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Turkish Federation of Breast Diseases Societies

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Société Internationale de Sénologie | Senologic International Society

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European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

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

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

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

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

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

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

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

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

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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Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
Current Opinion	300	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software,and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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

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

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

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

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

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

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

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

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

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European Journal of Breast Health

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Original Article

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Performance Benchmark Metrics and Clinicopathologic Outcomes of MRI-Guided Breast Biopsies: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To determine key performance metrics of magnetic resonance imaging (MRI)-guided breast biopsies (MRGB) to help identify reference benchmarks.

Materials and Methods: We identified studies reporting MRGB results up to 04.01.2021 in the Embase database, Ovid Medline (R) Process, Other Non-Indexed Citations, Ovid Medline (R) and completed a PRISMA checklist and sources of bias (QUADAS-2). The inclusion criteria were English language, available histopathological outcomes, or at least one imaging follow-up after biopsy. A random intercept logistic regression model was used to pool rates. Between-study heterogeneity was quantified by the I^2 statistic.

Results: A total of 11,215 lesions in 50 articles were analyzed. The technical success rate was 99.10% [95% confidence interval (CI): 97.89–99.62%]. The MRI indications were staging in 1,496 (28.05%, 95% CI: 26.85–29.28%), screening in 1,427 (26.76%, 95% CI: 25.57–27.97%), surveillance in 1,027 (19.26%, 95% CI: 18.21–20.34%), diagnostic in 1,038 (19.46%, 95% CI: 18.41–20.55%), unknown primary in 74 (1.39%, 95% CI: 1.09–1.74%), and other in 271 (5.08%, 95% CI: 4.51–5.71%). Histopathology was benign in 65.06% (95% CI: 59.15–70.54%), malignant in 29.64% (95% CI: 23.58–36.52%) and high risk in 16.69% (95% CI: 9.96–26.64%). Detection of malignancy was significantly lower in those patients who underwent MRI for screening purposes (odds ratio 0.47, 95% CI: 0.25–0.87; p = 0.02), while mass lesions were more likely to yield malignancy compared to non-mass and foci [27.39% vs 11.36% (non-mass),18.03% (foci); $p<0.001$]. Surgical upgrade to invasive cancer occurred in 12.24% of ductal carcinoma *in situ* (95% CI: 7.76–18.77%) and malignancy in 15.14% of high-risk lesions (95% CI: 10.69–21.17%). MRI follow-up was performed in 1,651 (20.92%) patients after benign results [median=25 months (range: 0.4–117)]. Radiology-pathology discordance (2.48%, 95% CI: 1.62–3.77%), false negative after a benign-concordant biopsy (0.75%, 95% CI: 0.34–1.62%) and biopsy complications (2.36%, 95% CI: 2.03–2.72%) were rare.

Conclusion: MRGB is a highly accurate minimally-invasive diagnostic technique with low false-negative and complication rates. MRI indication and lesion type should be considered when evaluating the performance of institutional MRGB programs.

Keywords: Breast; cancer; magnetic resonance imaging; biopsy

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Key Points

- Magnetic resonance imaging (MRI)-guided breast biopsy methods and clinicopathological outcomes may vary between institutions.
- MRI-guided breast biopsy is an efficient, highly accurate technique with high technical success [99.10%, 95% confidence interval (CI): 97.89–99.62%], low false-negative (0.75%, 95% CI: 0.34–1.62%), and low complication (2.36%, 95% CI: 2.03–2.72%) rates.
- The surgical upgrade to malignancy is common among high-risk lesions 15.14% (95% CI: 10.69-21.17%), especially atypical ductal hyperplasia (31.81% (95% CI: 25.57-38.77%).

Introduction

Magnetic resonance imaging (MRI) has a high sensitivity (88–92%) and a moderate specificity (67–77%) for the detection of breast cancer (1). It has been well established that MRI-guided tissue sampling is necessary for the histological verification of lesions that are otherwise occult (1-5). Furthermore, due to the overlap of the MRI findings of the benign and malignant lesions, in order to distinguish between them, an MRI-guided breast biopsy is necessary (6).

