, intraductal papillomatosis-1, gynaecomastia-1)	10 (FA-1, FA with epithelial hyperplasia-1, benign PT-5, borderline PT-1, granulomatous mastitis-1, lactational adenoma-1)	0	0
Histological malignant	0	1 (IDC)	7 (IDC-5, metaplastic carcinoma-2)	1 (IDC)	10 (IDC-6, IDC with medullary features-1, lobular carcinoma-1, NHL-1, metaplastic carcinoma-1)
Risk of malignancy %	**0**	**3.2**	**41.1**	**100**	**100**

FA: Fibroadenoma; PT: Phyllodes tumour; IDC: Invasive ductal carcinoma

Table 5. Sensitivity, specificity, PPV, NPV, accuracy of IAC Yokohama system

	Group A (category malignant considered positive)	Group B (category malignant and suspicious considered positive)	Group C (category malignant, suspicious and atypical considered positive)
Sensitivity	47.37%	52.63%	94.74%
Specificity	97.56%	97.56%	75.61%
PPV	90.0%	90.91%	64.29%
NPV	80.0%	81.63%	96.87%
Accuracy	81.67%	83.33%	81.67%

PPV: Positive predictive value; NPV: Negative predictive value. Table 5 shows sensitivity, specificity, PPV, NPV and accuracy of Yokohama classification when only category malignant considered as positive; when category malignant and suspicious of malignancy considered as positive and when category malignant, suspicious of malignancy and atypical considered as positive

Table 6. Comparison of diagnostic accuracy of breast FNAC in diagnosis of malignancy using Yokohama system in various studies (*n* = 60)

Category included		De Rosa et al. (13)	Wong et al. (15)	Montezuma et al. (12)	Agrawal et al. (6)	Ahuja and Malviya (9)	McHugh et al. (14)	Present study
	No. of cases	**1616**	**536**	**755**	**299**	**224**	**199**	**104**
(Group A) only malignant category taken as positive	**Sensitivity**	82.2	75.4	68.7	86.7	79.2	65.4	**47.37**
	Specificity	97.8	100	100	100	100	95.9	**97.56**
	PPV	98.8	100	100	100	100	91.9	**90.0**
	NPV	71.0	80.7	87.7	71.2	90.9	81.1	**80.0**
	Accuracy	87.0	87.9	90.3	90.0	93.2	83.9	**81.67**
(Group B) suspicious of malignancy and malignant taken as positive	**Sensitivity**	93.7	92.0	83.3	96.0	91.7	79.5	**52.63**
	Specificity	90.8	97.8	99.8	91.9	98.7	85.1	**97.56**
	PPV	95.8	97.6	99.5	97.3	97.1	77.5	**90.91**
	NPV	86.6	92.7	93.0	88.3	96.1	86.6	**81.63**
	Accuracy	92.8	95.0	94.7	95.0	96.4	82.9	**83.33**
(Group C) atypical, suspicious of malignancy and malignant taken as positive	**Sensitivity**	98.9	98.9	98.3	98.2	97.2	84.6	**94.74**
	Specificity	46.3	62.1	54.8	59.5	86.0	75.2	**75.61**
	PPV	80.5	71.7	49.2	88.0	77.0	68.8	**64.29**
	NPV	95.1	98.3	98.6	91.7	98.5	88..3	**96.87**
	Accuracy	82.7	80.2	68.2	88.6	89.6	78.9	**81.67**

The highest specificity (97.56%) was seen when only malignant cases (Group A) and malignant and suspicious (Group B) were included in positive test results, whereas maximum diagnostic accuracy (83.3%) was observed when malignant and suspicious (Group B) cases were included in positive results. Ahuja and Malviya (9), Wong et al. (15), Montezuma et al. (12), Agrawal et al. (6), and De Rosa et al. (13) demonstrated similar findings. McHugh et al. (14) observed highest sensitivity and specificity in similar scenarios, but they observed maximum accuracy when only malignant cases were considered as positive test results. FNAC: Fine needle aspiration cytology; PPV: Positive predictive value; NPV: Negative predictive value

et al. (11) McHugh et al. (14) also observed similar findings but they observed 46% ROM in suspicious of malignancy category.

In the current study, the maximum sensitivity (94.7%) was achieved when atypical, suspicious, and malignant cases (group C) were considered positive test results. However, the inclusion of atypical cases in positive results resulted in markedly decreased specificity and accuracy. The highest specificity (97.56%) was seen when only malignant cases (group A) and malignant and suspicious (group B) were included in positive test results, whereas maximum diagnostic accuracy (83.3%) was observed when malignant and suspicious (group B) cases were included in positive results (Table 5). Ahuja and Malviya (9), Wong et al. (15), Montezuma et al. (12), Agrawal et al. (6), and De Rosa et al. (13) demonstrated similar findings. McHugh et al. (14) observed highest sensitivity and specificity in similar scenarios, but they observed maximum accuracy when only malignant cases were considered as positive test results (Table 6).

The majority of breast lesions identified through cytology were categorized as proliferative mammary lesions, followed by proliferative breast lesions with atypia, and then carcinoma. Within the atypical category, breast lesions included fibroadenoma with epithelial hyperplasia, benign phyllodes, atypical ductal hyperplasia, metaplastic carcinoma, and invasive ductal carcinoma upon histological examination. Distinguishing between these lesions based solely on cytomorphology proved challenging. Misclassification of malignant lesions as atypical occurred due to low cellularity and a lesser degree of atypia. In addition, a few cases of invasive ductal carcinoma were incorrectly labelled as atypical, due to being deep-seated lesions resulting in hypocellular smears with only a small number of atypical cells exhibiting significant nuclear enlargement. One malignant lesion, which was reported as benign were possibly due to sampling error. Thus, whenever two out of three "triple test" parameters show discordant findings, we suggest followed up with a CNB. The two indeterminate categories in the Yokohama system - atypical and suspicious allow for the classification of borderline lesions like atypical ductal hyperplasia, which carry a greater risk of developing malignancy than benign lesions.

The experience of the cytopathologist plays a crucial role in diagnostic accuracy, ROM estimation and interobserver agreement. Experienced cytopathologists are better at distinguishing between benign, atypical, suspicious, and malignant categories based on cellular morphology. They are less likely to misinterpret borderline lesions, reducing the risk of false positives and false negatives. More experienced cytopathologists may provide more accurate ROM estimations for each category, aligning better with histopathological outcomes. Interobserver agreement improves with experience, particularly in distinguishing category 3 (atypical) from category 4 (suspicious).

In accordance with previous classification methods, such as the Bethesda System for Reporting Thyroid Cytopathology, the newly proposed IAC Yokohama System for Reporting Breast Cytopathology presents a straightforward approach that enhances diagnostic precision, thereby facilitating improved communication between pathologists and treating clinicians. It offers a standardized platform for reporting and enhancing reproducibility of reports, similar to the Milan systems used for salivary gland lesions and Bethesda system for thyroid cytopathology. Breast ultrasound, being a non-invasive imaging technique, can synergize with these diagnostic tools to aid in patient diagnosis and treatment planning. Furthermore, recent advances in both ultrasound and cytopathology techniques, such as immunocytochemistry, imaging-guided FNAC, and Doppler in sonomammography, have the potential to enhance their accuracy further.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the Institutional Ethics committee of Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan vide IEC registration number: BPSGMCW/RC/799/IEC/2022, dated 11/10/2022.

Informed Consent: A well-informed written consent was taken from all participants.

Footnotes

Authorship Contributions

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

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

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Original Article

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

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ABSTRACT

Objective: While prognostic and predictive factors in breast cancer are well established, data on aggressive behavior in luminal A subtype breast cancers are limited. The aim of this study was to investigate histomorphological and clinicopathological parameters that may predict treatment resistance and aggressive behavior in luminal A subtype, as well as the expression of two key proteins, PTEN and p53, involved in breast carcinoma development.

Materials and Methods: We included breast carcinoma cases diagnosed at a Turkish University Hospital between 2016 and 2017. Tumor tissue with internal control was available for all cases. PTEN and p53 expression were evaluated immunohistochemically, based on staining strength and percentage.

Results: Of the 114 cases diagnosed in the study period, 18 (%) were recurrent and 5 (%) were Luminal A subtype. We observed significantly lower overall and disease-free survival in patients with ≤50% tumor infiltrating lymphocytes density, which was present in all recurrent cases. PTEN immunoreactivity scores were <6 in all recurrent luminal A cases, but no significant difference was found between recurrent and non-recurrent cases (p>0.05). The p53 H-score for luminal A was significantly lower than in luminal B, triple negative, and human epidermal growth factor receptor 2+ groups (p<0.05). Furthermore, p53 H-scores <50 were more common in grade 2 tumors than in grade 3 (p<0.05).

Conclusion: PTEN loss, observed in all recurrent luminal A cases and 77.1% of all cases, supports its role as a tumor suppressor. The findings suggest that PTEN expression loss may be a prognostic marker, and immune-modulating treatments should be considered for breast cancer patients.

Keywords: Breast cancer subtypes; luminal A; molecular subtypes; p53; PTEN

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Key Points

- Predictive factors for aggressive behavior in luminal A breast cancer remain limited.
- Patients with tumor-infiltrating lymphocyte density ≤50% had significantly lower overall and disease-free survival.
- All recurrent luminal A cases had PTEN immunoreactivity scores <6, suggesting PTEN loss as a potential prognostic marker.
- p53 H-score was significantly lower in luminal A compared to other subtypes.
- Findings support the prognostic significance of PTEN loss and suggest that immune-modulating therapies should be considered for this patient group.

Introduction

Breast cancer is one of the most common cancers worldwide and the leading cause of cancer-related deaths in women (1). Molecular classification of invasive breast carcinoma, based on estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 immunohistochemical markers, are used to delineate differences in survival, prognosis, and treatment responses among subtypes.

Endocrine therapy (ET) targeting the ER is the primary treatment for luminal A (LumA) subtype breast cancer, with numerous agents improving survival outcomes. While LumA patients generally have better prognoses, up to 27% develop resistance to ET, resulting in metastases and fatal outcomes (2).

PTEN, a lipid phosphatase that suppresses the PI3K pathway, is lost in 15–50% of breast cancers, shortening progression-free survival (3-5). A study found a significant correlation between PTEN expression and

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smaller tumor size, lower tumor grade, ER/PR positivity and lower Ki-67 (a marker of cellular proliferation) levels (6). *TP53*, mutated in 30–35% of invasive breast cancers, varies by molecular subtype, with 17% in LumA, 41% in luminal B (LumB), 69% in apocrine, 88% in basal-like, and 50% in HER2-amplified tumors (7). Increased p53 expression was associated with larger tumor size, higher grade, nodal metastasis, reduced ER/PR levels and overexpression of HER2 (8). These mutations make p53 a potential biomarker and therapeutic target (9).

The aim of this study was to investigate the relationship between histomorphological and clinical features with prognosis in aggressive LumA carcinoma, defined as metastasis or local recurrence within five years, compare it with other subtypes, explore the independent and combined roles of PTEN and p53 in prognosis, and identify potential new therapeutic targets for this patient group.

Materials and Methods

Case Selection and Clinicopathological Features

In this study, breast cancer patients whose samples were sent to the Medical Pathology Clinic of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital between 2016 and 2017 were retrospectively analyzed. Patients who received neoadjuvant treatment, had metastatic or microinvasive carcinoma at diagnosis, or had insufficient tumor tissue for immunohistochemical staining were excluded. Histopathological parameters (subtype, grade, size, location) were determined by re-evaluating the preparations alongside pathology reports. Clinical data (gender, age, menopausal status, surgical procedure, recurrence, metastasis, treatments, and survival times) were collected from electronic records and physicians in general surgery and oncology. Ethics committee approval from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021-13-03) was granted on 05.07.2021. The antibodies and kits were funded by the hospital's fund.

Histomorphological Evaluation

Haematoxylin and eosin (H&E) and immunohistochemically stained slides of the cases were evaluated independently by two pathologists. Slides were stained for H&E and immunohistochemically for ER, PR, cellular erythroblastic oncogene B2 (CERBB2), Ki-67, and E-Cadherin. Key features, such as histological type, grade [using the Nottingham system (10)], molecular subtype (based on ER, PR, CERBB2, and Ki-67 status), presence of ductal carcinoma *in situ* (DCIS), lobular carcinoma *in situ* (LCIS), extensive intraductal component [extensive intraductal component (EIC): ≥25% DCIS], perineural invasion (PNI), lymphovascular invasion (LVI), microcalcification, surgical margin status, tumor-infiltrating lymphocyte (TIL) percentage (<50% defined as low, ≥50% as high) (11), and non-tumor breast tissue were assessed. Pathological staging was performed using the American Joint Committee on Cancer 8th edition TNM staging system (12).

Immunohistochemical Method and Evaluation

ER, PR, CERBB2, and Ki-67 mitotic index were assessed by re-evaluating immunohistochemical slides. Paraffin-embedded tissue blocks containing internal control tissue, lacking necrosis, and with adequate tumor tissue for immunohistochemical analysis were selected. External controls used were normal brain tissue and malignant melanoma for PTEN, and serous ovarian carcinoma for p53. Staining was performed on an automated immunohistochemistry device (Ventana Benchmark XT: Roche Diagnostics Corporation, Indianapolis, IN, USA) using p53 (Clone DO-7, Dako Omnis: Agilent Technologies, Inc., Santa Clara, CA, USA) and anti-PTEN [RM265] primary antibodies (RevMAb Biosciences, Burlingame, CA, USA).

Positive immunoreactivity for PTEN was defined as cytoplasmic and nuclear staining of tumor cells. Staining was graded by strength (0: no expression, 1: weak, 2: moderate, 3: strong) and by the percentage of reactive cells (0: <1%, 1: 1–10%, 2: 11–50%, 3: 51–80%, 4: >80%) (Figures 1, 2). The immunoreactivity score (IRS) was calculated by multiplying these values and categorized as 0, 1–6, or 7–12, with IRS ≤6 considered PTEN loss (13).

Nuclear staining of tumor cells with p53 was considered immunoreactive. Staining was evaluated by strength (0: no expression, 1: weak, 2: moderate, 3: strong) and by the percentage of reactive tumor cells (1: ≤10%, 2: 11–50%, 3: 51–70%, 4: >71%) (Figures 3, 4). The H-score, obtained by multiplying strength and percentage scores, was grouped as <50 or ≥50 (14).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics, version 22 (IBM Inc., Armonk, NY, USA). Normality was assessed with the Shapiro-Wilks test. Descriptive statistics (mean, standard deviation,

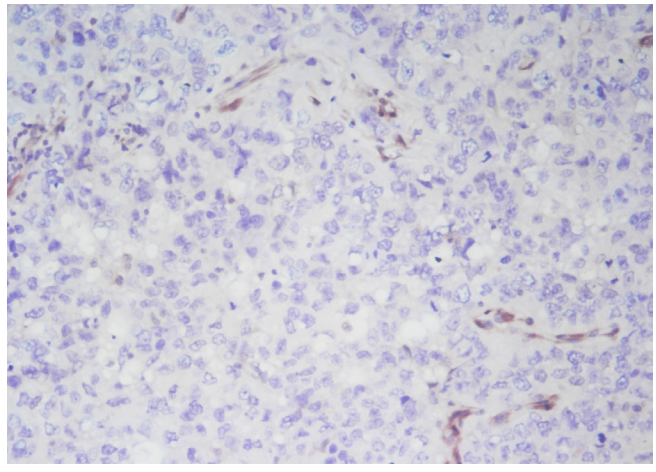


Figure 1. PTEN IRS 0x0 (strength group x % group; x100)

IRS: Immunoreactivity score

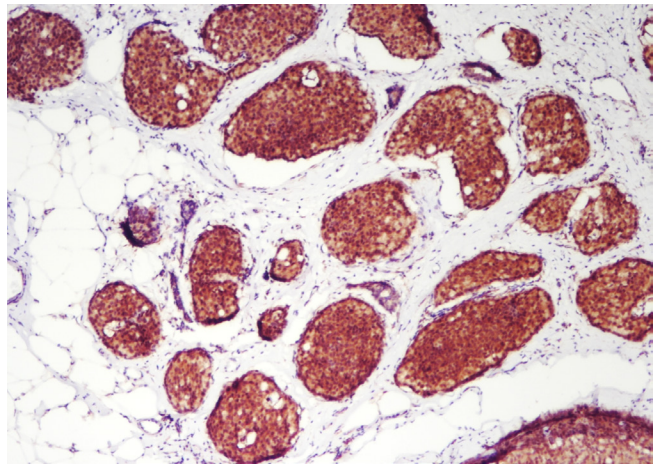


Figure 2. PTEN IRS 3x4 (strength group x % group; x100)

IRS: Immunoreactivity score

frequency) were calculated. Non-normally distributed data were analyzed using the Kruskal-Wallis test (with Dunn's test) and the Mann-Whitney U test for multi-group and two-group comparisons, respectively. Qualitative data comparisons utilized chi-square, Fisher's exact, Fisher-Freeman-Halton, and Yates' Correction tests. Significance was set at $p<0.05$.

Results

The study included 114 patients aged 27–80 years, (mean age 53.3±13.6 years). Most were female (98.2%, *n* = 112), with 2 males (1.8%). Of the patients, 44.6% (*n* = 50) were premenopausal, and 55.4% (*n* = 62) were postmenopausal. Tumor location was right breast in 41.2% (*n* = 47), left breast in 57% (*n* = 65), and bilateral in 1.8% (*n* = 2). Localization included upper outer (8.8%), upper inner (30.1%), lower outer (13.3%), lower inner (3.5%), retroareolar (15.9%), and multiple quadrants (28.3%).

Unifocal tumors were observed in 78.1% (*n* = 89), and multifocal tumors in 21.9% (*n* = 25). Surgical interventions included modified radical mastectomy (58.8%, *n* = 67), breast-conserving surgery (32.5%, *n* = 37), and simple mastectomy (8.8%, *n* = 10). Tumors at surgical margins were found in 3.5% (*n* = 4), while 42.5% (*n* = 48) were within 1 cm, and 54% (*n* = 61) were >1 cm distant from the margin.

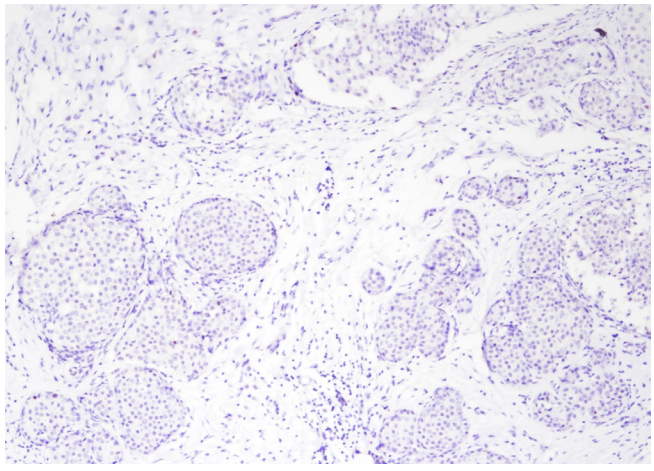


Figure 3. p53 H-score 0 (strength group x %; x100)

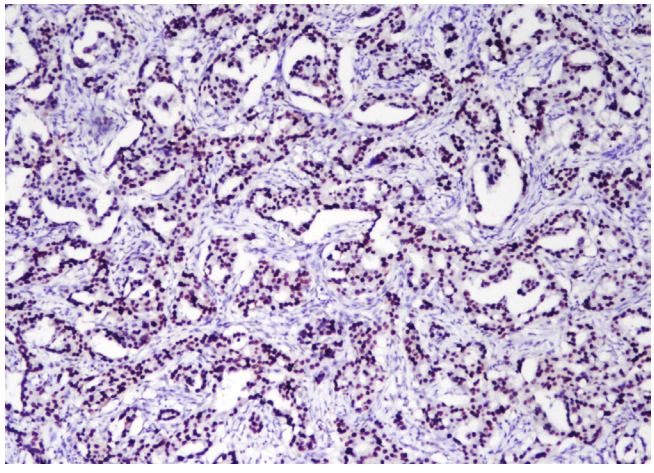


Figure 4. p53 H-score 3x95% = 285 (strength group x %; x100)

The histological subtypes of the cases were as: 91 (79.8%) invasive ductal carcinoma (IDC), 9 (7.9%) invasive lobular carcinoma (ILC), 9 (7.9%) mixed carcinoma, 2 (1.8%) mucinous carcinoma, 1 (0.9%) solid papillary carcinoma, 1 (0.9%) cribriform carcinoma and 1 (0.9%) metaplastic carcinoma.

Tumor size, grade, TIL status, DCIS, LCIS, PNI, microcalcifications, and non-tumor findings are detailed in Table 1.

Immunohistochemical study results and molecular subtype distribution are shown in Table 2.

Of the 114 patients, 59.6% had no LVI, while 40.4% did. EIC was absent in 77.2% and present in 22.8%. Tumor stages were distributed as follows: 1.8% pT1a, 4.4% pT1b, 21.2% pT1c, 61.1% pT2, 7.1% pT3, and 4.4% pT4. Regarding pN stages, 54.4% were pN0, 28.1% pN1a, 1.8% pN1mi, 9.6% pN2a, and 6.1% pN3a.

Overall survival (OS) ranged from 7 to 74 months (52.0±15.6), while disease free survival (DFS) ranged from 3 to 74 months (49.1±17.7). During follow-up, 15.8% of patients experienced recurrence/metastasis.

Table 1. Distribution of the parameters of tumor size, histological grade, TIL, non-tumor breast tissue status, DCIS, LCIS, PNI and presence of microcalcification

		Min-Max	Mean (SD)
Tumor size (cm)		0.5-10	2.9 (1.5)
		n	%
Histological grade	**G1**	18	15.8
	G2	73	64
	G3	23	20.2
TIL	**≤50%**	106	93
	>50%	8	7
Non-tumor breast tissue	**No features**	55	48.2
	Fibrocystic changes	40	35.1
	Atypical ductal hyperplasia	14	12.3
	Flat epithelial atypia	1	0.9
	Columnar cell change	4	3.5
DCIS	**Absent**	42	36.8
	Present	72	63.2
LCIS	**Absent**	101	88.6
	Present	13	11.4
PNI	**Absent**	101	88.6
	Present	13	11.4
Microcalcification	**Absent**	64	56.1
	Present	50	43.9

DCIS: Ductal carcinoma *in situ*; LCIS: Lobular carcinoma *in situ*; PNI: Perineural invasion; SD: Standard deviation; TIL: Tumor infiltrating lymphocyte; Min: Minimum; Max: Maximum

Adjuvant therapy was administered as follows: 71.1% received chemotherapy (CT) (various regimens), 19.3% did not receive CT, and 9.6% had less common regimens. Radiotherapy was given to 71.1% of patients, and 86.8% underwent ET (55.2% letrozole, 31.6% tamoxifen).

The p53 H-score ranged between 0 and 285, with 82.5% scoring <50 and 17.5% scoring ≥50. The PTEN IRS ranged between 0 and 12, with 15.8% scoring 0, 62.3% scoring 1–6, and 21.9% scoring 7–12 (Table 2).

Grade 2 group had a statistically significantly higher rate of p53 H-scores below 50 (89%) compared to grade 3 (56.5%) (p = 0.001), with no significant differences among other grades (p>0.05).

PTEN IRS distribution varied significantly between histological subtypes (p = 0.010). Mixed carcinoma had higher PTEN IRS of 7–12 (55.6%) compared to IDC (20.9%) and ILC (0%) (p_1 = 0.004 and p_2 = 0.003, respectively).

Table 2. Distribution of Ki-67, ER, PR and CERBB2 status, luminal A and recurrence status, molecular subtype, p53 H-score, PTEN IRS parameters

		n	%
Ki-67	<14%	59	52.2
	14-19%	14	12.4
	≥20%	40	35.4
ER	0	18	15.8
	1-80%	32	28.1
	>80%	64	56.1
PR	0	41	36
	1-80%	56	49.1
	>80%	17	14.9
CERBB2	Score 0	83	72.8
	Score 1	11	9.6
	Score 2	4	3.5
	Score 3	16	14
Luminal A with recurrence status	No recurrence	52	91.2
	Recurrence	5	8.8
Molecular subtype	Luminal A	57	50
	Luminal B	38	33.3
	TN	10	8.8
	HER2/NEU	9	7.9
p53 H-score	<50	94	82.5
	≥50	20	17.5
PTEN IRS	0	18	15.8
	1-6	71	62.3
	7-12	25	21.9

ER: Estrogen receptor; PR: Progestrone receptor; TN: Triple negative; CERBB2: Cellular erythroblastic oncogene B2; IRS: Immunoreactivity score; HER2: Human epidermal growth factor receptor 2

OS values for the TN group were lower than LumA and LumB (p_1 = 0.013, p_2 = 0.001, respectively).

LumA group had a higher rate of p53 H-scores below 50 (94.7%) compared to LumB (78.9%), TN (60%), and HER2/NEU (44.4%) (p_1 = 0.022, p_2 = 0.008 and p_3 = 0.001, respectively), with no significant differences among other subtypes (Table 3).

OS and DFS values were significantly lower in patients not receiving ET compared to those receiving Letrozole or Tamoxifen (p = 0.042 and p = 0.031, respectively), with no significant difference between Letrozole and Tamoxifen groups. A significant difference was found in p53 H-score distribution among ET groups (p = 0.005). Patients not receiving ET had fewer H-scores below 50 (53.3%), with no difference between Letrozole and Tamoxifen groups (p>0.05).

OS values were significantly higher in patients with upper inner tumor location compared to those with lower inner, lower outer, retroareolar, and multiple quadrant locations (p_1 = 0.021, p_2 = 0.007, p_3 = 0.049, and p_4 = 0.004, respectively). No significant differences were found between other tumor location groups (p>0.05).

DFS values were significantly lower in patients with multiple quadrant tumors compared to upper inner and upper outer locations (p_1 = 0.008 and p_2 = 0.022, respectively) and in lower outer tumors compared to the upper inner group (p = 0.034).

OS and DFS values were significantly higher in patients with EIC compared to those without EIC (p = 0.008 and p = 0.049, respectively).

Recurrence rates were significantly higher in patients with LCIS (38.5%) compared to those without LCIS (12.9%) (p = 0.032).

LumA with recurrence rates were significantly higher in patients with PNI (50%) compared to those without PNI (3.9%) (p = 0.006).

Recurrence rates were significantly higher in patients with LVI (30.4%) compared to those without LVI (5.9%) (p = 0.001).

DFS values in the pT3 group were significantly lower than those in the pT1b and pT1c groups (p_1 = 0.022 and p_2 = 0.018, respectively). No significant differences were found among other pT groups. Recurrence rates were lower in the pN0 (8.1%) and pN1a (6.3%) groups compared to pN2a (63.6%) and pN3a (42.9%) groups (p_1<0.001 and p_2<0.001, respectively).

OS and DFS values were lower in patients with TIL ≤50% compared to TIL>50% (p = 0.026 and p = 0.012, respectively).

DFS values were lower in cases without ER staining compared to 1–80% and >80% groups (p_1 = 0.013, and p_2 = 0.038), with no difference between the 1–80% and >80% groups (p>0.05).

A significant difference was identified between Ki-67 groups in the distribution rates of p53 H-score groups (p = 0.009). The proportion of cases with Ki-67 <14% (93.2%) was significantly higher than those with Ki-67>20% (70%) (p = 0.005).

Comparisons could not be made between grade groups, histological subtypes, ET groups, tumor locations, or the presence of DCIS, EIC, LCIS, PNI, LVI, as well as pT stage, pN stage, surgical margin groups, TIL groups, CERBB2 groups, and Ki-67 in the LumA sub-group with recurrence because of small sample size.

Table 3. Evaluation of OS, DFS, presence of recurrence, p53 H-score and PTEN IRS parameters according to molecular subtype groups

Luminal A (Min-Max)-Mean (SD)		Molecular subtype				*p*
		Luminal B	TN	HER2/NEU		
		(Min-Max)-Mean (SD)	(Min-Max)-Mean (SD)	(Min-Max)-Mean (SD)		
OS (months)		(8–71)–52.0 (15.1)	(7–74)–55.3 (15.7)	(24–62)–38.3 (13.6)	(22–69)–52.6 (14.1)	[1]**0.017***
DFS (months)		(4–71)–50.9 (16.3)	(3–74)–50.7 (18.1)	(10–62)–34.1 (17.6)	(6–69)–47.5 (19.5)	[1]0.057
		n (%)	n (%)	n (%)	n (%)	
Recurrence	**Absent**	52 (91.2)	30 (78.9)	7 (70)	7 (77.8)	[2]0.122
	Present	5 (8.8)	8 (21.1)	3 (30)	2 (22.2)	
p53 H-score	**<50**	54 (94.7)	30 (78.9)	6 (60)	4 (44.4)	[2]**<0.001***
	≥50	3 (5.3)	8 (21.1)	4 (40)	5 (55.6)	
PTEN IRS	**0**	8 (14)	7 (18.4)	3 (30)	0 (0)	[3]0.279
	1–6	36 (63.2)	23 (60.5)	7 (70)	5 (55.6)	
	7–12	13 (22.8)	8 (21.1)	0 (0)	4 (44.4)	

[1]: Kruskal-Wallis test
[2]: Fisher-Freeman-Halton test
[3]: Chi-squared test
DFS: Disease free survival; OS: Overall survival; SD: Standard deviation; TN: Triple negative; IRS: Immunoreactivity score; Min: Minimum; Max: Maximum; SD: Standard deviation

Similarly, comparisons for TIL in terms of recurrence were not possible due to insufficient data.

DFS values were significantly lower in cases with LumA with recurrence compared to those without (p = 0.010).

No comparison could be made between those with and without LumA and recurrence in p53 H-score groups due to insufficient numbers.

There was no significant difference between those with and without LumA and recurrence in terms of OS duration and PTEN IRS distribution rates.

Except for the significant differences mentioned above and statistical comparisons that could not be made due to insufficient numbers, no significant differences were observed in statistical comparisons between each of histological grade, histological subtype, molecular subtype, CT/RT/ET status, presence of DCIS/EIC/LCIS, presence of LVI, pT/pN stages, TIL groups, Ki-67 groups and each of OS/DFS durations, LumA with recurrence status, recurrence rates, p53 H-score/PTEN IRS.

Similarly, no significant differences were observed in the statistical comparisons between each of menopausal status, laterality, focality, tumor location, presence of microcalcification, presence of PNI, ER/PR staining percentages, CERBB2 scores and each of OS/DFS durations, LumA with recurrence status, recurrence rates.

In addition to the statistical findings, we share a detailed analysis of recurrent cases with tumors of the LumA subtype, which was the focus of our study (Table 4).

Discussion and Conclusion

The risk of local recurrence and metastasis, key indicators of aggressive breast cancer prognosis, is influenced by tumor stage and molecular characteristics. Saphner et al. (15) reported a 30% recurrence rate in patients undergoing appropriate treatment, while a meta-analysis of trials published in the Lancet (16) found a recurrence rate of 20–30% in early breast cancer. In the present study, involving both early and non-early-stage cases, 15% of patients developed distant metastasis with local recurrence during a 5-year follow-up, a relatively low rate.

Sørlie et al. (17) highlighted longer OS and DFS durations in LumA subtypes, with *TP53* mutations found in 13% of LumA, 71% of HER2+, and 82% of Basal-like subtypes. In the present study, OS values were significantly lower in TN compared to LumA and LumB groups. ER-negative cases also showed significantly lower DFS values than those with ER staining percentages of 1–80% and >80%. This finding may be due to the unique biology of molecular subtypes as discussed by Bosch et al. (18) on the molecular characteristics and pathogenesis of TNs. We also hypothesize that this may be explained by the scoring we used to show the presence of p53 overexpression, which is associated with poor prognosis in breast cancers (19), showed that the proportion with an H-score above 50 in the LumA group (5.3%) was significantly smaller than in the LumB (21.1%), TN (40%) and HER2+ (55.6%) groups.

Ki-67 is important for classifying luminal subtypes, but the optimal threshold value remains unclear. Following the Saint Gallen Consensus (20, 21), we used 14% as a threshold, analyzing cases as <14%, 14%–<20%, and ≥20%. No significant differences were found in OS, DFS,

or recurrence rates across Ki-67 groups. However, p53 overexpression (H-score >50) was significantly more common in Ki-67 >20% than in the <14% group, suggesting a 20% threshold may better predict poor prognosis and guide management.

Although the breast cancer tumor microenvironment harbors diverse cells, TILs are a key group. Studies have shown that TILs play critical roles in cancer progression (22). Korkaya et al. (23) demonstrated that interleukins secreted by certain TILs may promote tumor development. Another study found that higher TIL concentrations predicted response to neoadjuvant CT across all molecular subtypes and improved survival in HER2-positive and TN breast cancers, but were a negative prognostic factor for survival in luminal-HER2-negative cancers (24). In the present study, OS and DFS values were significantly poorer in cases with TIL values ≤50% compared to those >50%. Furthermore, all 18 recurrence cases had TIL values ≤50%, supporting the inclusion of immune-modulating therapies in breast cancer treatment.

Table 4. Study parameters in recurrent luminal A subtype cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	46	80	79	55	44
Gender	Female	Female	Female	Female	Female
Menopausal status	Pre	Post	Post	Post	Pre
Procedure	MRM	MRM	MRM	MRM	MRM
Laterality	Right	Left	Right	Right	Left
Focality	Uni	Uni	Multi	Multi	Uni
Tumor site	*	Multi quadrant	Lower outer	Upper outer	RA
Tumor size (cm)	*****	**10**	**4**	**2**	**2.2**
Histological subtype	IDC	IDC	IDC	ILC	IDC
Histological grade	G2	G2	G2	G2	G2
LVI	Present	Present	Present	Absent	Present
PNI	Present	Absent	Present	Absent	Present
DCIS	Present, HG	Absent	Present, IG	Absent	Present, HG
EIC	Absent	Absent	Absent	Absent	**Present**
LCIS	Absent	Absent	Absent	**Present**	Absent
Microcalcification	Absent	Absent	Present	Present	Present
TIL (%)	15	5	5	5	10
Surgical margins-tumor distance	*	<1 cm	**Positive**	<1 cm	>1 cm
pTN	T*N2a	T3N0	**T4N2a**	T1cN0	**T2N3a**
ER (%)	20	90	90	80	90
PR (%)	20	70	20	0	0
Ki-67 (%)	10	12	10	10	5
p53 H-score	0 (null)	<10	<10	<10	<10
PTEN IRS	**2**	**0**	**0**	**3**	**2**
Chemotherapy	STD	**Refused**	STD	STD	STD
Radiotherapy	Received	Received	Received	Received	Received
Endocrine therapy	Letrozole	Letrozole	Letrozole	Letrozole	Letrozole
OS (month)	29	36	8	65	59
DFS (month)	21	12	4	60	35
Location of metastasis	Bone	Bone, LN, liver	Bone, liver	Bone, liver	Bone, LN
Molecular subtype of metastasis biopsy	Luminal A	Luminal A	*	Luminal A	No biopsy performed

DCIS: Ductal carcinoma *in situ*; DFS: Disease free survival; EIC: Extensive intraductal component; ER: Estrogen receptor; HG: High grade; IDC: Invasive ductal carcinoma; IG: Intermediate grade; ILC: Invasive lobular carcinoma; LCIS: Lobular carcinoma *in situ*; LN: Lymph node; LVI: Lymphovascular invasion; MRM: Modified radical mastectomy; OS: Overall survival; PNI: Perineural invasion; PR: Progestrone receptor; RA: Retroareolar; STD: Standard treatment; Adriamycin+Cyclophosphamide+Docetaxel; TIL: Tumor infiltrating lymphocyte

*: Non-avaiable data

We believe the lower recurrence rate in the non-luminal group, despite its worse prognosis compared to luminal subtypes, is due to the significantly smaller number of cases in this group. Additionally, a detailed discussion of our five aggressive recurrent LumA cases, described in the findings section, will support the main aim of our study.

Case 1: The right mastectomy material of a patient, whose operation and initial pathology were conducted at another center, revealed axillary lymph node metastases (pN2a) at diagnosis with notable LVI. Axillary lymph node metastasis is a critical prognostic factor in early-stage breast cancer. Weigelt et al. (25) reported that 70–80% of lymph node-positive patients develop distant metastasis, compared to 20–30% of node-negative patients.

In the current study, the recurrence rate in the pN0 group (8.1%) was significantly lower than in the pN2a (63.6%) and pN3a (42.9%) groups. Similarly, the pN1a group (6.3%) had a significantly lower recurrence rate than the pN2a (63.6%) and pN3a (42.9%) groups.

Lymph node metastasis, influenced by patient clinical features and tumor biology, may explain the aggressive course in this case. Notably, this is the only patient among the five LumA cases with recurrence that had p53 H-score: 0 (null) and PTEN IRS: 2 (IRS<6), indicative of mutations associated with poor prognosis.

Case 2: The left mastectomy material of an 80-year-old patient revealed a tumor <1 cm from the posterior surgical margin, with prominent LVI, and a tumor size of 10 cm-the largest in our study. LVI is a poor prognostic indicator in breast cancer. Kuhn et al. (26) identified LVI as an independent prognostic factor linked to local recurrence, distant metastasis, and worse DFS and OS outcomes, even in lymph node-negative patients. It also influences radiotherapy decisions.

In our cohort, recurrence rates were significantly higher in patients with LVI (30.4%) than those without LVI (5.9%). The large tumor size and potentially inadequate surgical margins may explain the patient's aggressive disease course. Moreover, the patient had comorbidities due to advanced age, and she also declined CT. Fisusi and Akala (27) emphasized that tailored therapeutic strategies minimize toxicity and recurrence risk in breast cancer patients. Refusal of CT likely contributed to local recurrence and distant metastasis, seen in this patient.

The absence of PTEN immunoreactivity further supports the aggressive prognosis in this case.

Case 3: In this 79-year-old patient, examination of the right mastectomy material revealed tumor cells at the posterior surgical margin, with the tumor stage classified as T4 due to breast skin ulceration caused by two separate tumor foci. This case also exhibited diffuse columnar cell changes in non-tumor tissue, a unique finding among LumA cases with recurrence. The present study found a significantly higher recurrence rate (50%) in cases with positive tumor margins compared to those with a tumor-to-margin distance of <1 cm (6.3%).

In addition to the positive surgical margin, the presence of multifocal tumors, skin ulceration, axillary lymph node metastases (pN2a), and LVI likely contributed to local recurrence. Lymph node metastasis, as previously discussed, is a poor prognostic indicator. The patient's complete loss of PTEN expression is another factor that may have facilitated tumor recurrence.

Case 4: In this 55-year-old patient, the right mastectomy material revealed multifocal tumor foci with an ILC histological type, unlike the other LumA cases with recurrence. ILC is associated with a worse prognosis compared to IDC in luminal subtypes, as noted by Adachi et al. (28), although another study has shown better OS for hormone receptor-positive HER2-negative ILC compared to IDC (29).

This patient also had LCIS at the superior and posterior surgical margins, with tumor cells <1 cm from the superior, posterior, and anterior margins. Our study found a significantly higher recurrence rate (38.5%) in cases with LCIS compared to those without (12.9%). The presence of LCIS in the surgical margins and a PTEN score of 3 (IRS <6) likely contributed to the increased risk of recurrence, highlighting an aggressive prognosis in this case.

Case 5: In the left mastectomy specimen of a 44-year-old patient, the most striking finding was the presence of EIC, which was the only EIC among our patients having LumA with recurrence. EIC is known to complicate preoperative imaging assessments of tumor size and location and is linked to higher surgical margin positivity. A study by Chagpar et al. (30) demonstrated an increased risk of local recurrence in breast cancers with EIC. However, while Corsi et al. (31) found that EIC was not associated with local recurrence-free survival or distant metastasis, it was linked to improved 5-year OS in pT1-stage cancers, but not in pT2-stage cases.

In the current study, patients with EIC had statistically higher OS values than those without. Although EIC may have contributed to local recurrence in this patient, the development of distant metastasis at 35 months could be attributed to the advanced pathological stage at diagnosis (pT2N3a). Furthermore, the patient's PTEN score of 2 (IRS <6) suggested a poor prognosis.

Among LumA cases with recurrence, 4/5 had H-scores <10, and 1 had a score of 0. The LumA group had a significantly higher rate of H-scores <50 (94.7%) compared to LumB (78.9%), TN (60%), and HER2+ (44.4%) subtypes.

TP53 mutations in LumA were detected at a rate of 21%, comprising 15.7% with p53 loss (null type) and 5.2% with p53 overexpression. Deletions leading to p53 protein loss are more common in Apocrine and Basal-like subtypes (9).

Tumors with an H-score below 50 were significantly more frequent in grade 2 (89%) than grade 3 (56.5%). A previous study showed that p53 overexpression correlated with higher grades and reduced ET/CT response (32). However, immunohistochemical methods may miss non-missense mutations, potentially causing false negatives (33). Advanced methods, such as Next Generation Sequencing will improve detection accuracy.

A study showed that PTEN loss was associated with adverse clinicopathological features (6) while our study did not demonstrate a statistical relationship between PTEN loss and recurrence in LumA patients. However, the presence of PTEN loss in all recurrent cases and its overall rate of 77.1% (88/114) highlights its tumor suppressor role. These findings may support the use of PTEN as a prognostic marker in breast cancer.

Study Limitations

The study's main limitation was the small number of recurrent LumA cases, restricting some analyses. However, it is the first to focus on the relationship between p53 and PTEN status with aggressive prognosis in LumA tumors.

Understanding the biological variations within LumA subtype breast cancers is important for developing targeted treatment strategies. Larger studies, advanced sequencing techniques, and identifying pathways beyond PTEN and p53 mutations could enhance early diagnosis and improve survival outcomes for patients with aggressive LumA tumors.

Ethics

Ethics Committee Approval: Ethics committee approval from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021-13-03) was granted on 05.07.2021.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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Original Article

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Bayesian Model Prediction for Breast Cancer Survival: A Retrospective Analysis

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ABSTRACT

Objective: Over the recent years, machine learning (ML) models have been increasingly used in predicting breast cancer survival because of improvements in ML algorithms. However, cancer researchers still face a significant challenge in accurately predicting breast cancer patients' survival rates. The purpose was to predict breast cancer survival using a Bayesian network.

Materials and Methods: This retrospective study included 2,995 patients diagnosed with breast cancer and subsequently hospitalized between January 1, 2012, and December 30, 2024. SPSS Modeler version 18.0 was used to build prediction models. The data were randomly split into a training set (2,097 cases, 70%) and a test set (898 cases, 30%) for developing the Bayesian network model and predicting the overall survival of patients diagnosed with breast cancer. The model included demographic variables (age, marital status, and governorate), laboratory/clinical variables (hemoglobin level, white blood cell count, presence of hypertension, and diabetes mellitus) and the outcome variable, patient survival status (binary value: survived/died). The discriminative ability of models was evaluated by accuracy and the area under the curve (AUC) in terms of superior predictive performance for breast cancer outcomes.

Results: The Bayesian model exhibited the best discriminatory performance among the nine models, with an AUC of 0.859 and the highest accuracy of 96.661%. In the context of feature importance, white blood cell value at the time of diagnosis was the most important feature for predicting the survival of breast cancer. Patients who had below-normal hemoglobin and above-normal white blood count values had a higher death probability than patients who had normal white blood count and hemoglobin values. The presence of hypertension and diabetes mellitus in patients with breast cancer led to a reduced survival probability.

Conclusion: The Bayesian model outperformed the other models in predicting the survival probability of breast cancer. Routine laboratory testing and demographic data can be included in a ML model to predict breast cancer survival. Accurate prediction of breast cancer survival is vital for clinical decision-making.

Keywords: Bayesian model; breast cancer; machine learning; survival; prediction models

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Key Points

- Breast cancer is widely acknowledged as a serious global health problem.
- The study developed a Bayesian network/machine learning model using demographic and clinical variables to predict breast cancer survival with good discrimination (area under the curve 0.859) and accuracy (96.7%).
- The important variables for survival prediction were white blood cell count, presence of diabetes, age, hemoglobin concentration, presence of hypertension, and the governorate of residence.

Introduction

Breast cancer is a common and serious health concern on a worldwide scale (1). Statistics show that it is the most commonly diagnosed cancer among women, with millions of cases recorded each year (2). In 2020, almost 2.3 million new instances of breast cancer were reported, with 685,000 deaths (1). Breast cancer is expected to cause more than 3 million new cases and 1 million deaths per year by 2040 (1). It follows that it is essential to address the broad effects of breast cancer and to reduce breast cancer-related death rates (3).

Survival is defined as the duration of time a patient survives after the disease is diagnosed. Breast cancer is a complex disease with varying survival rates across individuals, despite gradual improvements in recent years (4). Predicting breast cancer survival effectively may help healthcare providers make better decisions regarding medical

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treatment intervention planning, preventing excessive therapy, and so develop the optimal clinical management (5). However, accurate survival prediction is also important for further research. The outcome variable of the present study was the prediction of survival at the time of data collection (6, 7).