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Surgical biopsy after MRI-guided wire localization and MRI-guided percutaneous needle biopsies have been described before the first experiences with MRI-guided vacuum-assisted biopsy were reported in the late 1990s (7, 8). Since then, MRI-guided vacuum-assisted biopsy has achieved broad acceptance in clinical practice due to its speed, accuracy, and safety, which has been found to be as good as MRI-guided wire localization without the associated complications and cost of surgery (7-13). MRI-guided needle biopsy also allows for the placement of marker clips and so aids the subsequent mammographic localization of the lesion if an operation becomes necessary.

Tissue sampling with fine-needle aspiration and core-needle biopsy devices requires visual confirmation of needle placement directly into the target to ensure accurate sampling. The suction of the MRI-guided vacuum-assisted biopsy device provides for adequate sampling when the needle is placed within a few millimeters of a small lesion, provided that the suction chamber is preferentially directed toward the target. Thus, the use of vacuum assistance has allowed for the accurate targeting of smaller lesions. In addition, because the vacuum system continuously suctions any hemorrhage which may occur during sampling, tissue shift and subsequent sampling errors are mitigated.

MRI-guided breast biopsy can be a challenging procedure for radiologists. Determining radiologic-pathologic concordance for MRI-guided biopsies is often more difficult than biopsies performed using other imaging modalities. Since it is not a real-time procedure, it lacks the direct needle visualization advantage of ultrasound-guided biopsies. Unlike stereotactic biopsies where intra-procedure specimen radiographs ensure the accuracy of targeting, *ex vivo* confirmation of sampling is not possible. Furthermore, wash-out of the gadolinium contrast agents during the procedure and post-biopsy changes including air, hemorrhage, and local anesthesia obscure the targeted lesion, making it more challenging to confirm the accuracy of sampling. It is a procedure which obligates sliding the table on the gantry to place the guiding system and performing the biopsy again, without real-time visualization of the lesion. These factors render radiologic-pathologic correlation critical. Lesion enhancement is another challenge while performing MRI-guided biopsy because lesion conspicuity decreases with time after contrast injection due to the enhancement kinetics. Compression of the breast needs to be adequate to immobilize the breast and to ensure hemostasis without obstructing lesion contrast enhancement.

MRI-guided breast biopsy is a time-consuming and complex procedure which requires specific equipment and expertise. Current MRI-guided breast biopsy methods and subsequent clinicopathological outcomes may vary between institutions. Our goal was to identify benchmark metrics to help define a successful breast MRI-guided biopsy program and guide institutional audits. To accomplish our goal, we identified and systematically reviewed studies in order to determine indications, technical success, histopathological outcomes, false-negatives, and upgrade rates of MRI-guided breast biopsies for institutional referencing.

Materials and Methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline was used for reporting (14).

Literature Search and Article Selection Criteria

The requirement to obtain institutional review board approval was waived for this literature review, which involved only publicly available data. The Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE®, and Embase databases were searched systematically for English language articles published from January, 1946 up to April, 2021 for articles on MRI-guided breast biopsy outcomes by an investigator trained in conducting comprehensive literature searches. Three investigators then independently reviewed and confirmed the selected articles and extracted the relevant information.

The search terms included breast neoplasm, MRI/MRI, and image-guided biopsy from articles involving human subjects. The search strategy is shown in Supplementary Table 1.

Our inclusion criteria were English language literature, the availability of reported histopathological outcomes of benign, malignant, and high-risk lesions, and the availability of final histopathology (gold standard) or at least one-time imaging/clinical follow-up after biopsy. We excluded meta-analyses, review papers, case-control studies, and matched-pair studies, and included original articles which reported novel data.

We excluded studies that were non-English in their full text, and those where the following information was not reported: Technical factors (magnet strength, needle type, needle gauge), imaging or clinical follow-up descriptions, or time unavailable after a high-risk or benign biopsies. The results of the literature search and applied study selection criteria are summarized in Figure 1.

Data Collection and Quality Assessment

We collected mean/median patient ages, indications for MRI biopsy, magnet strengths, needle types/gauges, the number of cores sampled, rates of successfully performed MRI biopsies, causes of unsuccessful biopsies and pathological outcomes (benign, malignant, high risk) along with false negative rates and underestimation rates for ductal carcinoma *in situ* (DCIS), atypical ductal hyperplasia (ADH) and other high-risk lesions [lobular carcinoma *in situ* (LCIS), atypical lobular hyperplasia (ALH), flat epithelial atypical (FEA) radial scar (RSL)/complex sclerosing lesions (CSL)]. The lesion characteristics (mass, non-mass enhancement, focus and size information for each), enhancement kinetics (wash-out, plateau, progressive), complications (if any), and the types and durations of follow-up were also recorded.