Breast cancer is considered a multifactorial disease. Research has identified several etiological risk factors that will change a woman's likelihood of getting breast cancer, such as lifestyle, social-psychological factors, genetic factors, and environmental factors (8). Thus, the effective prediction of breast cancer risk should include these different factors, including demographics, such as age and gender (9). Age increases the likelihood of developing breast cancer. The most common age group for developing breast cancer are women aged between 50 and 69 years (10). Furthermore, women are more vulnerable than men to develop breast cancer, because of exposure to estrogen and progesterone (11).

Clinical biomarkers such as white blood count (WBC), and hemoglobin (Hb) concentration are important in breast cancer, as high WBC and low Hb concentrations are associated with breast cancer (12). The presence of comorbidities, such as hypertension (HTN) and diabetes mellitus (DM) are also associated with worse outcomes in breast cancer (13, 14). Petrelli et al. (13) reported that HTN is characterized was associated with an increase in the probability of death among patients with breast cancer. Furthermore, DM, which is also a globally prevalent disease, is positively associated with breast cancer (15). DM has been associated with a higher incidence and a lower survival rate in breast cancer (16). Therefore, the presence of HTN and DM should be included in models that are attempting to predict breast cancer survival.

Machine learning (ML) models can play a significant role in predicting breast cancer. ML has numerous benefits, including survival prediction, earlier detection, and enhanced model accuracy. Furthermore, ML models can examine numerous risk variables, including genetics, lifestyle, and medical history, resulting in individualized risk estimations for patients with breast cancer (9). A Bayesian model is a type of ML algorithm, which includes a more advanced and sophisticated approach for parameter adjustment. The algorithm creates a probabilistic model that maps parameter values to the objective and evaluates it using a validation set (17, 18). Using this model, the algorithm selects the most promising parameters to assess in the objective function. This method is more efficient than grid and random search, particularly in high-dimensional parameter fields (17, 18). A Bayesian model has the potential to learn data models automatically, without any implicit assumptions, and it is able to handle multiple and non-linear relationships between variables (18).

Investigating breast cancer survival rates is one method for identifying risk factors for mortality and will thus address a major public health issue. The aim of this study was to predict breast cancer survival using a Bayesian network ML algorithm. The findings of the present study could be used to raise public awareness of the factors that contribute to breast cancer deaths. Furthermore, the results may be shared with the Jordanian Ministry of Health to help policymakers enhance public awareness about the factors that increase the risk of breast cancer-related death, which may allow disease avoidance, in some cases, and earlier detection and more successful, appropriate treatment once detected in future cases of breast cancer in Jordan.

Materials and Methods

This retrospective study was approved at Jordan University Hospital Ethics Committee (IRB approval no: 10/2024/1503, date: 16.01.2024). The obtained health records were from between January 1, 2012, and December 30, 2024. The complexity of the organizational processes and the electronic health system necessitated a four-month extraction period. The inclusion criteria specified that the patients should be female, with breast cancer, and aged above 18 years. We excluded patients with any cancer other than breast cancer.

An earlier retrospective study attempted to predict breast cancer using machine-learning approaches by applying demographic, mammographic, and laboratory data. It found that the random forest model resulted in an accuracy of 80% and an area under the curve (AUC) of 0.56, while a gradient boosting trees model showed an AUC of 0.59, a stronger performance compared to the neural network (9).

The dataset for the present study contained 2,995 records and eight variables. The initial variables that were requested included the stage of breast cancer, age, Hb concentration and WBC at the time of diagnosis, governorate, marital status, family history of cancer, patient outcome (survival versus death), presence of HTN, and DM at the time of diagnosis. However, the data concerning family history, the stage, and grade of breast cancer were excluded because they were not available in the electronic health records.

Before the study initiated, the institutional ethics committee authorized the procedure. The study was conducted retrospectively, hence, informed consent was waived. The patients' information was managed in confidence. Each record was given an anonymized ID, allowing for the secure unidentifiable processing of patient data. The retrieved data were saved to a password-protected file on a secure computer in the researcher's office. The study data were only available to the researchers. There was no funding for this study.

Statistical Analysis

Data Preparation

To build the Bayesian model, the following steps were performed as data preparation: Checking for missing data, cleaning, and removing duplicated and inconsistent data. All laboratory data were standardized using one international unit for analysis. All data were originally stored on an Excel sheet and exported to SPSS. Then the files were merged into one data sheet by matching the cases with the ID numbers. Descriptive statistics were conducted using Statistical Package for Social Sciences, version 29.1 (19).

Preprocess of Missing Data

Since the data were created and collected in a real medical setting, there were several observations with missing features. We excluded features with too many missing values to lessen the influence of missing variables on the training process for prediction models, such as family history, smoking, and the stage and grade of breast cancer (Table 1).

Data Mining

To apply the data mining step, SPSS Modeler version 18.0 was used (20) to generate multiple predictive models based on the available data. The database records were split 70/30% for training the network and testing data, respectively. Training data are used to develop a predictive model, whereas the testing data are used to evaluate the model's performance (21). The primary criteria for selecting the most effective

Table 1. Proportion of missing data for initial variables selected for inclusion

Variable	Missing (%)
Age	0 (0.0%)
Family history	2.995 (100%)
Smoking	2.993 (100%)
WBC count	0 (0.0%)
Hb concentration	0 (0.0%)
Governorates	0 (0.0%)
Breast cancer stage	2.995 (100%)
Breast cancer grade	2.995 (100%)
Marital status	0 (0.0%)
DM	0 (0.0%)
HTN	0 (0.0%)

Hb: Hemoglobin; WBC: White blood cell; DM: Diabetes mellitus; HTN: Hypertension

AI model are the overall accuracy and AUC (22). The accuracy is the percentage of all the used datasets that are properly predicted out of all the instances (23). The AUC represents the performance metrics that determine the predictive ability of ML models and it measures the overall performance of the model (24). Furthermore, the AUC assesses a model's discriminative ability by comparing projected probabilities to actual binary survival status and estimating the probability of death for censored data at a particular point (25). The AUC ranges from 0 to 1, and a value of 0.5 is comparable to random guessing, and a value of 1 represents perfect discrimination (25). The best model was selected using an iterative approach to select the superior model for accurate breast cancer mortality prediction. The Bayesian network was the most effective of the nine models in our study and achieved highest overall accuracy score (96.661%) and a greater discriminatory measure, AUC score (0.859).

A Bayesian network model is a probabilistic graphical model that illustrates variables and their interactions using an acyclic graph with a directed structure (26). Gashu and Aguade (27) demonstrated that the Bayesian network model is especially valuable in medical applications, like predicting the survival time of breast cancer, because a Bayesian network can model intricate correlations between risk variables and symptoms while successfully incorporating uncertainty and prior information. Furthermore, this model has edges that reflect the conditional probability and nodes that represent random variables for the related factors (26). In addition, a Bayesian network was chosen as it was likely to achieve the highest performance, the likelihood of survival versus death is estimated using only the available variables, successfully resolving the difficulty of risk assessment with partial knowledge, and their conditional likelihood correlations (18).

A Bayesian network model uses a probabilistic framework to generate predictions and interpret outcomes in terms of probabilities and uses expert knowledge to determine the conditional independence of predictors. Furthermore, they provide an intuitive visual representation of the correlations between survival and mortality parameters (28). As the model is based on available variables from daily clinical practice, it can be used as a predictive tool for particular breast cancer patients and for assisting doctors in the decision-making process (27).

Results

A total of 2,995 patients diagnosed with breast cancer were included (Figure 1). Age groups were categorized as young adults (19–45 years, 24.6%) and older adults (46–99 years, 75.4%). Most of the patients were married (73.3%). Furthermore, laboratory assessments included Hb concentration and WBC count. Below-normal Hb and above-normal WBC levels were observed in 28.0% and 45.2% of patients, respectively. Approximately 15% of the patients had a recorded history of HTN and 19% of the patients had DM. Geographically, 94.4% were from Middle Governorates, followed by North (3.1%) and South Governorates (2.5%). During the 12-year follow-up period from the start of EHR data storage in 2012 through the end of 2024, 96.6% of patients belonged to the survived category. Comparison of the study sample based on survive (n = 2.892) versus dead (n = 103) are presented in Table 2. The comparison revealed statistically significant differences in survival based on marital status, Hb levels, WBC counts, HTN, and DM (p<0.01), with lower survival rates associated with being married, having below-normal Hb, high white blood cell counts, and having diabetes.

Figure 2 illustrates Kaplan-Meier survival plots, depicting hazard functions for key variables. Low Hb and high WBC levels, as well as the presence of HTN, and DM, were associated with an increased cumulative hazard compared to normal levels or the absence of these conditions, suggesting a poorer prognosis. Marital status also showed differences, with potentially distinct hazard functions depending on whether patients were single, married, or divorced.

Structure of the Study Model

Among the nine generated models, the Bayesian network was the most effective of the nine models in our study, achieving the highest overall

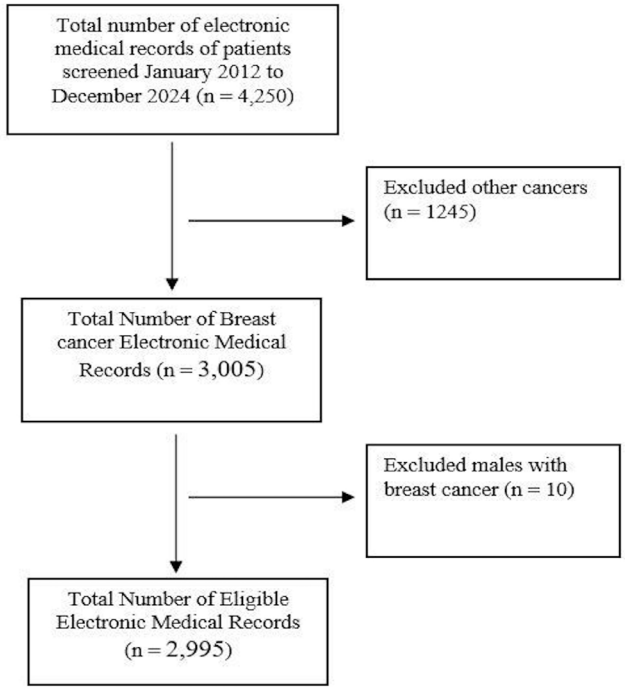


Figure 1. Patient flow chart

Table 2. Comparison of the study sample based on survival (*n* = 2.892) versus death (*n* = 103)

Characteristics	Dead n (%)	Survive n (%)	Chi-square
Age group			
Young adult (19–45)	24 (23.3)	712 (24.6)	0.093
Old adult (46–99)	79 (76.7)	2.180 (75.4)	
Marital status			
Single	7 (6.8)	362 (12.5)	
Married	72 (69.9)	2.123 (73.4)	8.694**
Divorced	24 (23.3)	407 (14.1)	
Hb			
Normal (12–15 g/dL for female)	45 (43.7)	2.110 (73.0)	42.225**
Below normal	58 (56.3)	782 (27.0)	
WBC			
Normal (WBC 4–11x10^3/microliter)	12 (11.7)	1.629 (56.3)	80.146**
Above normal (>11x10^3/microliter)	91 (88.3)	1.263 (43.7)	
HTN			
Yes	3 (2.9)	442 (15.3)	12.032**
No	100 (97.1)	2.450 (84.7)	
DM			
Yes	3 (2.9)	554 (19.2)	17.335**
No	100 (97.1)	2.338 (80.8)	
Governorates			
North	2 (1.9)	91 (3.1)	
Middle	99 (96.1)	2.729 (94.4)	0.618
South	2 (1.9)	74 (2.5)	

Hb: Hemoglobin; RBC: Red blood cell; WBC: White blood cell; DM: Diabetes mellitus; HTN: Hypertension; **p<0.01

accuracy score (96.661%) and the highest AUC score (0.859) (Table 3). This was followed by logistic regression (96.594%, AUC = 0.848), CHAID model (96.561, AUC = 0.826), neural network model (96.561, AUC = 0.688). Then, the C5 model, the Quest model, and the C&R Tree model had the same performance (96.561, AUC = 0.5). Followed by the decision list model (63.940, AUC= 0.788). The discriminant model (55.426, AUC = 0.532) had the lowest performance.

This study created a Bayesian network for binary classification to distinguish between patients who died and those who survived. The patient outcome node (survival versus death) in the graph represented a random variable, with 0 representing death and 1 representing survival. This encoding allowed for the discovery of probabilistic correlations between discrete variables, which made it easier to analyze linkages within the dataset. The Bayesian network model consisted of eight nodes, including the parent node. It comprised 13 edges, which indicate the factors that govern the interactions between these nodes (Figure 3). Every node in the network represents a random variable of interest. For the outcome (survival versus death) prediction of breast cancer, the predictor variables were age, marital status, governorate, Hb, WBC, HTN, and DM values. The parent node has direct edges that go to one or more child nodes (26). Directed edges between nodes reflect the probability link among the variables in the network (28).

Evaluation of Feature Importance

The Bayesian network found seven important predictors for survival outcome in breast cancer. The importance of WBC was 0.19, which was the most important predictor in our model, followed by DM and age predictors' importance (both 0.16), marital status (0.14), low Hb (0.13), presence of HTN (0.12), while the governorates predictor's importance was lowest at (0.10) (Figure 4).

Table 4 presents the conditional probabilities of survival versus death based on the Bayesian network model's analysis of key predictor variables. This table illustrates how the interplay of demographic factors (age, marital status, and governorate), laboratory/clinical variables (HB, WBC count, HTN and DM) influenced patient survival probabilities. For patients who had below-normal Hb and above normal WBC values, the conditional probability of death was 53%, while for patients who had normal WBC and Hb values, it was 0.17%. Survival probabilities are higher among individuals with normal WBC and Hb values (0.79%). Furthermore, survival probabilities among patients without DM and who had a normal WBC value (0.58%) were slightly higher than those of patients with an above normal WBC value and DM (0.51%). Survival probabilities among old patients who live in Middle Governorates (0.95%) were lower than among patients who live in South Governorates (0.02%).

The older adults who live in Middle Governorates had the highest probability of death (0.96%), while older adults residing in the South Governorates demonstrated the lowest recorded probability of death, at just 0.01%. Survival probabilities among married young adults (0.26%) were lower than that among single patients (0.40%). In addition, the survival probability among old-age patients who had HTN (0.17%) was lower than among young adults who did not have HTN (0.90%). However, the survival probabilities among young

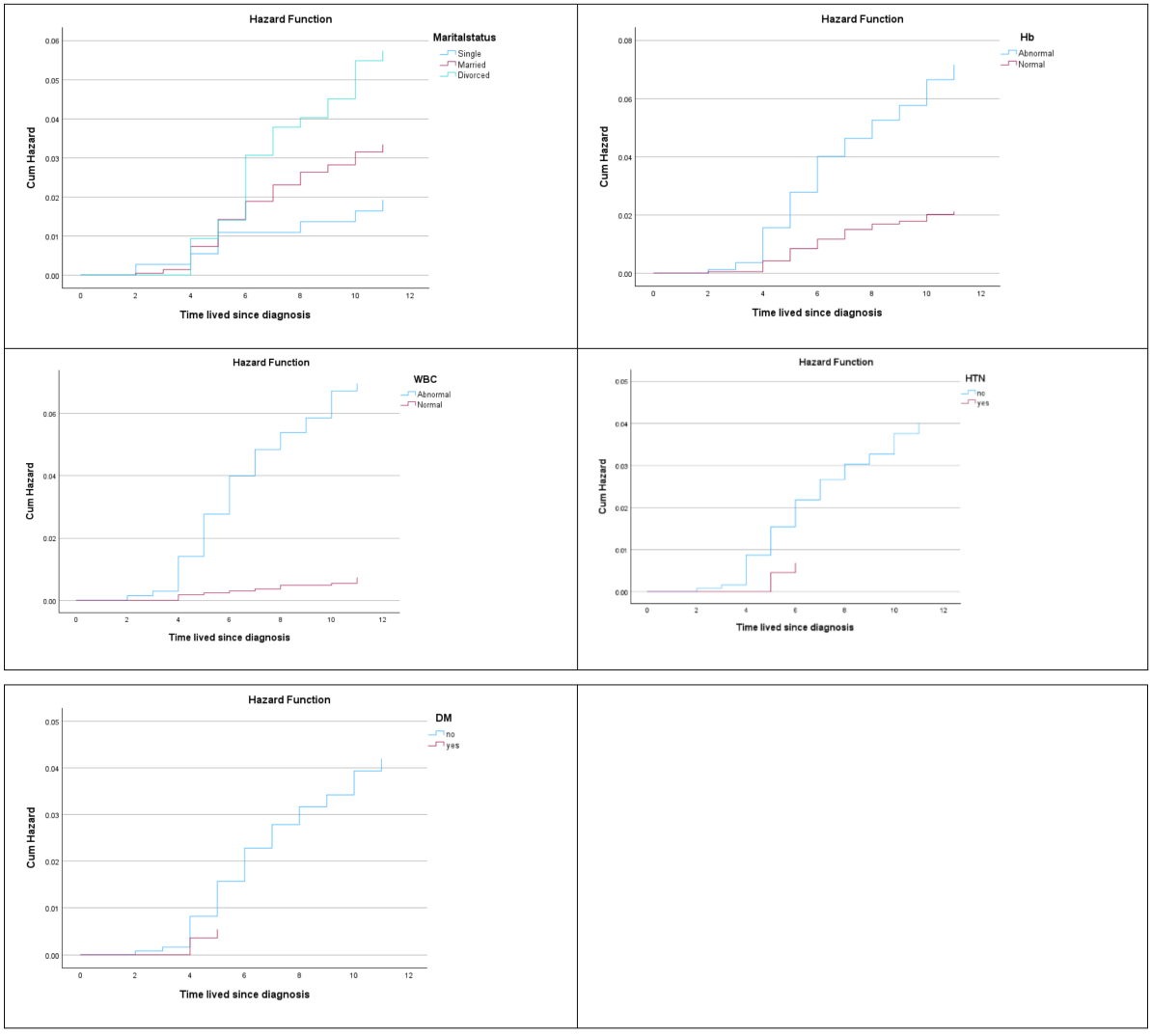


Figure 2. Kaplan-Meier survival plots and Hazard ratios

Table 3. The nine generated models in the study

Model	Overall accuracy (%)	Area under curve
Bayesian network	96.661	0.859
Logistic regression	96.594	0.848
CHAID	96.561	0.826
Neural net	96.561	0.688
C5	96.561	0.5
Quest	96.561	0.5
C&R tree	96.561	0.5
Decision list	63.940	0.788
Discriminant	55.426	0.532

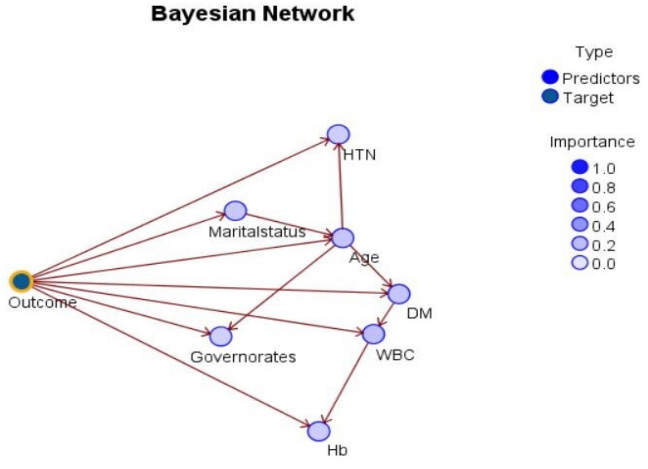


Figure 3. The structure of Bayesian network model

adult (0.24%) and older adult (0.17%) with DM had a lower survival probability compared to those young adults (0.76%) and older adult (0.83%) who did not have DM.

Discussion and Conclusion

This study investigated the connection between demographic characteristics, laboratory tests and presence of two key comorbidities, with the outcome (death or survival) via Bayesian network model in adult women diagnosed with breast cancer in Jordan over a 12-year period. Breast cancer incidence has increased over the past 30 years, while the death rate has decreased (9). The remarkably high survival rate in our 2012–2024 study cohort (96.6%) likely reflects a combination of factors: Increased breast cancer awareness leading to earlier detection through proactive screening programs; advancements in targeted therapies, chemotherapy, and surgical techniques; and limitations in data including exclusion of family history or cancer grade. The EHR data is a limitation, it does not account for socioeconomic variables. Further investigation into the relative contributions of these elements is important in improving future outcomes for the Jordanian population.

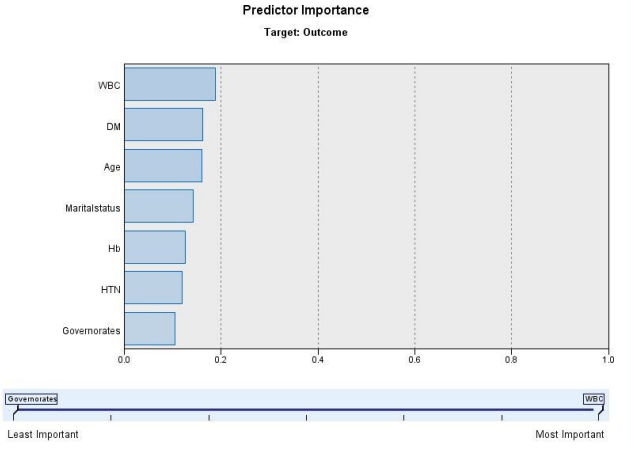


Figure 4. Predictors' importance for the outcome of breast cancer

Currently, ML is one of the most popular methods to create prediction models (29). It has been widely employed in medical science to assist healthcare providers with prognosis analysis. To analyze massive amounts of data, ML is important to create prediction models for predicting risk factors and can deal with real-world uncertainties and even missing data in training and test data sets. Using ML algorithms to analyze data can improve patient outcomes, specify needs, and improve quality of life (29, 30).

In this paper, a Bayesian network was used to predict survival versus death of adult female patients with breast cancer, based on a number of factors. Many researchers have assessed the usefulness of ML algorithms in predicting the risk of cancer, but few of them used a Bayesian network model to predict survival in breast cancer (31-36). The Bayesian network is a robust tool for predicting breast cancer survival. Its ability to integrate prior data makes it highly beneficial for medical decision support systems (34). Moreover, a Bayesian model is a type of probabilistic graphical model that predicts information about an uncertain area (27). In this paper, we predicted the survival of breast cancer using a Bayesian model. When comparing the performance of the Bayesian model to other models that are used for predicting the survival of breast cancer, the Bayesian model had the best performance. The results in this study were similar to those reported by some previous studies. For example, the Bayesian network model achieved the highest AUC value of 0.935 and a prediction accuracy of 87.2% for predicting breast cancer prognosis (32). Furthermore, previous research used the XGBoost method to predict breast cancer survival with a sample size of 4,575 patients (37). The results showed that the XGBoost model achieved a performance with an AUC of 0.8385. The possible reason for Bayesian model achieving better performance may be that Bayesian model is able to detect and account for higher-order interactions and non-linear relationships. However, the findings of this study provide insight into the efficacy of ML algorithms for predicting

Table 4. The Bayesian networks model's determination of the probabilities of survival versus death and predictors

Parents nodes	Conditional probability of HTN		Conditional probability of DM		Conditional probabilities of governorate			Conditional probabilities of marital status		
Dead or survive/age	**Yes**	**No**	**Yes**	**No**	**North**	**Middle**	**South**	**Single**	**Married**	**Divorced**
Survive/young adult	0.10	0.90	0.24	0.76	0.05	0.91	0.04	0.40	0.26	0.03
Death/young adult	0.04	0.96	0.04	0.96	0.00	0.96	0.04	0.00	0.33	0.00
Survive/old adult	0.17	0.83	0.17	0.83	0.03	0.95	0.02	0.60	0.74	0.97
Death/old adult	0.03	0.97	0.03	0.97	0.03	0.96	0.01	1.00	0.67	1.00

	Conditional probability of DM		Conditional probability of Hb	
Dead or survive/WBC	**Yes**	**No**	**Normal**	**Below normal**
Survive/normal	0.49	0.58	0.79	0.21
Death/normal	0.33	0.11	0.17	0.83
Survive/above normal	0.51	0.42	0.65	0.35
Death/above normal	0.67	0.89	0.47	0.53

Hb: Hemoglobin; RBC: Red blood cell; WBC: White blood cell; HTN: Hypertension; DM: Diabetes mellitus

survival probabilities among patients with breast cancer. The study's model illustrated the relationships between the outcome variable (survived or died) and the seven predictors. A Bayesian network model has several advantages over traditional survival models, including the elimination of the proportional hazard assumption, the imputation of missing data throughout the modeling process, and the ease with which results can be interpreted using graphical representations of variable interactions (31).

A growing number of studies using ML have been conducted on breast cancer diagnosis (5, 38). Furthermore, while the number of survival predictions grows gradually, the database set, modeling procedure, performance measures, methodological quality, and modeling of associated predictors vary significantly (5). Previous studies, that predicted breast cancer survivability using ML, identified predictors such as patient demographics, medical history, treatment information, and clinicopathological features of malignancies at various stages (36, 39-41).

Regarding factors influencing the survival of breast cancer, researchers have found many factors associated with breast cancer prognosis and survival. The most commonly used predictors are age, marital status, gender, laboratory tests, race, disease stage, grade, tumor size, number of nodes, histology, and primary site code, which have been entered into many predictive models as predictors (5, 31). Identifying the most significant predictors of survival in breast cancer can help healthcare providers in selecting effective treatment options and reducing data collection and treatment costs (5, 42). In the present study, there were seven important predictors of outcome in breast cancer, including WBC count, presence of DM, age, marital status, Hb value, presence of HTN, and governorate of residence. However, an earlier study found that the interpretation and identification of the important predictors was a key problem, and it was difficult to determine which variables had the greatest influence on survival (43).

Multiple studies have demonstrated that the age of patients with breast cancer is a significant factor in predicting their survival probability. In previous research, the age of patients has been considered a significant predictor for cancer among patients who have survived for more than 10 years (44). Moreover, researchers observed a significant relationship between age and the survival probability of patients experiencing cancer. In the present study, most of the patients were older adults. A previous study found that the age at the time of diagnosis of women with breast cancer was most commonly between 48 and 52 years old (45). However, Courtney and his colleagues only observed survival probability among patients aged 65 years and older (46). The evaluation of mortality among different ages that are vulnerable to breast cancer appears essential. In our study, patients' outcomes were predicted among young and older adults.

Laboratory tests can be used to help predict the survival and death probability of breast cancer (12). The most important predictor for determining the survival of breast cancer patients in the present study was WBC count. Below normal Hb and high WBC levels are considered as important predictors for low survival probability among patients with breast cancer. A recent study found that the overall mean difference for WBC between normal individuals and breast cancer patients was 8.554 (7.724) with a $p = 0.001$. Similarly, for Hb value in a breast cancer patient, the overall mean difference was 11.95 (12.19) compared to normal with a $p<0.05$ (12).

Other characteristics that have been investigated in patients include HTN or DM. Our results as shown in Table 4 indicated a lower survival probability among older patients with HTN. Several observational studies have established the relation between HTN in older women and breast cancer (13, 14). When analyzed according to cancer diagnosis, breast cancer was associated with increased mortality in patients with HTN (13, 47). Furthermore, the prevalence of HTN and breast cancer among women rises with age and could be caused by postmenopausal estrogen withdrawal (48, 49). In the present study, most of the patients had DM, while about 8.3% of patients with breast cancer had DM (50). Given that the existing DM with a breast cancer diagnosis was connected with decreased survival rates (51).

The marital status of the patients is fourth factor that influences patient survival and mortality rates. This study demonstrated that the marital status of patients exerts a notable impact on the survival outcomes of individuals. The survival probability was higher among young patients who were single than among those who were married. Conversely, the survival probability was slightly higher among older adults who were married than those who were unmarried. However, unmarried patients have been reported to have a worse overall survival (52). Other studies have also reported this association; married patients with breast cancer had a better survival rate than unmarried patients (53). Zhai and his colleague indicated that the mortality rate for unmarried patients was 24% higher than for married patients (54). The observed disparity in survival between married and unmarried patients may be influenced by the relatively small number of deceased patients in our sample. This limitation stems from the nature of the EHR used, which may not fully capture the range of survival outcomes within the studied population, nor allow for analysis of socioeconomic considerations which might influence these outcomes.

In the present study, the death probability was high in middle governorates (0.96), such as Amman, which is consistent with a Jordanian study showing that Amman, the capital of Jordan, had the highest incidence rates of breast cancer (45).

The Bayesian network provides a significant description of the correlations and effects of a number of variables on patient outcomes (55). Furthermore, the graphical presentation of Bayesian networks makes it easier to understand and communicate variable interactions than more sophisticated ML models. One of our study's strengths was that the Bayesian network can handle complex relationships efficiently, such as those having an effect in medical data. As leading tools in health informatics, ML has significant promise for use in normal healthcare. This study was especially unique in that it examined all patients with breast cancer, including young adults, rather than only the elderly. A Bayesian network model can overcome the issues of missing data in predicting patients' outcomes while retaining high accuracy in prediction. Furthermore, it was used in the study to analyze a big dataset.

While our study achieved robust performance using demographic and laboratory variables, we recognize that key prognostic factors, such as tumor stage, family history, and treatment details, were unavailable due to constraints in the electronic health records. These omissions may limit direct comparability to models incorporating full clinical staging data. However, our findings align with evidence that routine variables, such as WBC count and the presence of comorbidities at diagnosis are independently prognostic (12, 13), supporting their utility in settings where detailed pathological data are inaccessible.

Study Limitations

Our research has a few drawbacks. While it was intended to include critical characteristics relevant to predicting patient outcomes, such as breast cancer stage, grade, family history of cancer, and medical imaging, these were excluded due to their unavailability and high missing values in the electronic healthcare system. While the ideal dataset would include comprehensive data on tumor stage and grade, these variables were inconsistently documented within the available electronic health records in our study. Faced with this limitation, we focused on the most consistently available clinical and demographic variables to develop a predictive model based on real-world data, acknowledging that its performance is conditional on these constraints. Thus, the model's predictions are conditional on the available data and should be interpreted alongside standard clinical staging. In this study, a single 70–30 data split was used due to initial computational limitations, acknowledging this method's potential limitations compared to techniques like k-fold cross-validation. However, we mitigated bias through randomization and careful overfitting analysis, with plans to implement more robust validation methods in future research for improved model generalizability assessment. Furthermore, while our model does not replace comprehensive clinical staging, it demonstrates that readily available data can still offer valuable prognostic insights, particularly in settings with incomplete records.

Recommendations

Promoting awareness and global collaboration among medical professionals and researchers is essential in treating breast cancer. To fight breast cancer and reduce its impact on individuals and society globally, a comprehensive approach combining ML modeling of big data, research ideally including large inclusive prospective randomized trials, and accessible healthcare services is necessary. Future research should focus on finding additional risk factors, improving prediction approaches, and developing targeted treatment to reduce mortality associated with breast cancer. The level of anxiety and depression factors should be considered in the prediction. However, there is still tremendous room for improvement and development of ML modeling in breast cancer. Prospective research is recommended to verify the use of the Bayesian network in future research.

Implications for Practice

The Bayesian network can be used by healthcare providers to assess survival versus death probabilities and to guide hospital-based breast cancer treatment decisions, promoting tailored treatment options based on routine demographic and laboratory data. The Bayesian network identified the most influential determinants of breast cancer survival, including age, Hb concentration, WBC count at diagnosis, governorate of residence and the presence of important comorbidities, like HTN, and DM. This improved model interpretability and demonstrated its practical value. Furthermore, practice implications include using predictive models to deliver precise risk predictions, improve information systems, facilitate clinical decisions, enhance documentation, and estimate survival probabilities. Given Bayesian network model's simplicity and interpretability compared to other ML methods, the Bayesian network is becoming increasingly popular in healthcare and may be readily integrated into the practice of healthcare.

In summary, breast cancer remains a critical global health concern, affecting millions of people annually. This study has described the use of an ML approach for breast cancer survival prediction, highlighting various risk factors critical in survival prediction, using a Bayesian model. The Bayesian model outperformed the other ML models for discriminative ability, revealing the potential of the Bayesian method to be used as an effective approach to build prognostic prediction models in the context of survival analysis. Our future work will focus on additional predictors of the model using more complete data. Incorporating demographic data as well as routine laboratory tests improved the model's ability to predict survival outcomes, resulting in better clinical decision-making for breast cancer treatment.

Ethics

Ethics Committee Approval: This retrospective study was approved at Jordan University Hospital Ethics Committee (IRB approval no: 10/2024/1503, date: 16.01.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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Original Article

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Evaluation of Perforator Fasciocutaneous Flaps for Oncoplastic Immediate Reconstruction Following Breast Conservative Surgery in Lower and Lateral Breast Quadrant Lesions Perforator Fasciocutaneous Flaps for OBCS

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ABSTRACT

Objective: To compare the oncological safety and the cosmetic outcome of the techniques anterior intercostal artery perforator (AICAP), lateral intercostal artery perforator (LICAP) and thoracodorsal artery perforator (TDAP) flap as a volume replacement technique to eliminate deformity and preserve breast cosmesis by filling the excised defect.

Materials and Methods: This prospective study included women with lower outer quadrant, lower inner quadrant, and upper outer quadrant tumors who underwent upfront or post-neoadjuvant chemotherapy breast conserving surgery with immediate volume replacement surgery. Patients were allocated into three groups at a ratio of 1:1: Group A (n = 10): women who underwent LICAP flap, group B (n = 10): Women who underwent AICAP, and group C (n = 10): Women who underwent TDAP flap procedures.

Results: Regarding postoperative complications, wound infection took place in only one (10%) patient in LICAP group and one (10%) patient in the AICAP group; seroma occurred in only one (10%) patient in LICAP group and one (10%) patient in the TDAP group; and fat necrosis occurred in only one (10%) patient in the TDAP group. Incidence of wound infection, seroma, and fat necrosis was insignificantly different among the studied groups. Breast distortion occurred in one (10%) patient in the AICAP group and not observed in the other groups, and partial flap necrosis occurred in one (10%) patient in the LICAP group and one (10%) patient in the AICAP group and was not observed in the TDAP group. Incidence of distortion and partial flap necrosis were insignificantly different between the studied groups. The conservative treatment of breast cancer core results, surgeon's assessment, patient's satisfaction and breast Q scores did not differ between the three groups.

Conclusion: A better cosmetic outcome than level II oncoplastic techniques, the perforator fasciocutaneous flaps, LICAP, AICAP, and TDAP, were effective and safe options for immediate breast reconstruction after breast-conserving surgery. All three techniques showed similar surgical outcomes, low complication rates, and good aesthetic results. Patient satisfaction was high, with no significant differences between the groups.

Keywords: Perforator fasciocutaneous; oncoplastic; breast conservative surgery; breast quadrant lesions

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Key Points

- Perforator fasciocutaneous
- Oncoplastic
- Breast conservative surgery
- Breast quadrant lesions

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Introduction

Breast-conserving surgery (BCS) is now universally acknowledged as a standard method for treating early-stage breast cancer, demonstrating a disease-free survival rate similar to that of mastectomy. The impact of BCS on patients' psychological well-being and overall quality of life is evident (1). However, BCS may be associated with deformities, such as depression of or nipple-areolar complex (NAC) deviation, especially when the resulting lumpectomy defect is large in relation to small breast size or if the tumor is situated in cosmetically sensitive areas (2). Oncoplastic breast-conserving surgery (OBCS) uses plastic surgical procedures for breast cancer management. This expands the scope of BCS and avoids the associated deformities leading to improvement in the quality of life of the patients and optimal cosmesis (3). These methods use the typical breast reduction surgery markings to direct tumor removal and involve carefully choosing local flaps to replace the lost volume (4).

OBCS can be categorized into two methods: Volume displacement and volume replacement. Volume displacement often necessitates the balancing of the opposite breast by transferring a section of glandular or dermo-glandular breast tissue to replace the deficiency (5).

Over the years, various methods have been developed to maintain breast aesthetics while ensuring effective tumor removal. A relatively new method for partial breast reconstruction following cancer surgery is the use of pedicled local perforator flaps (LPF) that are attached to the chest wall. This includes methods like the lateral thoracic artery perforator (LTAP) and the intercostal artery perforator (ICAP) flaps (6).

The use of a skin-muscle flap with its intercostal neurovascular pedicle was first introduced in 1931. This method has been applied consistently over the years to treat various surface defects (7). The principle of using the intercostal neurovascular pedicle or its perforators is now applied in partial breast reconstructions, especially for large defects. By employing this technique, the underlying muscle is preserved, which aids in effective reconstruction and reduces the need for muscle removal (8). This approach minimizes the complications related to muscle dissection. The ICAP flap is categorized according to its nutrient artery and the location of its perforators. When the perforators arise from the vertebral segment of the intercostal vessels, the flap is called a dorsal ICAP (DICAP) flap. If the perforators are from the costal segment, it is referred to as a lateral ICAP (LICAP) flap. Alternatively, when the perforators come from the anterior intercostal artery and pass through the rectus abdominis or external oblique muscles, the flap is designated as an anterior ICAP (AICAP) flap (9).

The objective of this study was to evaluate the cosmetic outcome and the oncological safety of these techniques (AICAP, LICAP) and thoracodorsal artery perforator flaps (TDAP) as a volume replacement technique to eliminate deformity and preserve breast cosmesis by filling the excised defect.

Materials and Methods

This prospective randomized study was performed with women who had upper outer quadrant (UOQ), lower inner quadrant (LIQ) and lower outer quadrant (LOQ) tumors and who underwent immediate volume replacement surgery with upfront or post-neoadjuvant chemotherapy BCS, at the General Surgery Department of the Faculty of Medicine, Cairo University. The study was conducted from October 2023 to March 2024 and received approval from the Research Ethics Committee of the Faculty of Medicine, Cairo University, approval code MS-500-2023, date 04.04.2024. Patients gave their informed consent before taking part in the study.

Inclusion criteria were women diagnosed with UOQ, LOQ and LIQ tumors, carcinoma *in situ*, of any age group or invasive breast cancer who were candidates for breast OBCS with the need for volume replacement technique (either upfront or post neo adjuvant surgery).

Exclusion criteria were: Refusal of patients to participate; patients not meeting the criteria for BCS, such as having locally advanced tumors, inflammatory breast cancer, pregnancy, or lactation, women who had received radiation therapy to the affected side, metastatic breast cancer, and/or vasculitis.

The patients were assigned to one of three groups at a ratio of 1:1. The patient's assignment to each group was based on the tumor location and the size of suitable flap.

Group A (n = 10): Women who underwent LICAP flap.

Group B (n = 10): Women who underwent AICAP flap.

Group C (n = 10): Women who underwent TDAP flap.

Preoperative evaluations were performed for each patient. Demographic data collection included name, age, residence, marital status and occupation. In addition, a complete medical history was obtained including parity, menstrual history, contraceptive history, onset, lactation history, past history of breast cancer, breast or chest trauma, complaint, course and duration of the mass. A complete clinical examination was performed including general and local examination. Routine laboratory investigations were liver function test, complete blood count, kidney function test, coagulation profile, and random blood sugar. Imaging investigations included preoperative marking via Doppler, mammography, ultrasound, fine needle aspiration, bone scintigraphy, and chest X-ray. Breast volume assessment used the method with the preoperative mediolateral oblique to calculate the breast volume as an elliptical cone using the formula breast volume = $1/3\ \pi\ r^2\ h$ (10).

For lymph node surgery, which included dissection and/or sentinel node biopsy (SNB), The patient was positioned supine with the arm elevated to a 90-degree angle. The flap design was adjusted based on this positioning. It is important to highlight that we consistently employed the perforator that was closest to the anticipated defect. The introduction of the entire flap into the breast was facilitated by the meticulous and precise dissection of the perforator.

Surgical Technique

Axillary surgery was done through an axillary incision. The incision was deepened down till reaching the clavipectoral fascia, which was exposed and opened to enter the axillary space. Each patient underwent either axillary dissection or SNB in accordance with the preoperative decision. Axillary dissection was implemented in case of a positive SNB. Special attention was taken not to harm the thoracodorsal pedicle which should be spared. A single drain was left in the axilla if axillary dissection was performed. The standard quadrantectomy technique for tumor resection was done, the breast skin flap was created, and dissection continued overlying the whole tumor and the surrounding safety margin, the tumor was then, excised down to the pectoral fascia

with at least a 1-cm safety margin from all directions. The margins of the specimen were marked by threads and sent to the frozen section for histopathological examination for radial marginal assessment. In the case of certain margin infiltration, a wider re-excision would be performed. The epidermis would be included in the removal of the tumour if it was located in close proximity.

AICAP Flap

To achieve precise anatomical marking, the patient was marked while standing. The infra-mammary fold (IMF) served as the alignment point for the upper edge of the flap, while a pinch test was used to determine the flap's width and establish its lower boundary. For defects located away from the medial side of the breast, the medial edge of the flap extended to the medial end of the IMF near the xiphoid bone. The lateral boundary was drawn between the front and back axillary lines, ensuring that the top and bottom lines met correctly to avoid creating "dog-ears" at closure. The perforator location was more accurately assessed on the OR table using a hand-held Doppler in both the sitting and supine positions, as their locations typically fluctuate with position changes. We estimated the flap size using the pinch test to assure the donor site's wound closure feasibility.

After skin incision, the dissection began from the lower most point of the flap and the dissection continued in a direction from inferior to superior including the underlying fascia of the abdominal wall muscles, guided intraoperative by hand held Doppler. We relocalized the perforators sites and ensured their integrity during dissection; usually we needed to skeletonized the perforators to ensure additional length of flap rotation. Following the flap's complete mobilization. The flap was rotated to cover the breast gap following tumor resection.

We selected the perforators that were closest to the defect. The perforator was meticulously dissected to ensure that the entire flap was inserted into the breast without any tension or deformation of the pedicle. No aggressive isolation or dissection of the perforators is needed if the flap attains sufficient mobility. Other perforators were sometimes sacrificed, especially if they were not related to the defect.

The skin that overlies the excised flap was de-epithelized and its vascularity was ensured. If the skin overlying was removed with the tumor, then a skin paddle would be marked and designed to match the defect size and the remaining flap would be de-epithelized. The entire flap was placed into the breast defect, and its edge was secured to the pectoral fascia using 2/0 Vicryl sutures. Typically, only one surgical drain was left in the breast area. The lower edge of the incision was then elevated and attached to the chest wall with interrupted 2/0 PDS sutures, while the IMF was marked to prevent downward scar migration and distortion. The incision was then closed in layers (Figure 1).

TDAP Flap

After standing with their arms at their sides and their palms rested on their midsection, the patient proceeded to construct the flaps. After asking each patient to actively tense their back muscles, a cutaneous trace was used to outline the Latissimus dorsi muscle contraction leading edge. A point 8 centimeters below the axillary crease was identified using this trace. The proximal perforator branch of the descending thoracodorsal artery penetrates the muscle at a location that is 8 centimeters or more from the axillary fold. The descending branch of the proximal perforator artery is located about 2 centimeters laterally from this trace. The muscle might not be penetrated by this direct cutaneous branch; but it might pass immediately anterior to the muscle's lateral border. Consequently, to guarantee this branch's position in the elevated flap, the flap's design must transcend the muscle's edge. The flap's breadth was determined by the potential for site closure of direct donor. The planned width was determined by pinching the skin and underlying subcutaneous tissue.

The perforators' location was identified through preoperative Doppler ultrasonography and subsequently verified intraoperatively with a hand-held Doppler. The latissimus dorsi fascia was examined and lifted from the distal end towards the proximal end. Meticulous observation of the perforator arteries was monitored by the hemorrhage quality which was continuously and progressively controlled from the end portion of the flap and by continuous reassessment of the perforator sites and status using intra operative handheld Doppler. The flap's blood supply was evaluated when it was halfway detached from the dorsal muscle to confirm that the perforator was sufficient (with a diameter greater than 0.5 mm) and that the perfusion was optimal. Conversely, if a substantial reduction in perfusion was observed following the section of the intercostal perforators and the partial elevation of the flap, we elected to postpone the procedure.

Identifying the lateral edge of the muscle was necessary because the descending branch of the thoracodorsal artery runs parallel to it, within 2 to 4 centimeters. Consequently, the proximal perforator was located at a similar distance from this edge. This level was located at the margin of the muscle in cases involving a direct cutaneous branch. An accompanying vein was also present in the proximal perforator artery. After the artery was identified, we conducted a thorough dissection of the epidermis surrounding the island. In order to free the muscle and allow the flap to spin along this axis, the minimal dissection around the perforating artery forms the "flap helix" (propeller).

LICAP Flap

The choice of flap was guided by factors such as breast size, defect location and size after tumor removal, and individual patient needs. Prior to surgery, patients were marked in both standing and lying positions. For effective reconstruction, accurate assessment of the tumor and resection area was essential. A pinch test was used to evaluate excess skin in the axilla and back. LTAP were located with a preoperative color Doppler ultrasound while the patient was in both supine and



Figure 1. Preoperative marking for AICAP flap for 41 years old female patient, upfront surgery for 4*3 cm mass occupying lower outer surface of rt breast with scattered microcalcification

AICAP: Anterior intercostal artery perforator

sitting positions. To ensure effective closure and accommodate the defect size, the flap was designed to include one or more perforators, with its width tailored to the defect and the need for discreet closure along the bra line. Patients were intubated and placed supine with both arms abducted. Harvesting of the LICAP flap was performed either in the supine or lateral position, starting from the distal tip. An incision was made at the superior edge of the skin using a #15 blade, and dissection proceeded to the chest wall. The lateral border of the latissimus was identified, and dissection continued above the muscle fascia from lateral to medial, followed by incision of the inferior edge of the skin. The fascio-cutaneous flaps were then carefully elevated off the chest wall in the suprafascial plane towards the anterior axillary line. Preservation of the 5th and 6th intercostal artery perforators, which are located within 6–8 cm of the anterior axillary line, was confirmed using an intraoperative handheld Doppler. After rotating the flap and verifying bright red bleeding from the edges, it was placed into the breast pocket and secured to the anterior chest wall with interrupted 3–0 Vicryl sutures. The flap was fully de-epithelialized, and both the breast and skin incisions were closed with interrupted dermal sutures and a running subcuticular stitch. To minimize the risk of re-excision, intraoperative frozen section analysis was performed. If needed, a tube drain was placed into the breast cavity to prevent seroma formation.