One reader applied the modified quality assessment of diagnostic accuracy studies (QUADAS-2) items to assess study quality and the likelihood of bias (15). The risk of bias was judged as “low”, “high” or “unclear” on four domains: Patient selection, index test, reference standard, and flow and timing. Concerns about applicability were judged as “low”, “high” or “unclear” on three domains: Patient population, index test, and reference standard. A study was judged as “at risk of bias” or as having “concerns regarding applicability” when it was judged “high” or “unclear” in one or more domains. A second reader checked the results. If present, disagreement was solved in consensus. Detailed information on signaling questions in each domain is shown in Supplementary Table 2.

Table 1. Characteristics of the 50 studies included on MRI-guided breast biopsy

Author and publication year	Design	Setting	Years	n. Target lesion	n. Patients	Needle size (gauge)	n. Sampled cores†	Follow-up (months)†	False negative rate*,§	Underestimation rate§			Successful biopsy rate^,§
										DCIS	ADH	Other high risk¥	
An et al. (72)	Prospective	Single center	2009–2011	15	13	9	Mean, 9 (6–11)	Range, 6-12	0/9 (0)	-	-	-	13/15 (86.7)
Bahrs et al. (73)	Retrospective	Single center	N/A¶	299	252	8-11	Range 12–24	Median, 13 (5-24)	13/183 (7.1)	-	-	-	281/299 (94.0)
Belloni et al. (66)	Retrospective	Single center	2002–2008	70	66	12-18	Range 8–12	Mean 26 (11–68)	0/34 (0)	1/10 (10)	-	-	70/70 (100.0)
Carbognin et al. (74)	Retrospective	Single center	2007–2009	29	29	10	Mean, 18 (9–25)	At least 12	0/11 (0)	-	-	-	27/29 (93.0)
Chen et al. (75)	Retrospective	Single center	2001–2002	35	29	14	-	5–12	-	0/1 (0)	2/5 (40.0)	0/1 (0)	34/35 (97.1)
Crystal. et al. (76)	Retrospective	Single center	2006–2009	31	25	9	-	Mean, 14 (6-26)	-	-	3/6 (50.0)	10/20 (50.0)	31/31 (100.0)
Dogan et al. (77)	Retrospective	Single center	2008–2010	20	19	9	-	Range, 6–24	0/13 (0)	0/1 (0)	-	-	20/20 (100.0)
Dratwa et al. (68)	Retrospective	Multicenter (2 sites)	2009–2013	208	197	10-11	Median, 18 (6–27)	Range, 6–12	2/143 (1.4)	3/19 (15.8)	-	-	-
Ferre et al. (78)	Retrospective	Single center	2005–2013	259	255	10	Range, 6–18	Range, 6–24		3/40 (7.5)	8/15 (53.3)	8/32 (25.0)	253/259 (97.7)
Friedman et al. (69)	Retrospective	Single center	2006–2007	197	142	10	-	6	1/153 (0.7)	-	-	-	-
Gebauer et al. (48)	Retrospective	Single center	N/A	42	32	10	-	Mean, 18	0/27 (0)	-	-	0/3 (0)	42/42 (100.0)
Ghate et al. (79)	Retrospective	Single center	2004	20	19	10	Mean, 8 (5–12)	Range, 4–8	-	-	1/2 (50.0)	0/2 (0)	19/20 (95.0)
Han et al. (24)	Retrospective	Single center	2005	172	154	9-10	Range 4–10	12	4/89 (4.5)	1/15 (6.7)	-	0/17 (0)	150/172 (87.2)
Hauth et al. (80)	Prospective	Single center	2004–2006	34	33	10	Mean, 14.5 (2–25)	Mean, 7.5 (3–14)	1/20 (5.0)	-	-	-	29/34 (85.3)
Hayward et al. (70)	Retrospective	Single center	2005–2012	611	492	9	Range, 6–18	Mean, 33.1 (0.4–100.8)	2/367 (0.6)	-	-	-	-