All patients were discharged on the first postoperative day, provided that no early complications, such as hematoma or skin flap necrosis were detected. Discharge instructions were explained to each patient and follow-up schedule for all patients was to review the patient through our multidisciplinary team. Any complications including wound dehiscence, infected hematoma, adherent scar or any distortion to the breast shape or major asymmetry or any postponement to the start of adjuvant radiation therapy, together with donor site complications were documented. The cosmetic results were evaluated by having the patient rate the surgery outcome in terms of breast symmetry, scarring, and overall satisfaction using the Harvard 4-point Likert scale, which includes the categories poor, fair, good, and excellent (11).

Five criteria were used for surgical assessment including breast symmetry, defects in breast tissue, position and deformity in NAC, scarring, and retraction. The drains were removed postoperatively when discharging less than 50 cc/24 hours. Patients were evaluated for the presence of postoperative complications in the outpatient clinic at one- and two-weeks post-surgery and adjuvant therapy was planned according to the multidisciplinary team decision (Figure 2).



Figure 2. Preoperative marking for LICAP flap for upper outer quadrant multifocal breast mass

LICAP: Lateral intercostal artery perforator

Patient self-evaluation: Aesthetic status of patient related outcome PROM (breast Q) questionnaire was completed by all patients, after informed discussion and understanding of the following items. The final score was converted to a score out of 100 using the equivalent Rash transformed score table. The objective aesthetic assessment was conducted using frontal 2D digital photos that were captured by a single photographer using a 64-megapixel digital camera. The single light source was positioned at equal distances from both breasts, and a light-colored non-reflective background was used to prevent the use of flash and asymmetric illumination. The Conservative Treatment of Breast Cancer (BCCT) core software® was employed in a semi-automated way, which used for assessment of the aesthetic outcome and it is a good and reliable tool to measure objective asymmetries, and was also complemented by physicians' assessment and patients' self-assessment (12).

Outcomes

The study outcomes included evaluation the cosmetic outcome using three fasciocutaneous flaps, the LICAP, AICAP and TDAP flap as a method for volume replacement in patients who underwent breast cancer surgery. All enrolled patients were subjected to the following different assessment methods in the outpatient clinic after 2–3 months postoperative before starting radiotherapy. The secondary outcomes included were: Handheld Doppler advantages in detection of perforators location and for follow-up; comparing the accuracy of the preoperative radiological perforator mapping with the intraoperative findings; and expanding the volume of choices for the volume replacement options and to avoid the morbidities that occur secondary to use of myocutanous flaps for volume replacement (Figures 3-5).

Statistical Analysis

Statistical analysis was performed with SPSS version 26 (IBM Inc., Armonk, NY, USA). To compare quantitative variables between the three treatment groups, we used pairwise comparison with the ANOVA (F) test, reporting results as means and standard deviations. For qualitative variables, the chi-square test was employed, with results expressed as frequencies and percentages (%). A two-tailed p value <0.05 was deemed to indicate "statistical significance".



Figure 3. Postoperative results of AICAP flap with good cosmetic outcome and symmetry

AICAP: Anterior intercostal artery perforator

Results

Out of the 59 patients initially assessed for eligibility in this study, 18 did not fulfill the inclusion criteria, and 11 declined to participate. The remaining 30 patients were randomly assigned to three groups, each consisting of ten patients. Statistical analysis and follow-up were carried out for all patients who were allocated to the study groups (Figure 1).

The baseline characteristics and comorbidities of the analyzed groups, such as weight, age, height, and body mass index (BMI), as well as associated conditions such as hypertension and diabetes mellitus, were not different (Table 1). Table 2 shows that the cup size, tumor size, TNM staging (T/N), pathological findings, luminal classification, and ptosis degree were insignificantly different among the studied groups. Regarding the tumor location, all patients in LICAP group had tumors in the LOQ, in AICAP group; 5 (50%) patients had tumor in the UOQ, and 5 (50%) patients had tumor in the LIQ, an all patients in TDAP group had tumor in the UOQ.

For outcomes, 1 (10%) patient in LIICAP group, 3 (30%) patients in AICAP group and 2 (20%) patients in TDAP group received neoadjuvant chemotherapy, with no significant difference within the groups that were examined. The operative time was insignificantly different between the studied groups. The operative time was calculated starting from skin incision to skin closure including the time of waiting for the frozen section result (Table 3).

Table 4 shows that regarding postoperative complications, wound infection took place in only one (10%) patient in LICAP group and one (10%) patient in the AICAP group; seroma occurred in only one (10%) patient in LICAP group and one (10%) patient in the TDAP group; and fat necrosis occurred in only one (10%) patient in the TDAP group. Incidence of wound infection, seroma, and fat necrosis was insignificantly different among the studied groups. Breast distortion occurred in one (10%) patient in the AICAP group and not observed in the other groups, and partial flap necrosis occurred in one (10%) patient in the LICAP group and one (10%) patient in the AICAP group and was not observed in the TDAP group. Incidence of distortion and partial flap necrosis were insignificantly different between the studied groups.

The BCCT core results, surgeon's assessment, patient's satisfaction and breast Q scores did not differ between the three groups (Table 5 and Figure 2).

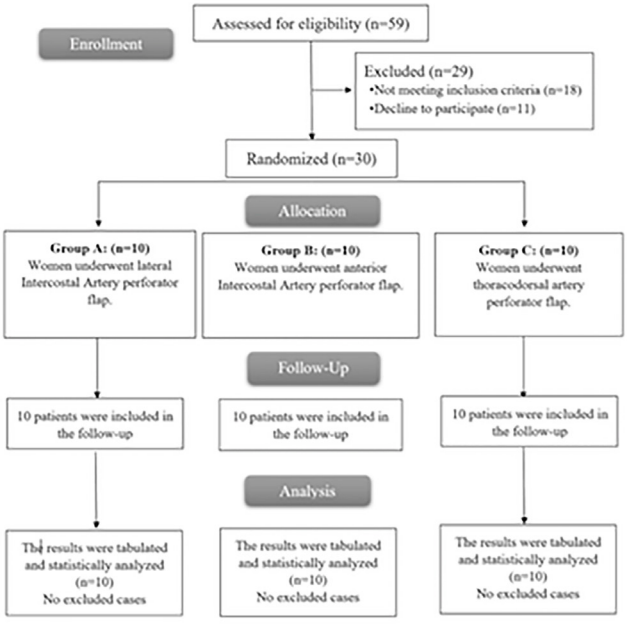


Figure 4. CONSORT flowchart of the enrolled patients



Figure 5. (A): Female patient 46 years old with grade 2 breast ptosis presented with luminal A RT breast UOQ cT2 N0 invasive duct carcinoma with extensive microcalcifications occupying the whole UOQ reaching the retro areolar area. She underwent a very wide local excision with negative margins and immediate reconstruction using a LICAP flap with good cosmetic outcome, (B): Female patient 52 years old female with grade 3 breast ptosis presented with cT3 N0 TNBC RT UOQ invasive duct carcinoma, with extensive microcalcifications affecting the whole outer half of the breast parenchyma, underwent neo adjuvant chemotherapy followed by upper outer and lower outer quadrantectomy with immediate reconstruction using advancement pedicled TDAP flap with poor cosmetic outcome with major breast distortion and asymmetry most probably due to marked breast ptosis with short pedicle arc of rotation, (C): Female patient 37 years old with grade 1 breast ptosis, presented with cT2 N0 RT 6 o'clock luminal A invasive breast carcinoma with close proximity to the overlying skin, underwent upfront wide local excision with immediate reconstruction using AICAP flap with excellent cosmetic outcome, (D): Female patient 65 years old with grade 3 breast ptosis underwent LICAP flap immediate reconstruction with excellent cosmetic outcome, (E): The scar at the donor site after a LICAP flap

UOQ: Upper outer quadrant; LICAP: Lateral intercostal artery perforator; TDAP: Thoracodorsal artery perforator; TNBC: Triple negative; AICAP: Anterior intercostal artery perforator

Table 1. Demographic characteristics and comorbidities among the studied group

	LICAP (*n* = 10) Mean ± SD	AICAP (*n* = 10)	TDAP (*n* = 10)	*p* value
Age (years)	43.8±5.2	39.2±9.57	44.8±6.88	0.218
Weight (kg)	79.7±8.65	81.1±5.84	78.7±6.09	0.744
Height (m)	1.68±0.01	1.66±0.05	1.64±0.07	0.221
BMI (kg/m²)	28.1±3.18	29.5±2.91	29.2±2.8	0.530
HTN	3 (30%)	1 (10%)	5 (50%)	0.149
DM	2 (20%)	3 (30%)	4 (40%)	0.621

Data presented as number (%) or mean ± SD. DM: Diabetes mellitus; BMI: Body mass index; HTN: Hypertension; AICAP: Anterior intercostal artery perforator; LICAP: Lateral intercostal artery perforator; TDAP: Thoracodorsal artery perforator; SD: Standard deviation

Table 2. Pre-operative assessment in the three studied group

		LICAP (*n* = 10)	AICAP (*n* = 10)	TDAP (*n* = 10)	*p* value
Cup size	**B**	6 (60%)	2 (20%)	4 (40%)	0.189
	C	4 (40%)	8 (80%)	6 (60%)	
Tumor size (cm)		2.7±0.63	2.4±0.28	2.7±1.35	0.676
TNM staging					
T1		3 (30%)	4 (40%)	3 (30%)	0.861
T2		7 (70%)	6 (60%)	7 (70%)	
N0		2 (20%)	3 (30%)	4 (40%)	0.621
N1		8 (80%)	7 (70%)	6 (60%)	
Tumor location					
LOQ		10 (100%)	0 (0%)	0 (0%)	-
UOQ		0 (0%)	5 (50%)	10 (100%)	-
LIQ		0 (0%)	5 (50%)	0 (0%)	-
Pathology of tumor					
DCIS		0 (0%)	2 (20%)	1 (10%)	0.338
IDC		10 (100%)	7 (70%)	9 (90%)	
ILC		0 (0%)	1 (10%)	0 (0%)	
Luminal classification					
Luminal A		5 (50%)	6 (60%)	4 (40%)	0.974
Luminal B1		1 (10%)	2 (20%)	2 (20%)	
Luminal B2		1 (10%)	1 (10%)	1 (10%)	
TNBC		1 (10%)	0	1 (10%)	
HER2/neu enriched		1 (10%)	1 (10%)	2 (20%)	
Ptosis degree		5.5±2.8	6.4±0.97	4.3±2.67	0.142

Data presented as number (%) or mean ± SD *: statistically significant as *p* value <0.05, LOQ: Lower outer quadrant; UOQ: Upper outer quadrant; LIQ: Lower internal quadrant; DCIS: Ductal carcinoma *in situ;* IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; TNBC: Triple negative; AICAP: Anterior intercostal artery perforator; TDAP: Thoracodorsal artery perforator; LIICAP: Lateral intercostal artery perforator; SD: Standard deviation; HER2: Human epidermal growth factor receptor 2

Table 3. Outcome and operative time among studied groups

	LICAP (*n* = 10)	AICAP (*n* = 10)	TDAP (*n* = 10)	*p* value
Neoadjuvant chemotherapy	1 (10%)	3 (30%)	2 (20%)	0.535
Operative time (min)	134.4±11.8	133.1±11.5	131.4±11.5	0.846

Data presented as number (%) or mean ± SD *: Statistically significant as *p* value <0.05; SD: Standard deviation

Table 4. Postoperative complications and incidence of distortion among studied groups

	LICAP (*n* = 10)	AICAP (*n* = 10)	TDAP (*n* = 10)	*p* value
Wound infection	1 (10%)	1 (10%)	0 (0%)	0.585
Seroma	1 (10%)	0 (0%)	1 (10%)	0.585
Fat necrosis	0 (0%)	0 (0%)	1 (10%)	0.355
Incidence of distortion				
Distortion	0 (0%)	1 (10%)	0 (0%)	0.355
Partial flap necrosis	1 (10%)	1 (10%)	0 (0%)	0.585

Data presented as number (%), *: Statistically significant as *p* value <0.05; AICAP: Anterior intercostal artery perforator; LIICAP: Lateral intercostal artery perforator; TDAP: Thoracodorsal artery perforator

Table 5. BCCT core, surgeon assessment and patient satisfaction among studied groups

	LICAP (*n* = 10)	AICAP (*n* = 10)	TDAP (*n* = 10)	*p* value
BCCT core				
Excellent	4 (40%)	3 (30%)	4 (40%)	
Good	5 (50%)	3 (30%)	3 (30%)	0.608
Fair	1 (10%)	3 (30%)	1 (10%)	
Poor	0 (0%)	1 (10%)	2 (20%)	
Surgeon assessment				
Excellent	8 (80%)	8 (80%)	7 (70%)	0.830
Good	2 (20%)	2 (20%)	3 (30%)	
Patient satisfaction				
Excellent	8 (80%)	9 (90%)	8 (80%)	0.786
Good	2 (20%)	1 (10%)	2 (20%)	
Breast Q score	83.1±7.13	85.4±9.14	82.5±9.16	0.727

Data presented as mean ± SD or number (%); TDAP: Thoracodorsal artery perforator; AICAP: Anterior intercostal artery perforator; LIICAP: Lateral intercostal artery perforator; SD: Standard deviation

Discussion and Conclusion

BCS has become the standard approach for managing early-stage breast cancer, aiming to achieve oncologic safety while preserving breast aesthetics. However, excision of tumors in the lower and lateral breast quadrants often results in significant volume deficits, leading to contour deformities and asymmetry (13).

Immediate oncoplastic reconstruction plays an important role in addressing these concerns by restoring breast shape and maintaining cosmetic outcomes. Perforator fasciocutaneous flaps have emerged as reliable options for immediate breast reconstruction following BCS. These flaps provide well-vascularized tissue with minimal donor site morbidity while preserving muscle integrity (14). This study aimed to evaluate the cosmetic outcome and the oncological safety of three techniques (AICAP, LICAP, and TDAP flaps) as a volume replacement technique to eliminate deformity and preserve breast cosmesis by filling the excised defect.

The baseline characteristics and comorbidities of the three analyzed groups, did not differ. Similarly, Hashem et al. (14) who also compared LICAP and TDAP flaps in reconstructing partial breast defects found no statistically significant difference between studied groups regarding age and BMI as well as the prevalence of comorbidities. Awin et al. (15) evaluated the use of ICAP flaps versus LTAP flaps in partial breast reconstruction. These authors reported that the average age was 40.60±8.62 versus 43.07±8.01 years, and the average BMI was

32.19±6.80 versus 33.74±4.60 kg/m^2 for the ICAPs versus LTAP groups, respectively and again these demographics and the prevalence of comorbidities did not differ between the two study groups.

Regarding pre-operative assessment, the cup size, tumor size, TNM staging, pathological findings, luminal classification, and ptosis degree were insignificantly different among the studied groups.

Our results are consistent with Awin et al. (15) who reported that most of the tumors were located in the UOQ in both the ICAP and LTAP groups in their study. However, lesions in the LOQ were present exclusively in the ICAP group, while lesions in the UIQ were present exclusively in the LTAP group, without statistically significant difference.

In terms of tumor characteristics in the present study, there was no statistically significant difference between AICAP and LICAP groups as regard tumor sizes and TNM staging. Similarly, the study by Hashem et al. (14) demonstrated that there was no significant difference between studied groups in terms of TNM staging and tumour size. Zeeshan et al. (8) reported that eight patients underwent a LICAP flap for LOQ tumors (n = 5) and UOQ tumors (n = 3) cases, seven AICAP flaps were done, all for LIQ tumors and 10 LTAP flaps were performed for seven tumors in the UOQ and three tumors at 12 o'clock locations.

Furthermore, Agrawal et al. (16) reported that the LTAP flap was used in 23 patients (57.5%), AICAP in 4 patients (10%), and LICAP in 2 patients (5%), while 11 patients (27.5%) received a combination of LTAP and LICAP. AICAP was used for medial quadrant defects (4/40), whereas lateral quadrant defects (33/40) were reconstructed with LICAP, LTAP, or both.

The operative time was insignificantly different between the three studied groups in the present study. The mean operative time (min) was 134.4±11.8, 133.1±11.5, and 131.4±11.5 in LICAP, AICAP, and TDAP groups respectively. Our operative time results are in concordance with Hashem et al. (14) who demonstrated that there was no significant difference between TDAP and LICAP groups as regard operative time. Mohsen et al. (17) who evaluated the utility of AICAP in immediate reconstruction following BCS in 20 patients with small to medium-sized breasts. The mean operative time of the procedure was 130 minutes and ranged between 122–148 minutes, while the mean reconstruction time was 35 minutes and ranged from 22–40 minutes.

In contrast, Hamdi et al. (9) assessed the versatility of ICAP flaps. There were two DICAP flaps, two AICAP flaps and 16 LICAP flaps. All but two flaps were based on one perforator. Bilateral breast augmentation with LICAP flap necessitated longer operative time of two to three hours (120–180 minutes) depending whether it was combined with or without mastopexy.

All postoperative complications (wound infection, seroma and fat necrosis) affected only one patient (10%) in each group, if they occurred at all. The incidence of wound infection, seroma, or fat necrosis was insignificantly different among the studied groups. Distortion occurred in one (10%) patient in the AICAP group and was not observed in the other groups, and partial flap necrosis occurred in 1 (10%) patient in LICAP group and 1 (10%) patient in AICAP group and was not observed in TDAP group. Incidence of distortion and partial flap necrosis were insignificantly different among the studied groups. Hashem et al. (14) reported that complications occurred in 8 (17.4%) in the TDAP group while the complication rate was 11% in the LICAP group. There was no statistically significant difference between TDAP and LICAP groups as regard postoperative complications including wound infection, hematoma, seroma and fat necrosis. However, Mohsen et al. (17) reported that the postoperative complications were observed in only one patient (5%) in the form of mild wound infection.

Furthermore, Awin et al. (15) also reported that complications were infrequent, with seroma and wound dehiscence each occurring in five cases across both groups, showing no significant difference. Traumatic fat necrosis was observed in four cases, while flap retraction, partial flap necrosis, and hematoma each occurred in one patient.

In the present study, the secondary outcomes BCCT core results, surgeon's assessment, patient's satisfaction and breast Q score did not differ between the studied groups. This is in agreement with Zeeshan et al. (8) who reported that median postoperative patient satisfaction was 100 (41). They found high satisfaction with breasts and comparable physical well-being among Pakistani women after LPF in oncoplastic breast-conserving surgeries. Hashem et al. (14) demonstrated that cosmetic outcome in the TDAP group as evaluated by the BCCT core software showed 11% (5 cases) to have excellent, 59% (27) good, 28% (13) fair and 2% (1) with poor result. The LICAP group on the other hand had 22% excellent (8 cases), 51% (19) good and 27% (10) fair cosmetic result, although these BCCT ratings did not differ between the TDAP and LICAP groups in their study. Carrasco-López et al. (18) reported that the AICAP technique did not appear to negatively affect patient satisfaction with treatment outcomes. They used the breast Q scores which is a patient-reported outcome measure (PROM) designed specifically to measure patient satisfaction and quality of life in breast cancer patients, and has been widely adopted worldwide as the gold-standard PROM following breast surgery. The scales used in their study were satisfaction with breast that addresses issues such as satisfaction with breast shape, symmetry, feel to the touch, and appearance clothed or unclothed; satisfaction outcomes: Feelings about the breast; psychosocial well-being; sexual well-being that addresses the impact of a woman's breast condition and surgery on her sex life; and physical well-being on how often women experience pain or discomfort in the breast area and upper body. A Q score was obtained for all most the domains and converted to a 0–100 scale. They found that the mean BREAST-Q scores changes were 0 in satisfaction with the breast, 5 in satisfaction with outcome, 0 in psychosocial well-being, 6.15 in sexual well-being, and 34.69 in physical well-being. Awin et al. (15) also reported that most of the cases were very satisfied in (n = 19, 95.0%) versus (n = 12, 85.7%) for the ICAP versus the LTAP flaps respectively, again with no significant difference between the groups (p = 0.455).

Study Limitations

The main limitations of the present study were the small group sizes and the difference between the preoperative duplex marking of the perforators and the intraoperative findings though the perforators have almost fixed sites. Further multicenter studies with larger cohorts and longer follow-up are needed to validate the findings.

The perforator fasciocutaneous flaps, LICAP, AICAP, and TDAP, were effective and safe options for immediate breast reconstruction after BCS. All three techniques showed similar surgical outcomes, low complication rates, and good aesthetic results. Patient satisfaction was high, with no significant differences between the groups. Further

studies with larger sample sizes and longer follow-up are needed to confirm these findings and improve patient selection.

Ethics

Ethics Committee Approval: The study was conducted from October 2023 to March 2024 and received approval from the Research Ethics Committee of the Faculty of Medicine, Cairo University, approval code MS-500-2023, date 04.04.2024.

Informed Consent: Patients gave their informed consent before taking part in the study.

Footnotes

Authorship Contributions

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

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

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Case Report

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Breast Lymphedema Secondary to Lymph Node Tuberculosis: Case Report

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ABSTRACT

Breast lymphedema is a common but underdiagnosed condition that affects the quality of life of patients. It may be caused by any pathology that disrupts lymphatic drainage in the breast. We present the case of a woman with axillary lymph node tuberculous infection with breast edema, clinically and radiographically indistinguishable from tuberculous mastitis. After six months of comprehensive antituberculosis pharmacological treatment, the persistence of breast edema required repeating diagnostic tests searching for malignancy, all of which were negative. Rehabilitation treatment with complex physical therapy improved the patient's clinical and symptomatic condition. Clinical suspicion of secondary lymphedema is crucial to avoid unnecessary diagnostic procedures and ensure adequate and timely treatment.

Keywords: Lymphedema; breast disease; tuberculosis; mastitis; extrapulmonary tuberculosis

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Key Points

- Breast lymphedema may occur due to any cause that affects the lymphatic drainage of the breast.
- The differential diagnosis should include disseminated breast tuberculosis.
- Breast lymphedema rehabilitation treatment improves patients' symptoms and quality of life.

Introduction

Breast lymphedema is a common but underdiagnosed condition. It may occur due to any cause affecting the drainage of the breast's lymphatic system and it is more common after breast cancer surgery and radiotherapy. There is no clear definition for this condition, and its diagnosis is not well established. The main symptoms are breast enlargement, orange-peel skin, and heaviness or pain, and they can be confused with other conditions affecting the breast, such as mastitis or inflammatory carcinoma (1).

We present a clinical case of tuberculous lymph node infection presenting with breast edema, clinically and radiographically indistinguishable from tuberculous mastitis.

Case Presentation

A 69-year-old woman, with no significant medical history, attended the Emergency Department with a painful mass in her right axilla for one week, evening fever, weight loss of approximately six kilograms, fatigue, and night sweats. Examination revealed a 12 cm mass in the right axilla with blurred borders and tenderness. The breast was also significantly edematous without erythema.

Blood tests showed mild microcytosis, elevated acute-phase reactants, a positive quantiFERON-TB, and negative serologies for hepatitis B virus, hepatitis C virus and human immunodeficiency virus.

A body computed tomography scan revealed bilateral clavicular and axillary lymphadenopathy, predominantly on the right side, with a pathological appearance, along with skin thickening of the right breast and no lung lesions.

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Ultrasonography and mammography (Figure 1) showed a slightly heterogeneous breast pattern, with diffuse increased breast and right axillary density, skin thickening, and multiple bilateral pathological axillary lymphadenopathy, measuring 4–5 cm. No signs suggesting malignancy were observed.

Axillary lymph node biopsy was reported as non-suppurative granulomatous lymphadenitis of infectious origin. Zhiel-Nelsen test for mycobacteria was negative, but the DNA of *Mycobacterium tuberculosis* was detected.

With the initial diagnosis of lymph node tuberculosis and tuberculous mastitis, specific treatment with four medicines was prescribed, according to guidelines. Six months later, the ultrasound revealed a size decrease and cortical thickening of the axillary lymph nodes. However, a severe increase in volume persisted in the right breast on the magnetic resonance imaging (Figure 2). A skin punch and breast biopsy ruled out histological findings of tuberculous involvement or malignancy.

The patient was referred to the Physical Medicine and Rehabilitation Department, where breast edema with orange peel skin, generalized pastiness, mainly in the lower quadrants, and a feeling of heaviness were observed. Clinical and ultrasound-based findings were consistent with breast lymphedema. Fifteen sessions of manual lymphatic drainage, exercises, skin care, and kinesiology tape were prescribed, adding compression with a bra and a partial breast prosthesis. Six weeks after starting treatment, there was a significant clinical improvement, although ultrasound revealed persistent free fluid in the lower outer quadrant (Figure 3). Compression was maintained 23 hours a day, and the treatment described above was followed, with progressive improvement (Figure 4). After six months, the breast volume was normal, the discomfort disappeared, and the patient was very satisfied, so the compression was gradually discontinued without further incidents. Informed consent was obtained from the patient for the publication of this case.



Figure 1. Mammography of the right breast with axillary adenopathy and skin thickening, without suspicious lesions in the breast parenchyma

Discussion and Conclusion

There is no clear definition of breast lymphedema in the literature, and the diagnostic methods commonly used for extremity lymphedema, such as volumetry or lymphoscintigraphy, are not applicable. The use of ultrasound when investigating lymphedema has gained relevance in recent years, although there are no standardized criteria to date. The most common findings include increased dermal thickness, hyperechogenicity of the subcutaneous tissue, and the presence of fluid in the dermis, interlobular space, and superficial fascia (2, 3).

The differential diagnosis of breast lymphedema should include inflammatory breast carcinoma, fibroadenoma, chronic abscess caused by another microorganism, sarcoidosis, granulomatous mastitis, plasma cell mastitis, or fat necrosis.

Tuberculous involvement accounts for 0.1% of all breast lesions in developed countries. Its most common clinical presentation is a painless mass usually located in the upper outer quadrant, and less frequently, edema, localized abscess, or bilateral mastitis (4).

Tewari and Shukla (5) divided breast tuberculosis into three types: nodular caseous tuberculous mastitis, disseminated tuberculous mastitis, and tuberculous breast abscesses. Longman et al. (6) described the radiological findings of each one. The disseminated form presents as an ill-defined textural change within the parenchyma and multiple small collections of anechoic fluid scattered in one or more quadrants, findings very similar to breast lymphedema.

In the clinical case presented herein, due to a positive lymph node biopsy for tuberculosis, the breast was not initially biopsied, mistaking breast lymphedema for disseminated mastitis. This led to repeated exclusion of malignancy and delayed an optimal treatment.

Breast lymphedema causes discomfort, pain, alterations in body image, and affects self-esteem, impacting the quality of life of the patients (7). Rehabilitative treatment with decongestive physical therapy, which includes skin care, manual lymphatic drainage, compression,

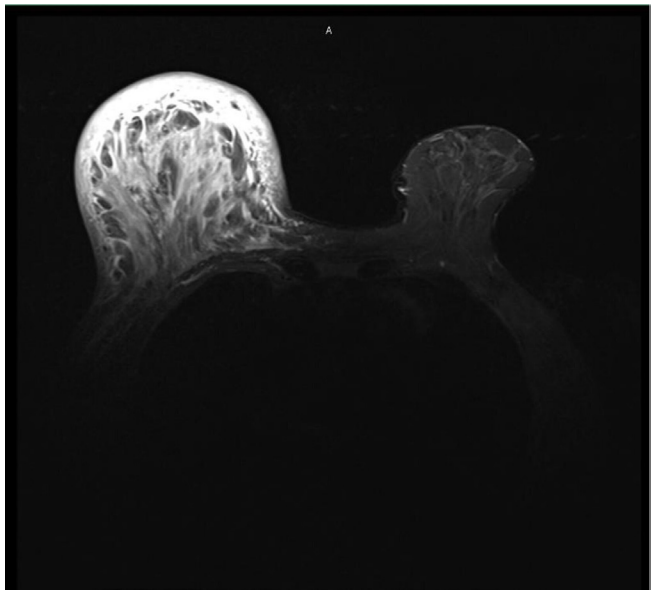


Figure 2. Breast magnetic resonance imaging showed asymmetrical breast size, the right breast was larger than the left one and displayed a diffuse homogeneous parenchymal enhancement with diffuse trabecular and skin edema, no suspicious mass

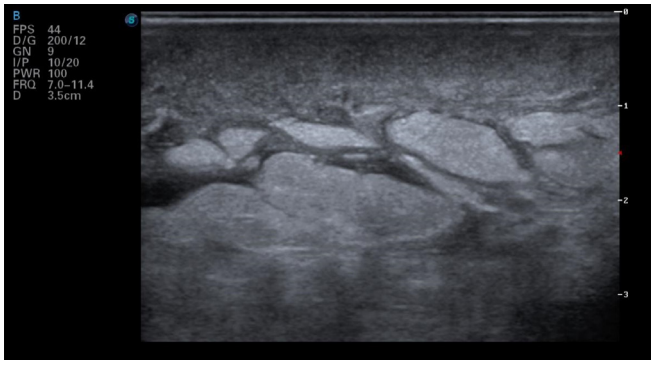


Figure 3. Ultrasound image showing persistence of hypoechoic lines of free fluid in subcutaneous cellular tissue of the lower external quadrant of the right breast



Figure 4. Mild right breast edema three months after rehabilitation treatment. Note the marks on the skin of the ribbed partial prosthesis used for breast compression

and exercises, is effective (8). Breast compression with bandages is difficult and uncomfortable, so some authors recommend the use of kinesiotape (9) and a compression bra with wide straps, few seams, and a cup that contains the entire breast. Additional use of silicone partial prostheses, although not standardized, may contribute to improved compression.

An early and accurate diagnosis of the origin of breast edema is required to determine the most appropriate treatment, especially given the multitude of potential etiologies.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case.

Footnotes

Authorship Contributions

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

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Case Report

Eur J Breast Health 2025; 21(3): 277-280
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Leiomyosarcoma of the Breast: Case Report and Review of the Literature

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ABSTRACT

Primary breast leiomyosarcoma is an extremely rare malignancy, accounting for approximately 1% of breast tumors and less than 5% of soft tissue sarcomas. Due to its rarity, standardized treatment guidelines remain unclear. We report the case of a 38-year-old woman who presented with a 3 cm, freely mobile breast nodule, initially classified as American College of Radiology Breast Imaging Reporting and Data System 4 on imaging. Core needle biopsy confirmed primary breast leiomyosarcoma, with histopathological and immunohistochemical analysis revealing strong positivity for α-smooth muscle actin, desmin, and H-caldesmon, consistent with smooth muscle differentiation. Epithelial, neural, and vascular markers were negative, ruling out differential diagnoses. The Ki-67 index was 15%, indicating moderate proliferative activity. Staging classified the tumor as T2N0M0 (Stage IIA, the American Joint Committee on Cancer 8th edition), and the patient underwent radical mastectomy with sentinel lymph node exploration, followed by adjuvant radiotherapy. Despite the aggressive nature of leiomyosarcomas, this case exhibited favorable prognostic factors, including small tumor size, intermediate grade, negative margins, and no lymphatic spread, suggesting a less aggressive course. After four years of follow-up, the patient remains free of complications, underscoring the importance of long-term monitoring and the need for further research to refine therapeutic approaches.

Keywords: Breast cancer subtypes; immunohistochemistry; leiomyosarcoma; mastectomy; rare tumors

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Key Points

- Primary sarcomas can affect any organ but their occurrence in the breast remains exceptional. Only a few isolated cases have been reported in the literature.
- Given the clinical and epidemiological diversity and rarity of this subtype of cancer, its positive diagnosis is based on anatomopathological examination where immunohistochemistry is often used.
- The treatment follows the same rules as those used in the treatment of soft tissue sarcomas.

Introduction

Primary breast sarcoma (PBS) is a rare and aggressive entity that fits into the nosological framework of non-epithelial tumors of the breast. They account for about 1% of breast tumors and less than 5% of all soft tissue sarcomas (1). Two groups can be distinguished: Phyllodes sarcomas, which are specific to the breast, and non-phyllodes sarcomas, such as leiomyosarcomas, which are ubiquitous but rarely, if ever, found in the breast (2).

These tumors are characterized by non-specific clinical manifestations that often mimic benign pathology, significant histological diversity, and a poor prognosis (3).

We report a case of primary breast leiomyosarcoma, discovered through self-palpation and treated surgically, followed by additional radiotherapy.

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

Case Report

A 38-year-old woman with no significant medical history or familial history of mastopathy presented with a right breast nodule. She is multiparous with two children and a history of breastfeeding. She has never used hormonal contraceptives.

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Clinical examination revealed a 3 cm nodule in the lower outer quadrant of the right breast, freely mobile with no overlying skin changes. The axillary fossa was unremarkable. A breast ultrasound, performed for better lesion characterization, revealed a mass suggestive of a phyllodes tumor classified as American College of Radiology Breast Imaging Reporting and Data System category 4 (ACR4). A breast ultrasound, performed for better lesion characterization, revealed a mass suggestive of a phyllodes tumor classified as ACR4, indicating a suspicious lesion.

A core needle biopsy established the diagnosis of primary breast leiomyosarcoma, confirmed through histopathological evaluation and immunohistochemical analysis. The tumor exhibited strong positivity for α- smooth muscle actin, desmin, and H-caldesmon, supporting its smooth muscle differentiation. In contrast, epithelial (Cytokeratin AE1/AE3, EMA), neural (S-100), and vascular markers (CD34, CD31) were negative, effectively excluding metaplastic carcinoma, malignant peripheral nerve sheath tumors, and angiosarcoma. The Ki-67 proliferation index was 15%, suggesting a moderate proliferative activity.

A thoracic-abdominal-pelvic CT scan and bone scintigraphy showed no evidence of metastatic spread.

The tumor was therefore classified as T2N0M0 (Stage IIA, the American Joint Committee on Cancer 8th edition), indicating a tumor size between 2–5 cm (T2) with no regional lymph node involvement (N0) and no distant metastasis (M0).

The patient then underwent radical surgery with axillary fossa exploration using the sentinel lymph node technique using patent blue dye.

Final pathology confirmed the initial biopsy diagnosis and revealed no lymph node involvement (Figures 1-5). Surgical margins were clear. Subsequently, to achieve better local disease control, the patient was offered additional radiotherapy without chemotherapy.

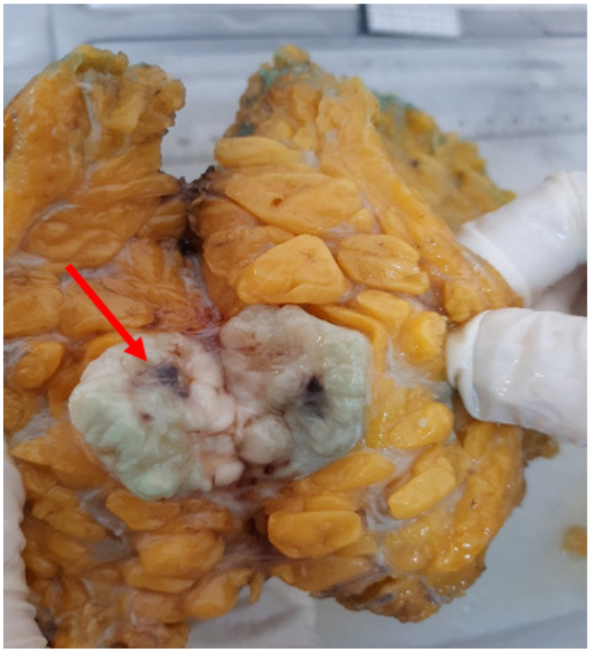


Figure 1. Macroscopic study of the mastectomy specimen with patent blue dye used for the exploration of the axillary fossa

After four years of follow-up, the patient remains free of local recurrence, distant metastasis, and treatment-related complications.

Discussion and Conclusion

A rare occurrence, primary sarcomas can develop in any organ, but their presence in the breast is exceptional, accounting for about 1% of breast tumors and less than 5% of all soft tissue sarcomas (1). A few isolated cases have been reported in the literature. A study by Amberger et al. (4), which compiled all documented cases, identified 68 cases between 1968 and 2017. This highlights the rarity of this pathology, complicating the study of its characteristics and the standardization of its management (Table 1).



Figure 2. Study of the specimen by a section through the nodule showing a 3 cm pearly white lesion (arrow) with healthy borders

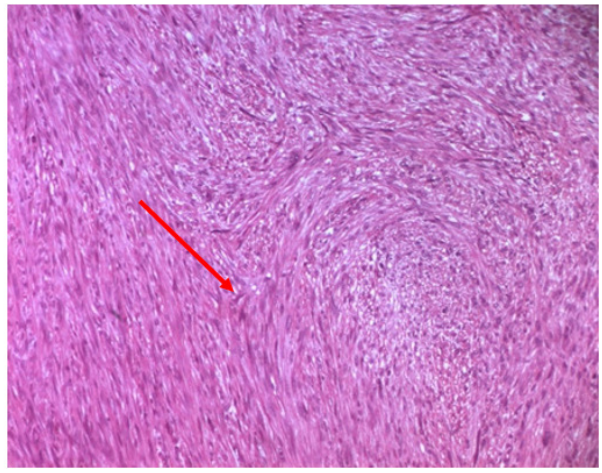


Figure 3. Microscopic study showing proliferation of elongated muscle fibers with round-ended nuclei with nuclear atypia of monstrosity type without epithelial proliferation (arrow) (hematoxylin and eosin stain ×40)

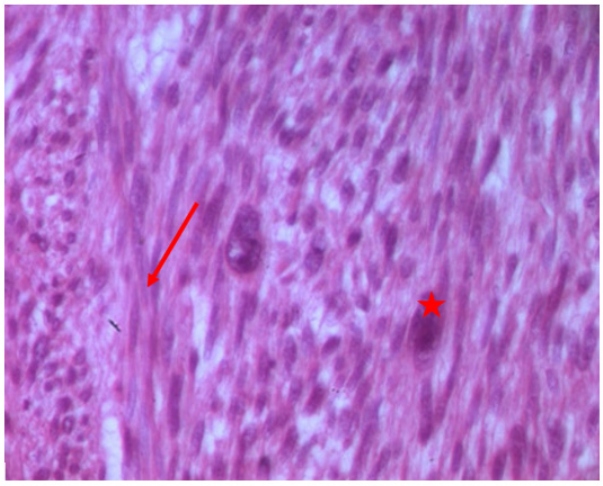


Figure 4. Microscopic study showing proliferation of elongated muscle fibers (arrow) with round-ended nuclei with nuclear atypia of monstrosity type without epithelial proliferation (asterisk) (hematoxylin and eosin stain ×400)

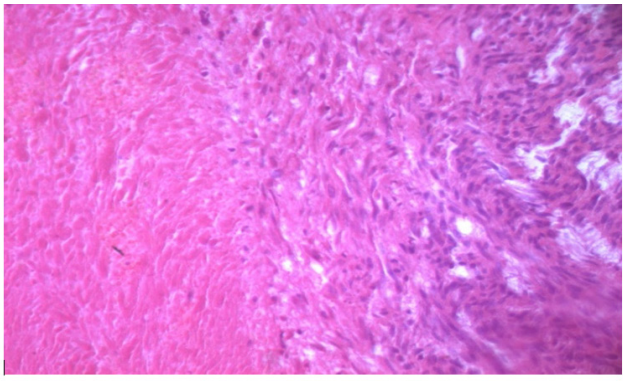


Figure 5. Microscopic study with hematoxylin and eosin stain ×100 showing a proliferation of muscle fibers with the presence of some mammary lobules in the middle of the lesion

Although primary sarcomas most commonly affect women during the first decade after menopause, cases in younger individuals have been reported, including at ages 20 Amberger et al. (4) and 24 Waterworth et al. (5). More recently, Masadah et al. (6) reported a 30-year-old female patient with a 12×8 cm breast leiomyosarcoma managed by wide local excision with 2 cm surgical margins, without the use of adjuvant therapy. At 8-month follow-up, there was no recurrence.

The most common reason for consultation is the detection of a large palpable mass, which may sometimes grow rapidly and be painful (7). At diagnosis, this is reflected in the mean size of the mass, which is 4 cm, with extremes ranging from 1.5 to 9 cm. These masses are typically well-circumscribed and mobile with respect to the pectoral muscle and the overlying skin (5). However, given the clinical and epidemiological diversity and rarity of this subtype of cancer, histopathological and immunohistochemical analysis remain the gold standard for diagnosis (8).

The treatment of primary breast leiomyosarcoma follows the same rules as those used in the treatment of soft tissue sarcomas. Surgical excision, either by breast-conserving surgery or mastectomy, is the cornerstone of treatment. While some studies suggest that wide local excision with negative margins may be sufficient, others advocate for mastectomy to minimize recurrence risk. Horton et al. (9) described a case of breast leiomyosarcoma treated successfully with lumpectomy and breast reduction surgery, with no recurrence at follow-up.

Since axillary lymph node metastases are not common in PBS, several authors do not recommend lymph node dissection as it does not affect prognosis and tends to increase the risk of morbidity from lymphedema.

Yet, because of the rarity of this disease and the limited number of studies to guide treatment decisions, the sentinel node technique is often performed to confirm the absence of lymph node involvement, as was the case in the presented patient (8).

Table 1. Summary of reported cases of primary breast leiomyosarcoma: Clinicopathological features, surgical approaches, and outcomes

Study	Years	Sex	Size (cm)	Approach	Margin width	Adjuvant radiotherapy	Adjuvant chemothrapy	Outcome	Follow-up
Masadah et al. (6) (2023)	30	Female	12*8	Wide local excision	2 cm	Not administered	Not administered	No recurrence	8 moths
Horton et al. (9) (2020)	61	Female	Not specified	Lumpectomy + breast reduction surgery	Not specified	Not administered	Not administered	No recurrence	Not specified
Amberger et al. (4) (2018)	44	Female	Rapidly increasing size	Chemotherapy followed by surgery	Not specified	Not specified	administred	Tumor progression	Metastases after 3 years
Waterworth et al. (5) (1992)	24	Female	Not specified	Mastectomy	Not specified	Not administred	Not administred	No recurrence	14 years
Zelek et al. (13) (2003)	37	Female	2.5	Wide local excision	Not specified	Not administred	Not administred	Tumor progression	Metastases after 20 years

The role of radiotherapy in the treatment of PBS remains controversial because of its rarity and the lack of randomized studies, but it is still the second most important therapeutic tool after surgery (10, 11). Zelek et al. (13) advocated an extrapolation of the principles of treatment of soft tissue sarcomas (12). Thus, they recommended adjuvant radiotherapy to improve the local control rate. However, the latter contributes to a better local control rate of breast sarcomas but does not improve the overall survival rate. In the absence of specific data for breast sarcoma, the indications for the use of adjuvant radiotherapy at this location should follow those of soft tissue sarcomas. Thus, the indications widely accepted in the literature are (10, 11):

-The high histological grade of the tumor

- A tumor diameter of more than 5 cm

- Clear surgical margins of less than 1 cm

- Conservative treatment

The role of adjuvant chemotherapy in the treatment of breast sarcoma is not currently well established. Indeed, a meta-analysis supported the role of adjuvant doxorubicin-based chemotherapy in improving the probability of recurrence-free survival, though without appreciable effect on overall survival (12). The role of adjuvant chemotherapy remains uncertain, with some studies suggesting a modest improvement in recurrence-free survival but no effect on overall survival (13). Chemotherapy is typically reserved for high-risk tumors (>5 cm, high histological grade, or metastatic disease) (14). The most commonly used agents are doxorubicin and ifosfamide (13, 15).

The occurrence of leiomyosarcoma metastases has been reported, most commonly involving the lungs, although cases of liver and brain metastases have been documented up to 20 years post-treatment (4). Masadah et al. (6) and Horton et al. (9) did not observe metastatic progression in their respective cases, reinforcing the notion that early-stage low-grade tumors may have a better prognosis.

In summary, despite the aggressive nature of leiomyosarcomas, the surgical management of this case followed established practices and proved effective, with a favorable clinical outcome**.** The presence of favorable prognostic factors-including tumor size <5 cm, intermediate grade, Ki-67 index of 15%, no lymphatic spread, and clear margins (>1 cm)-suggests a less aggressive progression**.** Given the rarity of this tumor, long-term follow-up and further studies remain crucial to optimize treatment strategies.