Table 1. continued

Author and publication year	Design	Setting	Years	n. Target lesion	n. Patients	Needle size (gauge)	n. Sampled cores†	Follow-up (months)†	False negative rate*,§	Underestimation rate§			Successful biopsy rate^,§
										DCIS	ADH	Other high risk¥	
Heller et al. (38)	Retrospective	Single center	2007–2012	1,145	1003	9	10-12	Mean, 44 (36–54)	-	-	12/35 (12.9)	18/116 (15.5)	-
Huang et al. (21)	Retrospective	Single center	2007–2012	169	160	9	Median, 12 (6–27)	At least 24	1/168 (0.6)	-	-	-	-
Imschweiler et al. (13)	Retrospective	Multicenter (53 sites)	2009–2011	557	-	≤11	At least 12	-	8/283 (2.8)	-	-	-	548/557 (98.4)
Jung et al. (81)	Retrospective	Single center	2009–2011	22	22	9	Range, 12–18	Mean, 32.1 (15–44)	-	0/2 (0)	1/1 (100.0)	0/4 (0)	21/22 (95.5)
Kılıç et al. (82)	Retrospective	Single center	2011–2013	90	90	10–12	Range, 6–12	Range, 6–12	0/63 (0)	-	-	-	90/90 (100.0)
Lee et al. (83)	Retrospective	Single center	N/A¶	34	34	9	-	-	-	5/34 (14.7)	-	-	-
Lee et al. (71)	Retrospective	Single center	N/A¶	76	-	9	Median, 12 (6–20)	-	-	-	-	-	-
Lee et al. (84)	Retrospective	Single center	2006-2011	85	70	7, 8, 10	At least 9	Mean, 18 (3–75)	1/77 (1.3)	-	-	-	-
Lehman et al. (85)	Prospective	Single center	N/A	5	5	14	Range, 6–10	6	-	-	-	-	5/5 (100.0)
Lehman et al. (45)	Retrospective	Multicenter (2 sites)	2003	38	28	9–12	-	-	-	1/4 (25.0)	1/2 (50.0)	-	38/38 (100.0)
Li et al. (20)	Retrospective	Single center	N/A¶	543	514	9	-	Mean, 24 (7–53)	4/308 (1.3)	-	-	-	-
Liberman et al. (46)	Prospective	Single center	N/A	27	20	9	Median, 8 (6–14)	-	2/20 (10.0)	0/1 (0)	1/1 (100.0)	-	19/20 patients (95.0)
Liberman et al. (11)	Retrospective	Single center	N/A	112	106	9	Median, 12 (6–20)	Median, 7 (1–14)	1/52 (1.9)	1/13 (7.7)	2/4 (50.0)	1/6 (16.6)	95/112 (84.8)
Liberman et al. (86)	Retrospective	Single center	N/A¶	15	15	9	Median, 9 (8–18)	-	-	-	5/15 (33.3)	-	-

Table 1. continued

Author and publication year	Design	Setting	Years	n. Target lesion	n. Patients	Needle size (gauge)	n. Sampled cores†	Follow-up (months)†	False negative rate*,§	Underestimation rate§			Successful biopsy rate^,§
										DCIS	ADH	Other high risk¥	
Lourenco et al. (39)	Retrospective	Single center	2006–2010	96	96	9	Mean, 10 (6–13)	Mean, 31.2 (6–60)	-	-	6/20 (30.0)	10/76 (13.2)	-
Mahoney et al. (23)	Retrospective	Single center	2004–2007	55	47	10	At least 12	Minimum 6	-	-	2/3 (66.7)	2/4 (50.0)	55/55 (100.0)
Malhaire et al. (25)	Retrospective	Single center	2003–2008	72	72	10	Median, 18 (6–48)	Median, 12.8 (1–53)	3/26 (11.5)	2/9 (22.2)	1/1 (100.0)	0/9 (0)	-
Meeuwis et al. (87)	Retrospective	Single center	2007–2010	119	119	9–14	Up to 12	Range, 6–24	-	-	-	-	118/119 patients (99.2)
Myers et al. (88)	Retrospective	Single center	2006–2012	200	168	10	At least 6	Mean, 20.5 (4–67)	3/142 (2.1)	1/5 (20.0)	4/7 (57.1)	0/32 (0)	-
Noroozian et al. (89)	Retrospective	Single center	2006–2007	75	75	9	At least 6	Range, 6–12	-	3/3 (100.0)	0/2 (0)	1/5 (20.0)	-
O'Connor et al. (90)	Retrospective	Single center	2007–2012	126	126	9	Range, 8–24	Range, 10-74	-	5/16 (31.3)	-	-	-
Orel et al. (47)	Retrospective	Single center	2003–2004	85	75	9	-	-	0/13(0)	4/17 (23.5)	2/8 (25.0)	0/10 (0)	-
Perlet et al. (10)	Retrospective	Multicenter (5 sites)	N/A	538	517	11	At least 20	Median 32 (4–48)	0/354 (0)	3/64 (4.7)	5/17 (29.4)	-	517/538 (96.1)
Perretta et al. (91)	Retrospective	Single center	2003–2006	47	47	10	-	Mean 18	0/28 (0)	1/7 (14.3)	1/4 (25.0)	-	47/47 (100.0)
Peters et al. (92)	Retrospective	Single center	2005–2008	31	30	14	Range, 3–5	-	2/19 (10.5)	-	-	-	29/31 (93.5)
Rauch et al. (31)	Retrospective	Single center	2005–2010	218	197	9	Range, 6–12	Mean, 29 (6–69)	0/132 (0)	4/22 (18.2)	3/13 (23.1)	1/6 (16.6)	-
Schrading et al. (93)	Retrospective	Single center	2005–2007	316	200	9–10	11	Range, 6–12	0/186 (0)	-	-	-	-