Ethics

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

Footnotes

Authorship Contributions

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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Letter to the Editor

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Optimizing Breast Imaging: Needs and Opportunities for Refugee Women in Italy and Low-Income Countries

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Dear Editor,

Mammographic screening is a key tool for early detection and improved survival in breast cancer. However, access to such screening remains inconsistent and far from a universal right. Refugee women, asylum seekers, and undocumented migrants are often excluded from national programs due to legal, bureaucratic, and cultural barriers. This exclusion leads to a higher risk of late-stage diagnosis and consequently increased morbidity and mortality (1, 2).

1. Refugee Populations: Clinical Invisibility and Systemic Barriers

Screening rates among refugee women in Europe, including Italy, are significantly low. The lack of formal documentation, limited health literacy, and widespread mistrust toward institutional healthcare systems are major obstacles. While the reported incidence of breast cancer in these populations appears low, this is often an artifact of underdiagnosis. In reality, cancer is frequently detected at an advanced stage, and mortality rates are higher due to the absence of structured and continuous care pathways.

2. Low-Income Countries: Symptomatic Focus and Accessible Technologies

In low-income settings, breast cancer incidence is traditionally lower (ranging between 40 and 80 cases per 100,000 women), yet mortality is disproportionately high, again due to late diagnosis and insufficient diagnostic infrastructure. In this context, systematic screening programs are rarely feasible and a more pragmatic approach centers on evaluating symptomatic cases. In this regard, mobile ultrasound systems combined with artificial intelligence and teleradiology offer a viable strategy to provide preliminary breast assessments in areas without radiologists on-site (3, 4).

3. High-Income Countries: Higher Incidence, Better Outcomes

In high-income nations, breast cancer incidence is higher (130–150 cases per 100,000 women) than in low-income countries, but survival has improved significantly thanks largely to early detection and timely treatment. This contrast highlights the critical role of access to prevention, diagnosis and treatment and the urgent need to adapt and simplify protocols to include women in marginalized conditions.

Toward an Integrated and Culturally Sensitive Vision

It is essential to recognize that access to breast diagnostics is not only a matter of technology or public health policy but also of social vulnerability. Refugee and displaced women often experience chronic trauma and gender-based violence, which can affect their willingness or psychological readiness to undergo breast examinations. A culturally aware approach that integrates education, symptom-based screening, mental health support, and accessible imaging technologies may help reduce inequities and promote more inclusive breast health care (5).

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.D.G., T.I., G.G.; Concept: G.D.G., T.I., G.G.; Design: G.D.G., T.I., G.G.; Data Collection or Processing: G.D.G., T.I., G.G.; Analysis or Interpretation: G.D.G., T.I., G.G.; Literature Search: G.D.G., T.I., G.G.; Writing: G.D.G., T.I., G.G.

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

Financial Disclosure: The authors declare that they received no financial support for this study.

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Letter to the Editor

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Aromatase Inhibitor-Related Lower Limb Tendinopathies: Ultrasound is on the Agenda

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Dear Editor,

A 60-year-old woman was seen for chronic bilateral ankle pain which had persisted for almost one year and gradually worsened in the last months. She also had bilateral knee pain, more prominent on the left side. She described that the pain was aggravated with movements and relieved at rest. She denied any trauma or other symptoms. Her past medical history was unremarkable except for breast cancer (mastectomy three years previously) after which she had been placed on aromatase inhibitor (AI) therapy (letrozole 2.5 mg/day). She did not benefit from non-steroidal anti-inflammatory drugs (NSAID), switching the AI or physical therapy.

Physical examination revealed tenderness in entheseal sites, including the bilateral tibial and calcaneal tuberosities. Ultrasound (US) examination revealed bilateral Achilles tendinitis (Figure 1A, 1B), bilateral patellar enthesopathy/tendinitis. Sono-palpation was also positive on bilateral Achilles tendons. Doppler activity was not detected. Serologic tests and magnetic resonance imaging of the sacroiliac joints were non-contributory in terms of inflammatory arthritis. As the patient had not benefited from conservative treatment, US-guided corticosteroid and local anesthetic injections were performed for both retrocalcaneal bursae (Video 1). At the second-week follow-up visit, although the US examination showed no significant morphological changes in the tendons, her ankle and knee pain had significantly improved. At the time of writing, the patient is still under follow-up.

AIs have been used for the long-term treatment of breast cancer. Recently, physiatrists have encountered musculoskeletal side effects associated with them, known as AI-associated musculoskeletal syndrome. The scenario is that of arthralgia, myalgia, joint stiffness, bone loss/osteoporosis, fractures, and rarely, tendon disorders (1, 2). Tendon problems include tendinitis, tear/rupture, and tenosynovitis (3), affecting various tendons, mostly in the hand/wrist and, less frequently, the ankle (4). It has been suggested that the pathogenic mechanism may be associated with disruption of collagen production. AIs inactivate the aromatase enzyme which converts androgens to estrogens, thereby reducing plasma estrogen levels. However, estrogen increases collagen synthesis in tendons and reduces their stiffness. Therefore, decreased estrogen levels may have negative impact on tendons and can lead to tendon pathologies (5, 6).

Treatment for AI-related tendinopathies is mainly conservative, including NSAIDs and/or physical therapy, in addition to drug discontinuation or change. If needed, a therapeutic injection may also be performed. In the presented patient, a steroid injection was used, deep to the Achilles tendon and also targeting the retrocalcaneal bursa, as we believed it would be more effective for Achilles tendinitis (7). Treating her ankle pain may have alleviated her knee pain by mitigating biomechanical overload associated with altered kinetic chains due to ankle dysfunction. Moreover, we hypothesize that the localized steroid injections might have distributed systemically, thereby contributing to the resolution of knee pain. To the best of our knowledge, although

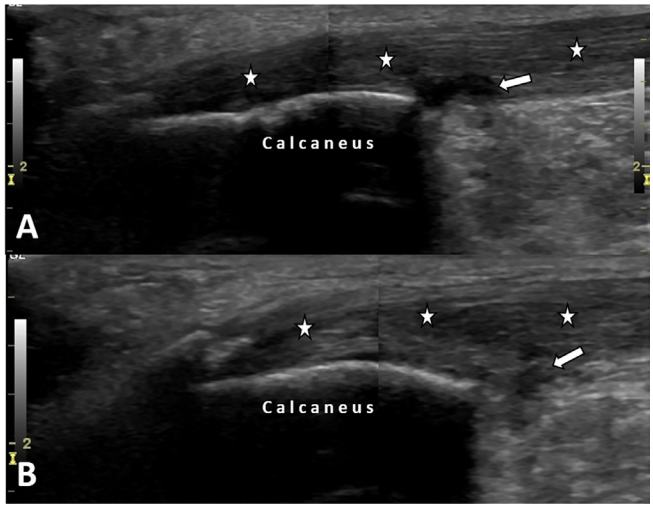


Figure 1. Longitudinal ultrasound imaging demonstrates the swollen, hypoechoic right **(A)** and left **(B)** Achilles tendons (*stars*) and the retrocalcaneal bursae (*arrows*)

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several cases involving tendons of the upper extremities have been reported, bilateral Achilles and patellar tendinitis associated with AI use has not been reported. As demonstrated by our case, US is beneficial for diagnosis, medical decision-making, interventional procedures and follow up monitoring in relevant cases.

Footnotes

Authorship Contributions

Concept: S.A., M.K., L.Ö.; Design: S.A., M.K., L.Ö.; Literature Search: B.Y., A.F.Ç.; Writing: B.Y., A.F.Ç. S.A., M.K., L.Ö.

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Video 1. Ultrasound-guided (direct in-plane) injection deep to the Achilles tendon (*star*) inside the retrocalcaneal bursa. *Arrowhead*; needle, *asterisk*; injectate

Category I

Cancer Genetic Risk Assessment (CGRA) Certification: Experience from the First Five Years

Edie Smith, Kimberly Samuels-Bolin, Kristie Bobolis

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Objective: Integrating cancer genetics, genomics and cancer risk assessment has become increasingly relevant to the care of patients and there is a need for clinicians across the spectrum of practice settings to acquire and demonstrate knowledge and competency in cancer genetics and risk assessment. National Consortium of Breast Centers (NCBC's) Certification Program in Cancer Genetics Risk Assessment (CGRA) is a voluntary, nationally accredited, examination-based certification program created to provide the assurance that healthcare providers with certification in CGRA possess the knowledge, skills and competency to provide cancer risk assessment services to patients and families. NCBC's CGRA certification was developed by a multidisciplinary committee of dedicated breast care, oncology, and cancer genetics professionals and approved by NCBC's board of trustees. Testing first became available in May 2020 with testing opportunities provided throughout the year. Testing options include both remote and in-person examination. The target audiences for certification are physicians, advanced practice nurses, physician assistants, and other skilled health care practitioners who care for at-risk unaffected and affected patients and their families.

Materials and Methods: A retrospective cohort of CGRA examination takers was collected from May 2020 (start of examination availability) through December 2024.

Analyzed data includes: total number of examination takers, pass/fail rates, and professional background and practice setting of passing cohort. Descriptive statistics were used for analysis.

Results: 2020-2024.

Total number of CGRA examination takers: 212

Total number (percent) passed: 187/212 (88.2%); failed: 25/212 (11.8%)

Professional background of CGRA certificants:

APP - 123/187 (65.8%)

MD - 25/187 (13.4%)

Other (RN/RT) - 39/187 (20.9%)

RN: 34/187 (18.2%); RT: 5/187 (2.7%)

Practice focus of CGRA certificants:

Breast Center - 12/187 (6.4%)

Gynecology - 14/187 (7.5%)

High Risk/Genetics - 16/187 (8.6%)

Oncology - 115/187 (61.5%)

Primary Care - 1/187 (0.5%)

Radiology - 4/187 (2.1%)

Surgery - 25/187 (13.4%)

Conclusion: During the first 5 years of CGRA certification eligibility, a notable number of healthcare providers and other healthcare professionals have sought and obtained certification in cancer genetic risk assessment through NCBC's CGRA certification program. The largest percentage of certificant holders are APPs, followed by other healthcare professionals (RNs and RTs), and physicians. The most prominent practice setting for certificant holders is oncology, with many other specialty practice settings represented, including the screening and preventive care spaces. In conclusion, the CGRA certification is a sought-after credential appealing to a broad group of healthcare providers/professionals across practice disciplines allowing for a diverse patient population to obtain cancer genetic and risk assessment-related care. It is anticipated that there will be continued provider interest to attain certification in this rapidly expanding field, particularly with recognition of CGRA by several nationally recognized accrediting bodies.

Keywords: CGRA, certifications

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Category I-C. Education and Outreach

What's Best for Breast? An Annual Free Community Health Education Event

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Objective: To establish a free community health event open to the public, featuring presentations and interactive information sessions aimed at educating the North Carolina Community on breast cancer risk, prevention, and treatment, while providing resources and support for survivors.

Materials and Methods: What's Best for Breast was initiated in 2017 as an annual event at Duke University Medical Center. In 2017, colleagues met to address the lack of community education and engagement by creating a free breast cancer-focused event. Speakers, advocates, and sponsors were recruited. Flyers were distributed through clinics, in local public areas, and online. Marketing was also done through local TV and radio in various years. During the COVID-19 pandemic, the event transitioned to a virtual format (2020–2022). Participant demographics were recorded, and post-event surveys were distributed/collected at the event. The event's format and topics were refined yearly based on feedback. A women's health research symposium was added in 2024.

Results: Registration increased from 112 participants in 2018 to 423 in 2024. In 2020, only 47 participants registered for the virtual event.

• Participant Demographics:

Participant age distribution broadened over time: in 2017, no attendees were over 70 years, compared to 15% in 2024. The majority shifted from ages 51–60 yrs (44% in 2017) to 61–70 yrs (28% in 2024). When the event was virtual (2020), the majority of attendees were <30 yrs (24%).

The distribution of race and ethnicity has remained consistent for in-person events, but shifted during the pandemic:

• 2017: African American (27%), Caucasian (63%), Hispanic (5%), Asian (5%).

• 2020: African American (15%), Caucasian (76%), Hispanic (10%), Asian (12%).

• 2024: African American (31%), Caucasian (52%), Hispanic (6%), Asian (6%).

Participants with no personal breast cancer experience decreased – 2020: 42% *vs.* 2024: 9%

• Event Engagement:

In 2024, 89% of participants were first-time attendees.

• Participant feedback:

89% of participants say the event motivated them to improve their breast care.

93% of participants would consider attending the event again.

98% of participants would recommend the event to others.

Conclusion: "What's Best for Breast" has successfully engaged and educated the local community, as demonstrated by rising attendance and overwhelmingly positive feedback. The event continues to fulfill its mission of raising awareness and providing support for breast cancer patients, survivors, and previvors.

Keywords: Community health, free event, education

Category 1-C. Programs 2. Education and Outreach

Family History Assessment and the Impact on Breast Cancer Diagnosis

Claire Sutherby, Megan Cochenour, Samer Schuman

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Objective: The breast surgical nurse navigator and high-risk breast program (HRBP) advanced practice provider noticed a significant number of women, with a family history of breast cancer, coming through the organizations multidisciplinary breast cancer program (MDBP). These women should have been referred to the HRBP for validated risk assessments and screening recommendations based on family history of breast cancer, or a prior personal history of breast cancer diagnosed before age 50. Obtaining an accurate family history at each encounter with the patient is instrumental in identifying women who might qualify for enhanced screening and monitoring. Identifying women for high-risk screening can in turn detect breast cancer at an earlier stage, resulting in less aggressive treatment and better overall outcomes for the patient.

Materials and Methods: A retrospective review of the women seen in the MDBP identified an educational opportunity regarding the importance of screening patients to identify the need for a risk assessment. Identifying high risk patients before the development of a breast cancer, provides the opportunity for earlier interventions, which has the potential to ultimately decrease the amount of treatment indicated. This approach would then potentially result in less invasive treatment and decreased morbidity and mortality for the patient.

Results: Three hundred and twelve women diagnosed with breast cancer went through the MDBP at Deaconess Hospital, Inc. in 2024. Of those women, 142 had a family history of breast cancer that would have qualified them for a referral to the HRBP for formal risk assessment prior to their cancer diagnosis.

Conclusion: A total of 46% of patients that were seen in the MDBP in 2024 qualified for high risk assessment for breast cancer based on retrospective review of family history. Had these patients been assessed prior to their diagnosis of breast cancer, it is possible that they would have qualified for increased breast screening resulting in earlier diagnosis and decreased need for treatment interventions. Improvement in obtaining and documenting an accurate family history at each patient encounter helps to identify patients at increased risk for developing a breast cancer.

Keywords: Family history assessment, breast cancer diagnosis

Category I

Improving Adherence to National Guidelines Regarding Neoadjuvant Systemic Therapy in the Management of Breast Cancer: A Single-Institution Quality Improvement Initiative

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Objective: Breast cancer remains one of the most frequently diagnosed cancers worldwide. There are various treatment options for breast cancer and many women will require neoadjuvant systemic therapy (NST) as part of their multi-modal treatment plan. As part of the Commission on Cancer Standard 7.2, this study assessed our institution's adherence to national guidelines in the multidisciplinary management of NST, aiming to highlight practices necessitating improvement.

Materials and Methods: A retrospective analysis included 100 patients at our institution who underwent NST between 2019 and 2023. Patients who completed NST and surgery were included in the analysis. Baseline, pre-intervention adherence to The American Society of Breast Surgeons (ASBrS) Consensus Guidelines was obtained. Using this data, three standards (Articles V, VIII, and IX) were selected to perform a quality improvement initiative. A second retrospective review was conducted of patients at the same institution from January 1, 2024 to December 31, 2024, using the same inclusion criteria as above. Adherence to the selected standards was obtained and compared to pre-intervention.

Results: After the initial review, there were 100 female patients [average age 52.5, average body mass index (BMI) = 29.1 60% African American] who had completed NST and surgery. Of 39 ASBrS guidelines, our institution was more than 90% compliant in 74% of the categories. Compliance fell below 90% in genetic testing (88%), timing of surgery after NST (80%), repeat imaging after NST (80%), appropriate placement of surgical clips along the lumpectomy cavity (57%), delayed breast reconstruction with planned radiation (39%), and radiation initiation within six weeks of surgery (75%). Improvement initiatives focused on genetic testing, timing of surgery after NST, and repeat imaging. Interventions for each included: in-clinic saliva genetic testing with invitae and hiring a second genetic counselor; earlier coordination between medical oncology and surgery to refer patients to surgery when patients had at least two chemotherapy cycles to complete; and post-NST imaging performed at the time of surgery referral. These initiatives were implemented in December of 2023. Our second review included 30 female patients (average age 55, average BMI = 29, 57% African American) who completed NST and surgery. Compared to the pre-initiative group, our compliance with genetic testing and timing of surgery both improved to 90%. Repeat imaging post-NST improved to 89%.

Conclusion: Quality improvement initiatives targeting three key areas of breast cancer care over the course of one year led to improved compliance and better patient outcomes. These findings highlight the importance of a multidisciplinary team and the value of regular conferences for fostering collaboration and ensuring the most effective care for patients.

Keywords: Neoadjuvant systemic therapy, management, quality improvement

Category II

Transformative, Patient-Centric Care: Digital Screening Program Provides Equitable Access to Breast Cancer Risk Assessment and Genetic Testing

Jenna Cooke, Meghan E. Burgess, Heather Fecteau

Midstate Radiology Associates

Objective: Breast cancer screening disparities persist in the United States, underscoring the need for universal tools to provide equitable care. This study analyzes two years of data from 15 Midstate Radiology Associates (MRA) sites through Connecticut, where all women were offered a digital risk stratification platform. The platform is offered in five different languages and was designed to identify individuals at an elevated risk for breast cancer and determine eligibility for genetic testing based on national guidelines.

Materials and Methods: A retrospective analysis was conducted across MRA sites from 1/1/2023 to 12/31/2024 to evaluate patient demographics. Before mammograms, all patients were invited to the Ambry CARE Program to assess breast cancer risk using the Tyrer-Cuzick (v8.0) algorithm and determine eligibility for genetic testing based on NCCN® guidelines for hereditary cancers conditions. We analyzed patient ethnicity, age, and language preferences for those who completed the digital screening tool. High-risk patients, those eligible for genetic testing, and individuals who underwent testing—including those with positive mutations—were compared.

Results: Between 1/1/2023 and 12/31/2024, 91,513 assessments were sent to patients via SMS, email, and kiosks, with each method opened over 95% of the time. 77,095 assessments were completed, achieving an 84.2% completion rate. The tool supported over 1,100 patients in languages like Spanish, Polish, Chinese, and Vietnamese. Patient ethnicity was recorded as: White (73%), Hispanic/Latino (11%), Black/African American (6%), Asian (4%), French Canadian/Cajun (3%), Ashkenazi Jewish (2%), and 1% each for other ethnicities. 52% of respondents were aged 51-70, and 8,025 women (10.4%) had a Tyrer-Cuzick score over 20%. Among women with elevated lifetime breast cancer risk: White (71%), Hispanic/Latino (7.2%), Black/African American (5%), Asian (1.8%), French Canadian/Cajun (3.4%), Ashkenazi Jewish (2.6%), and 9% for other ethnicities. 67% were aged 41-60. Of 20,063 women (26%) eligible for genetic testing based on NCCN® guidelines, 69.4% were White, 8.6% Hispanic/Latino, 4.6% Black/African American, 1.7% Asian, 3.2% French Canadian/Cajun, 3.6% Ashkenazi Jewish, and 8.9% other ethnicities. 52% were aged 51-70. 6,051 women chose genetic testing, with 451 (9%) receiving positive results. Age and ethnicity distributions were similar across these groups with increase in percentage of Latin/Hispanic opting for genetic testing.

Conclusion: The digital tool effectively stratified breast cancer risk across diverse patient population, promoting equitable screening and education through multilingual options and personalized support.

Keywords: Digital screening, risk assessment, genetic testing

Category II

The Young Women's Program for Cancer Care at White Plains Hospital

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Objective: The incidence of cancer among young women has been rising at an alarming rate over the past several years. Moreover, as published in January 2025 by the American Cancer Society, those cancer incidence rates even surpass those among their male counterparts. At White Plains Hospital over the past 5 years, there have been over 1700 women under the age of 50 diagnosed with cancer.

Materials and Methods: The Young Women's Program for Cancer Care, established at White Plains Hospital in October of 2023, aims to recognize and address the unique needs of women under the age of 50 who have been diagnosed with cancer. Beyond providing exceptional medical care, the program encompasses all of the multidisciplinary and psychosocial aspects of care via dedicated navigation, education, programming, and support groups to treat and guide our patients with the most holistic approach.

Results: The Program has grown tremendously over the past year, already having enrolled 160 patients. There is a dedicated support group specifically tailored to this patient population, that meets regularly and is facilitated by our clinical social worker and clinical navigator, and that is even separate from the partnership that we have formed with psycho oncology providers for easy access for our patients. There is also scheduled educational programming that happens multiple times per month, led by speakers from our multidisciplinary team; topics have included important and relevant issues such as genetic testing, fertility preservation, nutrition, impact of alcohol on cancer risk, various exercise programs, meditation and wellness. There is also a separate ongoing sexual health series for our patients facilitated by a sexual health specialist.

Conclusion: In addition, we have been able to implement community building events such as group walks, holiday gatherings for patients and their loved ones, cosmetics events for those undergoing chemotherapy, and art therapy sessions, among others. Our goal is to help expedite excellent oncologic care while creating a warm and supportive environment that addresses all of the interdisciplinary needs of this patient population.

Keywords: Young women, support group

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Category II

BMI, Cancer Risk Behaviors, and Readiness for Dietary Change Among Women Surviving with Breast Cancer

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Objective: Breast cancer survivors (BCS) are at increased risk of recurrence and poorer outcomes if they are overweight [bod mass index (BMI) = 25–29.9] or obese (BMI = 30+) compared to those with a healthy weight; nutrition counseling is a key component of their secondary prevention and supportive care. The stages of change (SoC) continuum, part of the transtheoretical model (TTM), conceptualizes dietary behavior change as a progression from not yet considering change (Precontemplation) to sustained change (Maintenance). We studied BCS readiness to change diet, along with other cancer risk behaviors, in relationship to BMI.

Materials and Methods: A secondary data analysis was conducted among N = 936 BCS who contacted a community-based cancer control organization for information and support services during and after cancer treatment. Data (demographics, cancer prevention awareness, BMI, tobacco and alcohol use, physical activity) were collected 30 days later, including BCS dietary SoC.