Table 1. continued

Author and publication year	Design	Setting	Years	n. Target lesion	n. Patients	Needle size (gauge)	n. Sampled cores†	Follow-up (months)†	False negative rate*,§	Underestimation rate§			Successful biopsy rate^,§
										DCIS	ADH	Other high risk¥	
Spick et al. (65)	Prospective	Single center	2009–2013	1,432	865	9	Mean, 39 (24–60)	Median, 28 (24–51)	0/571 (0)	3/276 (1.1)	-	-	1412/1432 (98.6)
Schrading et al. (64)	Retrospective	Single center	2007–2010	376	336	9	Range, 10–12	Mean, 27 (5–63)	1/233 (0.4)	-	-	-	-
Speer et al. (42)	Retrospective	Single center	2007–2012	99	90	9	Median, 12 (min. 6)	Mean, 70.8 (12-117)	-	-	4/21 (19.04)	2/78 (2.6)	-
Spick et al. (65)	Retrospective	Single center	2006–2013	487	467	8–10	Range, 12–24	At least 12	0/317 (0)	5/34 (14.7)	-	-	-
Tozaki et al. (94)	Retrospective	Single center	2007–2009	102	100	11	-	6	0/59 (0)	3/28 (10.7)	2/4 (50.0)	-	102/102 (100.0)
Verheyden et al. (41)	Retrospective	Multicenter (9 sites)	2007–2014	1,509	180	7–10	Mean, 12 (12–14)	-	-	27/118 (22.9)	17/72 (23.6)	-	-
Weindfurtner et al. (40)	Retrospective	Single center	2007–2013	257	247	9	At least 6	-	-	-	4/18 (22.2)	0/11 (0)	-
Zebic-Sinkovec et al. (95)	Retrospective	Single center	N/A	15	15	9	Median, 8 (4–17)	-	-	-	-	-	14/15 patients (93.3)

n.: number; ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma *in situ*; N/A: not applicable; *: the false-negative rate was defined as the rate of malignancy identified in patients with benign-concordant magnetic resonance imaging guided needle biopsies; ¥: other high-risk lesions include lobular carcinoma *in situ*, papillary lesions (intraductal papilloma and papilloma with atypia), atypical lobular hyperplasia, flat epithelial atypical radial scars/complex sclerosing lesions; ^: successful biopsy rate is calculated as the number of successfully completed biopsies divided by the number of recommended biopsies. Recommended biopsy number includes the number of non-enhancing lesions on the day of biopsy.

¶: exact date not provided: Bahrs et al. (73) 6-year, Lee et al. (83) 42-month, Lee et al. (71) 45-month, Li et al. (20) 54-month, Liberman et al. (86) 33-month period; †: data in parentheses are range;

§: data in parentheses are percentages

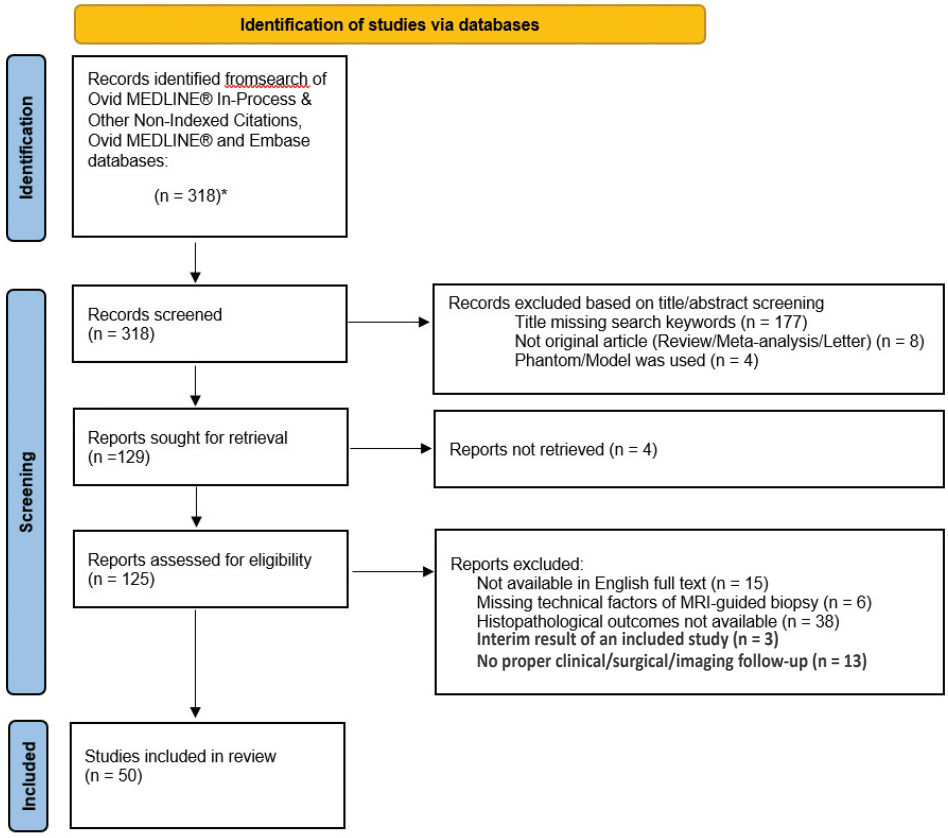

Figure 1. Flow diagram of study selection process

**: after exclusion of duplicates*

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table 2. Pooled rates of malignant, benign and high-risk lesions identified in 4,647 MRI guided breast biopsies

Lesion type	Benign	Malignant	High risk	Total
Mass	2,417 (60.35%)	1,097 (27.39%)	491 (12.26%)	4,005*
Non-mass enhancement	360 (61.96%)	66 (11.36%)	155 (26.67%)	581*
Focus	42 (68.85%)	11 (18.03%)	8 (13.12%)	61*
Total				4647**

*: corresponding histopathological results were missing in 1,140 of masses (1,140/5,145, 22.16%), 1,571 of non-mass enhancements (1,571/2,152, 73.00%) and 82 of foci (82/143, 57.34%); **: lesion type on MRI was available for 67.11% of total successful biopsies (7,440/11,087). In 4,647 of them (4,647/7,440, 62.46%) corresponding histopathology results were also available; MRI: magnetic resonance imaging

Our primary outcomes were:

1) Rate of successfully performed MRI biopsies, 2) rate of pathological outcomes of benign, malignant, high-risk, 3) false negative rate, 4) follow-up outcomes after a benign MRI-guided breast biopsy.

We aimed to identify potential technical and patient clinicopathological factors which may have influenced MRI-guided breast biopsy outcomes.

Reference Standards

A false-negative result was defined as a pathologically proven malignancy after follow-up or immediate excision or re-biopsy following an MRI-guided benign biopsy. Discordant biopsy results occur when benign pathology results do not account for the imaging findings and MRI-guided benign histopathology results include both imaging-concordant and -discordant ones. The false-negative rate was defined as the rate of malignancy identified in those patients with benign-concordant MRI-guided breast biopsies.

High-risk lesions were ADH, LCIS, papillary lesions (intraductal papilloma and papilloma with atypia), ALH, FEA, and RSL/CSL (16). High-risk lesions which were diagnosed at MRI-guided biopsy, and in which a subsequent diagnosis of invasive cancer or DCIS lesion was made at surgical excision or follow-up re-biopsy, were considered as underestimations.