Results: Among BCS, 37% were ≤45 years, 18.3% were non-white, 22.3% rated their general health as fair/poor, and 46.9% carried a pathogenic variant in BRCA. The M (SD) BMI was 27.1 (6.4), and 56.1% were overweight/obese. Among the risk behaviors assessed, 27.9% of BCS were current or former tobacco users, 33.5% had consumed 2+ drinks containing alcohol in the past 30 days (16.5% consumed 4+ alcohol drinks in 1 sitting), and 30% were not physically active: a majority were aware of cancer prevention guidelines for alcohol (92.7%), physical activity (95%), and nutrition (92.7%). Regarding TTM's SoC, Maintenance consistently had the largest percentage across all dietary behaviors: avoiding red meat (65.6%) and increasing fiber consumption (63.6) showed the highest maintenance. The Preparation and Action stages varied, with the highest proportion (29.8%) increasing fruit/vegetable consumption. The Precontemplation and Contemplation stages were relatively low for all behaviors (<20%). In bivariate analyses, BCS who were overweight/obese ($t = -4.23$, $df = 728$, $p<0.001$), and engaged in less physical activity ($t = 6.8$, $df = 781$, $p<0.001$), reported less dietary change readiness.

Conclusion: Effective dietary interventions may depend on BCS readiness for change (e.g., raising awareness for those in Precontemplation). The TTM can help tailor behavior change strategies to enhance BCS motivation, especially for overweight/obese and less physically active BCS at greatest risk for recurrence.

Keywords: BMI, survivorship, dietary changes

Table 1a. TTM stage of change for diet

	Precontemplation	Contemplation	Preparation	Action	Maintenance
Avoid high fat foods	8.2%	9.4%	13.0%	12.8%	56.6%
Avoid red meat	7.9%	4.9%	7.9%	13.8%	65.6%
Fiber consumption	5.0%	7.5%	11.4%	12.5%	63.6%
Fruit/vegetable consumption	3.0%	8.8%	16.0%	13.8%	58.4%

Table 1b. TTM stage of change (consolidated) for diet

	Precontemplation/contemplation	Preparation/action	Maintenance
Avoid high fat foods	17.6%	25.8%	56.6%
Avoid red meat	12.8%	21.7%	65.6%
Fiber consumption	12.5%	23.9%	63.6%
Fruit/vegetable consumption	11.8%	29.8%	58.4%

Category II. Subcategory F Survivorship Care

The Role of Structured Exercise in Breast Cancer Survivorship

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Objective: Survivorship care in breast cancer patients includes focusing on quality of life and lifestyle modification. Despite the known benefits of exercise during and after cancer treatment, breast cancer survivors often decrease their total physical activity post-diagnosis due to the fear of excessive exercise exertion. Our pilot interventional study investigates the effect of a structured exercise program on breast cancer survivorship and quality of life when a physician endorses exercise.

Materials and Methods: An observational study including female breast cancer patients aged 18 and older who completed their active cancer treatment between 6 to 12 months prior and were enrolled in a structured exercise program endorsed by their primary oncologic physician. A certified cancer fitness instructor led the 10-week exercise program. The program was offered by a third-party, not-for-profit organization and included evidence-based exercises recommended for cancer patients, targeting strength, resistance training, cardio, balance, and flexibility. Patients consented to complete the RAND 36-item Health Survey before and after the program. Primary outcomes were quality of life and compliance with the exercise program. The surveys were scored and formed eight scales. Within-subject changes in each scale were calculated and summarized across subjects with the mean change and 95% confidence interval (CI). Higher scores indicate greater improvement.

Results: Five female breast cancer patients participated in the exercise program. Compliance was 100%. Overall, there was a significant improvement in various components of quality of life, including physical functioning (mean within-subject change 13.0 points, 95% CI: 5.9 to 20.1), energy/fatigue (mean change 16.0, CI: 2.5 to 29.5), emotional well-being (mean change 9.6, CI: 1.3 to 17.9), and social functioning (mean change 12.5, 1.5 to 23.5).

Conclusion: Participating in a physician-endorsed structured exercise program during the survivorship period improves the quality of life of breast cancer patients. When regular exercise is endorsed explicitly by a treating physician, there are high compliance rates.

Keywords: Survivorship care, structured exercise

Category: Category II. Patient Care and Support

Subcategory B. Breast Cancer Navigation

Pre-Operative Education in Breast Surgery, A Quality Improvement Project

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Objective: Effective patient education before surgery is a critical component of care that impacts patient outcomes, satisfaction, and overall surgical success. Lack of standardization of this education and prolonged time between pre-operative consults and surgery could result in inadequate patient knowledge on the day of surgery and subsequent uncertainty, anxiety, and poor adherence to post-operative instructions or delays in accessing adjuvant care. This project aims to address this concern by implementing a standardized pre-operative video visit focused on patient education before upcoming breast surgery.

Materials and Methods: Patients undergoing breast surgery in a comprehensive cancer center at a tertiary academic center were enrolled. Pre-operative video visits were conducted by a Nurse Navigator (NN) one week before surgery. The NN covers logistical information about the surgery, addresses any missing orders, schedules needed postoperative appointments, addresses potential scheduling issues, and answers patient questions. Two validated surveys were administered anonymously to evaluate the effectiveness and impact of this preoperative visit: The state-trait anxiety inventory (STAI) and short assessment of patient satisfaction (SAPS). The STAI was administered before and after the visit. The Wilcoxon signed-rank test and unpaired t test were used to conduct comparative analysis of the pre- and post-appointment STAI values. Analysis was conducted on the overall anxiety score and scores for each individual question.

Results: In total, 50 patients completed the SAPS, 69 completed the pre-visit STAI, and 59 completed the post-visit STAI. There was no statically significant difference between the overall STAI score [mean (standard deviation)] before [34.71 (10.5)] versus after [34.56 (11.4)] the visit (p = 0.8) (Figure 1). However, there were p-values below 0.2 for two STAI questions and between 0.2–0.3 for two others (Table 1). When considering trends with a p-value below 0.2, patients felt more secure and pleasant after the visit. When considering trends with a p-value below 0.3, patients felt less frightened but more nervous after the visit. All patients felt satisfied (12%) or very satisfied (88%) with the effect of the preoperative visit, and other SAPS markers of satisfaction were similarly high (Table 2).

Conclusion: This educational initiative offers a quality improvement solution to standardizing patient education before breast surgery. Measures of patient satisfaction following the appointment were high, however the impact on anxiety levels remains nuanced. These finding highlight the complexity of pre-operative emotions that patients may experience as their breast surgery date approaches.

Keywords: Pre-operative education, quality improvement, educational

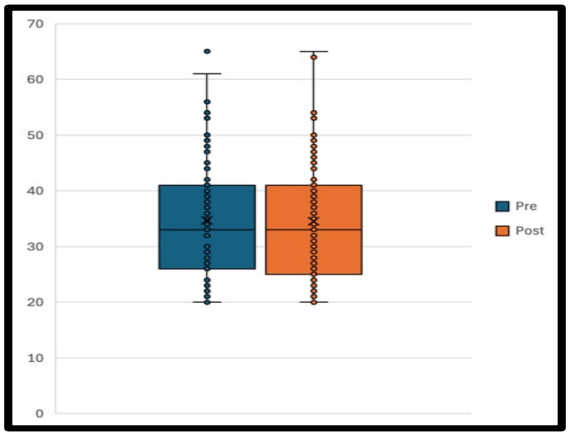


Figure 1. Total state-trait anxiety Inventory scores pre- versus post-educational visit

Table 1. Scores for each state-trait anxiety inventory question pre- versus post-educational visit. A value of 1 corresponds to "not at all" and 4 corresponds to "very much so". The Wilcoxon Signed-Rank test was used to calculate the reported p-values

Question	Pre-visit	Post-visit	p-value	Question	Pre-visit	Post-visit	p-value
I feel calm	3.20	3.17	1.0	I feel strained	1.64	1.68	0.98
I feel secure	3.38	3.54	0.14	I feel upset	1.49	1.41	0.56
I feel at ease	3.07	3.07	0.94	I am worrying over possible misfortunes	1.84	1.76	0.77
I feel satisfied	3.25	3.27	0.62	I feel frightened	1.90	1.73	0.25
I feel self-confident	3.33	3.31	0.91	I feel uncomfortable	1.49	1.63	0.71
I am relaxed	2.81	2.85	0.79	I feel nervous	2.16	2.36	0.29
I feel content	3.26	3.31	0.67	I feel jittery	1.55	1.46	0.54
I feel steady	3.38	3.41	0.96	I feel indecisive	1.38	1.47	0.61
I feel pleasant	3.33	3.54	0.13	I am worried	2.12	2.14	0.86
I feel tense	2.06	2.15	0.59	I feel confused	1.19	1.24	0.79

Key: [1 = Not at all] [2 = A little] [3 = Somewhat] [4 = Very much so]

Table 2. Percentage of respondents selecting each answer for the short assessment of patient satisfaction questions

Question	Very dissatisfied	Dissatisfied	Neither	Satisfied	Very satisfied
How satisfied are you with the effect of your pre-operative visit?	0	0	0	12	88
How satisfied are you with the education you have been given about the details of your surgery?	12	2	0	14	72
Do you feel satisfied that you were able to ask any questions that may affect your upcoming surgery?	4	0	0	4	92
Are you satisfied with the education you received during the pre-operative visit?	0	0	0	10	90
Statement	**Strongly disagree**	**Disagree**	**Not sure**	**Agree**	**Strongly Agree**
The healthcare professional who spoke with me was very thorough when going over my preoperative education.	4	0	0	8	88
The time you had with the healthcare professional during the pre-operative visit was too short.	50	40	4	0	4
Question	**None of the time**	**Some of the time**	**Half the time**	**Most of the time**	**All of the time**
How much of the visit time did you feel respected by the healthcare professional you spoke with?	0	0	0	0	100

Category III

Comparison of Surgical Complications With Direct-to-Implant *vs.* Tissue Expander Reconstruction After Wise Pattern Skin-Sparing Mastectomy

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Objective: Wise Pattern Mastectomy is a common incision utilized in patients with large, ptotic breasts undergoing skin-sparing mastectomy and immediate breast reconstruction (IBR). This incision pattern is associated with an increased risk of delayed wound healing and skin necrosis which may be further influenced by the type of IBR performed. We compared surgical complications in patients undergoing IBR with Direct-to-Implant (DTI) *vs.* Tissue Expander (TE) after Wise Pattern Skin-Sparing Mastectomy (WSSM).

Materials and Methods: Patients who underwent WSSM and IBR from 2019–2023 were selected. Patient characteristics, clinical features, and surgical complications were compared between patients who underwent DTI vs. TE IBR. Multivariable logistic regression analysis was performed to identify factors associated with major complications [surgical site infection (SSI), skin necrosis requiring reoperation, and reconstruction loss] and any 30-day complication controlling for patient age, race, ethnicity, body mass index (BMI), presence of diabetes, tobacco use, neoadjuvant chemotherapy (NAC), reason for mastectomy, axillary surgery, mastectomy weight, and type of reconstruction.

Results: A total of 144 patients who underwent 217 mastectomies were evaluated: 73 bilateral (51%) and 71 unilateral (49%); 117 DTI (54%) and 100 TE (46%) (Table). Most patients were ≥50 years old (64%), White (83%), Hispanic (64%), and had a BMI <30 kg/m^2 (58%). NAC was utilized in 35% of patients. The reason for mastectomy was cancer in 64%, and axillary surgery was performed in 66% of cases. The mastectomy weight was ≥1000 grams in 41% of cases. Major complications occurred in 21% of cases: SSI in 12% (DTI 15% *vs.* TE 9%), skin necrosis requiring reoperation in 11% (DTI 12% *vs.* TE 10%), and reconstruction loss in 13% (DTI 15% *vs.* TE 10%). SSI and skin necrosis requiring reoperation were associated with reconstruction loss (SSI $p \leq 0.001$, skin necrosis $p \leq 0.001$). Multivariable analysis showed that breast weight ≥1000 grams was associated with major complications [odds ratio (OR) 2.82, 95% confidence interval (CI) 1.27–6.26, $p = 0.011$] and Hispanic ethnicity, current smoking, and DTI reconstruction were associated with any 30-day complication (Hispanic ethnicity: OR 3.33, 95% CI 1.62–6.87, $p = 0.001$; current smoking: OR 5.57, 95% CI 1.05–29.02, $p = 0.044$; DTI: OR 2.40, 95% CI 1.31–4.40, $p = 0.005$).

Conclusion: In patients undergoing WSSM with IBR, mastectomy weight ≥1000 grams was associated with an increased likelihood of major complications and Hispanic ethnicity, current smoking, and DTI reconstruction were associated with an increased likelihood of any 30-day complication. These factors should be considered when counseling patients regarding risk of complications and plans for IBR after WSSM.

Keywords: Surgical complications, direct-to-implant, tissue expander reconstruction, wise pattern

Category III

Patient Reported Satisfaction Outcomes After Breast Radiation Using Intraoperative Radiation Therapy *vs.* External Beam Radiation Therapy

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Objective: Intraoperative radiation therapy (IORT), is an alternative to postoperative whole breast irradiation for early-stage breast cancer. The aim of this study was to assess patient reported outcomes (PRO) on cosmetic results and radiation related adverse effects after IORT vs. external beam radiation therapy (EBRT).

Materials and Methods: Patients treated with IORT for ductal carcinoma *in situ* (DCIS) or early-stage breast cancer between 2017–2023 were asked to submit the pre-validated BREAST-Q survey tool for objective aesthetic evaluation. A matching cohort of patients treated with EBRT during the same time interval was also asked to submit the same survey.

Results: Eighty-eight patients were included, 56 (63.0%) with invasive ductal carcinoma (IDC) and 32 (36%) with DCIS. Thirty (68%) patients with IDC and 14 (31%) patients with DCIS had IORT. Patient satisfaction scores with breast cosmesis was higher in IORT group compared to EBRT (mean, 83.7 *vs.* 74.2; $p = 0.05$). Less radiation related adverse effects were reported after IORT (mean, 7.7) as compared with EBRT (mean, 10.6) ($p<0.05$).

Conclusion: This study suggests that in comparison to EBRT, patients treated with IORT have higher satisfaction scores related to breast cosmesis and less radiation related adverse effects.

Keywords: Intraoperative radiation, external beam, outcomes

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	EBR	IORT	Total	p-value
Patients	44 (50%)	44 (50%)	88 (100%)	
Age				
30-39 y	1 (1%)	0	1 (1%)	
40-49 y	9 (20%)	1 (1%)	10 (11%)	0.046
50-60 y	7 (16%)	7 (16%)	14 (16%)	
≥60 y	27 (61%)	36 (82%)	63 (72%)	
Race				
White	34 (77%)	37 (84%)	71 (81%)	
Black	10 (23%)	7 (16%)	17 (19%)	0.417
Other	0	0		
Ethnicity				
Hispanic	28 (64%)	22 (50%)	50 (57%)	0.196
Non-hispanic	16 (36%)	22 (50%)	38 (43%)	
BMI				
<18.4	0	1 (2%)	1 (1%)	
18.5-24.9	12 (27%)	10 (23%)	22 (25%)	0.658
25-29.9	19 (43%)	19 (43%)	38 (43%)	
>30	13 (30%)	14 (32%)	27 (31%)	
Clinical stage				
Tis	18 (41%)	14 (32%)	32 (36%)	
T1	22 (50%)	9 (66%)	51 (58%)	0.183
T2	4 (9%)	1 (2%)	5 (6%)	

Table 1. Comparison of BREAST Q Rasch score (satisfaction with breast)

	EBRT	IORT	*p*-value (t-test)
Total (for all stages)	74.2 (23.9)	83.7 (17.4)	
Tis mean (SD)	67.8 (28.1)	87.9 (16.8)	**0.050**
T1 mean (SD)	79.5 (20.4)	81.6 (17.9)	
T2 mean (SD)	74.3 (18.5)	82 (0)	

Table 2. Comparison of BREAST Q Rasch score (adverse effects of radiation)

	EBRT	IORT	*p*-value (t-test)
Total (for all stages) mean [SD]	10.6 (5.1)	7.7 (3.0)	
Tis mean (SD)	11 (5.7)	6.6 (1.0)	**0.004**
T1 mean (SD)	9.6 (4.6)	8.2 (3.6)	
T2 mean (SD)	14.5 (4.4)	8 (0)	

Category III

IntraOperative Cryoablation Therapy (IOCT): A Novel Alternative to Post-Lumpectomy Radiation Therapy

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Objective: Today, breast cancer patients have two choices for initial treatment of their breast cancer: 1) surgical excision of the cancer followed by radiation therapy or 2) removal of the cancerous breast (mastectomy). SenoGuard, an investigational intraoperative cryoablative therapy (IOCT) administered by a surgical team as an essential element of breast sparing surgery, offers a third option that would eliminate the need for radiation. We aimed to evaluate the feasibility and safety of cryoablation of the surgical cavity using a new 2 cm cryoablation probe and cryogenic system as a potential alternative to RT.

Materials and Methods: An excision was made within the breast tissue of a porcine animal model to simulate the technique used for tumor lumpectomy. A probe delivering a novel nitrogen-based cryogen was inserted into the surgical cavity to cryoablate the surrounding cavity. Data on the delivery of specific isotherms at various depths and time points within the surgical cavity using engineering and ex-vivo models was collected to assess the technique's precision and efficacy.

Results: The study found that the cryoprobe was able to deliver -20 °C isotherm to a depth of 1 cm from the cryoprobe surface following a 3-minute freeze cycle, demonstrating the potential for effective tissue cell destruction within this range. Extending the freeze cycle to 5 minutes resulted in delivery of the -40 °C isotherm to reach a depth of 1 cm, indicating a more intense and potentially more effective treatment for slightly larger tumor cavities.

Conclusion: Data from this feasibility study demonstrates that cryoablation could achieve similar results as those created by radiation therapy and that adjusting the duration of the freeze cycle could provide flexibility in treating a range of tumor cavity sizes. The ability to adjust freeze cycle duration based on tumor cavity size could eliminate the need for post-lumpectomy radiation therapy in certain patients. IOCT of the surgical cavity tissue immediately following tumor lumpectomy offers several potential advantages over traditional radiation therapy, including improved cosmetic outcome, a lower risk of side effects and greater accessibility and affordability for all patients.

Keywords: Cryoablation therapy, post-lumpectomy radiation therapy

Category III-A. Diagnostic Imaging, 1. Screening and Diagnostic Mammography

Do Not Overlook Me: Breast Cancer in Appalachian Women Ages 28–49 Diagnosed Through A Mobile Mammogram Unit (MMU) Program

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Objective: Unfortunately, both the incidence and mortality rates for women ages 20-49 diagnosed with breast cancer have continued to rise in the USA for the past two decades. Causality remains unknown; however, the controversy regarding screening this population persists. A paucity of data exists to define the effectiveness and diagnostic yield of mobile mammogram unit (MMU) screening in this cohort. Our data supports the screening recommendations of organizations such as the American College of Radiology, the Society of Breast Imaging, the American Society of Breast Surgeons, the National Comprehensive Cancer Network, the American Cancer Society, and the USPSTF among others, emphasizing the importance of screening this vulnerable population that otherwise would not have been screened.

Materials and Methods: A retrospective analysis of a prospectively maintained database including these women screened between 2008 and 2023 was performed. Frequency (n) and percentage (%) statistics along with Medians (Mdn) and interquartile ranges (IQR) were used to generate measures of prevalence within the population. The patient electronic health record was used to record demographic information.

Results: A total of n = 15,124 screenings were performed in this unique demographic population. The median age for the cohort was 44.7 years (IQR: 42.0–47.0). Most screenings were completed using 2D technology (n = 10,209, 67.5%). A total of n = 2,779 received their first-ever mammogram (18.4%). There were n = 41 malignancies detected (prevalence - 0.3%; age range 37–49) in 39 women. Interestingly, n = 13 of these 41 malignancies (32%) were detected in women having their first mammogram.

Conclusion: This data provides compelling evidence for utilization of MMU programs to screen this young, vulnerable population and revealed that 32% of breast cancers were identified at the time of their first ever mammogram with a median age of 44.7. Further studies are needed to validate early screening in this patient population.

Keywords: Mobile mammogram, demographic information, early screening

Category III

Comparative Analysis of Clinical Breast Exam *vs.* Bexa Breast Exam for Detection of Breast Abnormalities in Colombian Women Aged 40–50 Years Old

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Objective: Breast cancer (BC) remains a significant public health challenge in Cali Colombia, where mortality rates are second highest- particularly in women <50 years old, often presenting at advanced stages. Cancer control initiatives to coordinate care and reduce diagnostic delays are underway, however, initiatives aimed at addressing technology-assisted early detection in women age 40–49 are needed as clinical breast exam (CBE) is the national screening guideline for this age group. Bexa is a unique, painless, radiation-free, FDA-cleared, high-resolution pressure elastography device for detection of abnormal masses in the breast. To evaluate the performance of Bexa breast exam (BBE) vs CBE in the detection of abnormal breast masses.

Materials and Methods: Two hundred and eighty asymptomatic women aged 40–50 presenting for routine CBE at the Clínica de Mama in Cali, Colombia were enrolled in the study. All patients received CBE by a clinic physician, followed by BBE, which consists of a quadrant-by-quadrant clinical evaluation of the entire breast using the proprietary form of high-resolution breast elastography as previously described by Kaufman et al. When a mass was localized by either modality, the area underwent focused ultrasound to characterize the finding. Ultrasounds were interpreted by fellowship trained breast radiologist.

Results: Of 270 eligible women, CBE and BBE were (negatively) concordant in 204 women. A total of 70 women had a confirmed mass (positive on two modalities). CBE detected a mass in 15 women (5.6%), vs BBE in 71 women (26.3%). Accuracy was significantly higher with BBE compared to CBE (99.6% *vs.* 75.9% $p<0.001$). While sensitivity was similar for both groups (BBE: 99.5%, CBE: 97.5%), the specificity for BBE was 85% higher than CBE. CBE detected 5 false positives and 60 false negatives. Bexa detected one false positive. Of the false negatives detected by CBE, 16 had BIRADS scores of 3 or higher (n = 9 BIRADS-3, n = 7 BIRADS-4), indicating 26.7% were clinically important misses, with 11.7% suspicious for malignancy (BIRADS 4).

Clinical Significance of Masses Detected by Bexa: Of the 255 women with negative CBE, 23.9% (n = 61) were true masses as confirmed by BBE + focused ultrasound. with 75% classified as BIRADS 2, 14.7% BIRADS 3, and 10.3% BIRADS 4.

Conclusion: These data suggest that Bexa exhibits superior performance over CBE for detection of masses in women age 40–49 who are ineligible for mammography due to national guidelines. The BBE process stratifies risk and can identify women for whom further diagnostic evaluation is necessary: of the true masses found by BBE, 27% warranted either short-term surveillance or biopsy (BIRADS 3 or 4). While BBE is not intended to replace recommendations for early detection, it can support access, accuracy and adoption in women for whom CBE is their primary form of early detection. Evaluation of Bexa vs screening mammography is underway and will provide further insight into the expansive clinical utility of Bexa for technology-assisted early detection.

Keywords: Clinical breast exam, bexa breast exam, comparative