The high-risk lesion underestimation rate was defined as the number of these underestimated lesions divided by their high-risk lesion category (ADH vs other high-risk lesions) at MRI-guided biopsy on histologic examination.

The underestimation rate in DCIS was considered if a pathologically proven invasive carcinoma was seen at surgical excision or follow-up re-biopsy when the MRI-guided biopsy result was DCIS.

A biopsy was counted as technically successful if it was possible to see the target lesion on MRI on the day of the procedure, and the biopsy could be safely performed according to the performing physician.

Statistical Analysis

We performed descriptive statistics on our database using IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY). Qualitative variables were summarized by count and percentage, which included MRI indication, lesion type, and post-biopsy complications. Quantitative variables such as the average core number, age, follow-up time, and lesion size were reported as mean/median.

We tabulated numbers from all studies but some studies were excluded on a per-question basis when they did not report the numbers we were investigating. A random intercept logistic regression model was used to pool technical success rates, canceled biopsy rates, histopathology results, false-negative results, discordant rates, false-negative rates after excluding benign-discordant biopsies and upgrade rates in DCIS, ADH, and other high-risk lesion types. Weighted mean proportion and 95% confidence intervals (CIs) were reported. Of note, the random effects model uses weighted proportions, so: 1) pooled rates were not calculated by dividing the nominator by the denominator, 2) the denominators were different for each analysis, and 3) the pooled rates might not add up to 100%. Clopper-Pearson exact binomial intervals were calculated for each pooled proportion. Between-study heterogeneity was quantified by Higgin's & Thompson's I-squared statistic (25% low heterogeneity, 25–50% medium, >50% high) (17). Odds ratios were pooled using the random effects model.

Meta-regression with mixed-effects models was used to test the moderator effect of the year that the study was published (before or in 2010 versus after 2010), the average number of cores sampled (more than 13 cores sampled vs others), needle size (≤11G vs >11G) and mean lesion size (≤12 mm vs >12 mm) with the outcomes of false-negative rates, DCIS upgrade rates, ADH upgrades, and other high-risk lesions upgrade rates. The corresponding *p*-values were reported and $p<0.05$ was considered statistically significant. We used the R 4.2.1 (R core team, Vienna, Austria) and meta package (18).

Results

Analyzed Data Cohort and Included Studies

A total of 318 abstracts were identified after the exclusion of the repeated articles. Of these 318 abstracts, 189 (59.43%) were excluded after title/abstract screening due to the title missing key research words (n = 177), not being an original article with novel data (n = 8), and using phantoms/models (n = 4). The remaining 129 studies (40.57%) were retrieved and 125 (39.31%) were reviewed in their full text. Seventy-five (25.58%) were excluded due to not being available fully in English (n = 15, 4.72%), missing technical factors of the MRI-guided biopsy (n = 6, 1.89%), not having histopathological outcomes (n = 38, 11.95%), being an interim result of an included study (n = 3, 0.94%) or lacking proper clinical/surgical/imaging follow-up (n = 13, 4.10%). The remaining 50 (15.72%) studies were included in this study and reviewed systematically (Figure 1). Table 1 summarizes the remaining 50 studies which met our inclusion criteria.

The studies we included in this meta-analysis had an overall moderate to low risk of bias. Detailed information on the risk of biases of the studies included is shown in Figure 2.

Technical factors and biopsy success

Pooled reported data from 50 studies with 11,215 target lesions were reviewed. Varying magnet strength (1.5 or 3 Tesla), needle gauges (7–18), and needle types were used for biopsy.

Twenty-five studies out of 50 (50.00%) provided the number of recommended biopsies along with the number of successful ones. The rates were pooled using the random effects model. The pooled rate for canceled biopsies due to non-enhancement on the day of the procedure was 4.58% (95% CI: 1.81–11.11%) (Figure 3a). Canceled biopsies due to non-enhancement were excluded from the technical success analysis yielding a final technical success rate of 99.10% (95% CI: 97.89–99.62%) (Figure 3b).

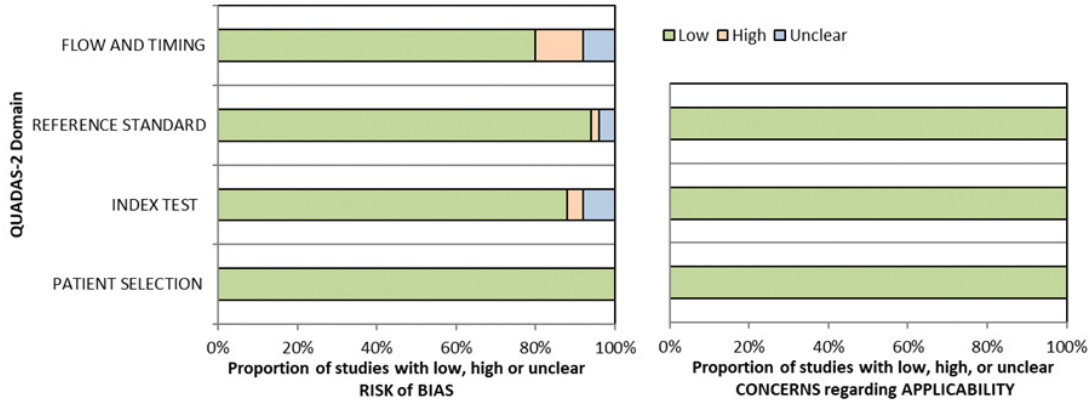

Figure 2. QUADAS-2 graph demonstrates the risk of bias and the applicability of assessment results

A total of 11,087 successful MRI-guided biopsies were included in this review. A median of 13 cores (range: 2–60) was obtained per biopsy. Despite collecting enhancement kinetics data, these were not included in our analysis due to the insufficient number of studies describing lesion enhancement kinetics.

The number of patients was reported in 48/50 (96.0%) studies. In 10,463 successful biopsies in 7,893 women, the mean patient age was 51.8 years (range of mean/median, 45.5–58, standard deviation: ±2.8).

Indications for breast MRI

MRI indication information was available for 5,333 patients (5,333/7,893, 67.57%). The indication was breast cancer staging in 1,496 (28.05%, 95% CI: 26.85–29.28%), screening in 1,427 (26.76%, 95% CI: 25.57–27.97%), breast cancer surveillance in 1,027 (19.26%, 95% CI: 18.21–20.34%), diagnostic (abnormal mammogram/ultrasound or clinical symptoms) in 1,038 (19.46%, 95% CI: 18.41–20.55%), unknown primary in 74 (1.39%, 95% CI: 1.09–1.74%), and other in 271 (5.08%, 95% CI: 4.51–5.71%) (Supplementary Figure 1).

Those patients undergoing MRI for breast cancer surveillance [odds ratio (OR) 1.36 (95% CI: 0.96–1.93; p = 0.09)], diagnostic indication (OR 1.20, 95% CI: 0.87–1.67; p = 0.27) or breast cancer staging (OR 1.20, 95% CI: 0.79–1.82; p = 0.40) had higher rates of malignant outcomes. Of the MRI indications, fewer malignant outcomes were observed in screening (OR 0.47, 95% CI: 0.25–0.87; p = 0.02) (Figure 4).

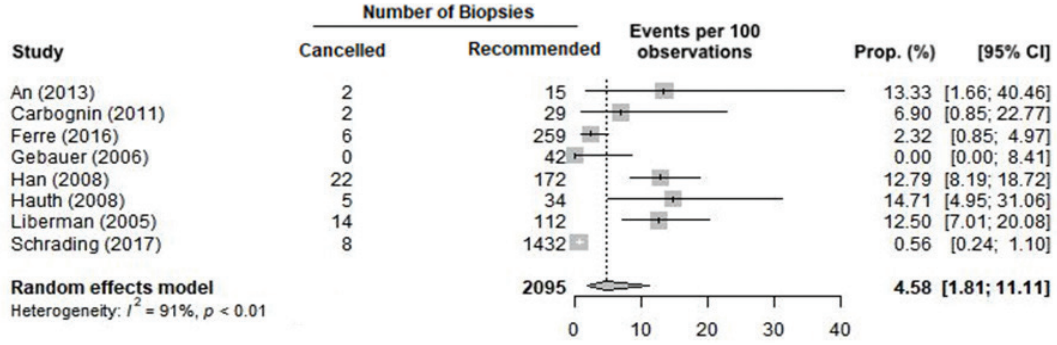

Figure 3a. Forest plot of the rate of the cancelled biopsies due to non-enhancement on the day of the MRI-guided breast biopsy

CI: confidence interval; I²: I squared; Prop.: proportion; MRI: magnetic resonance imaging

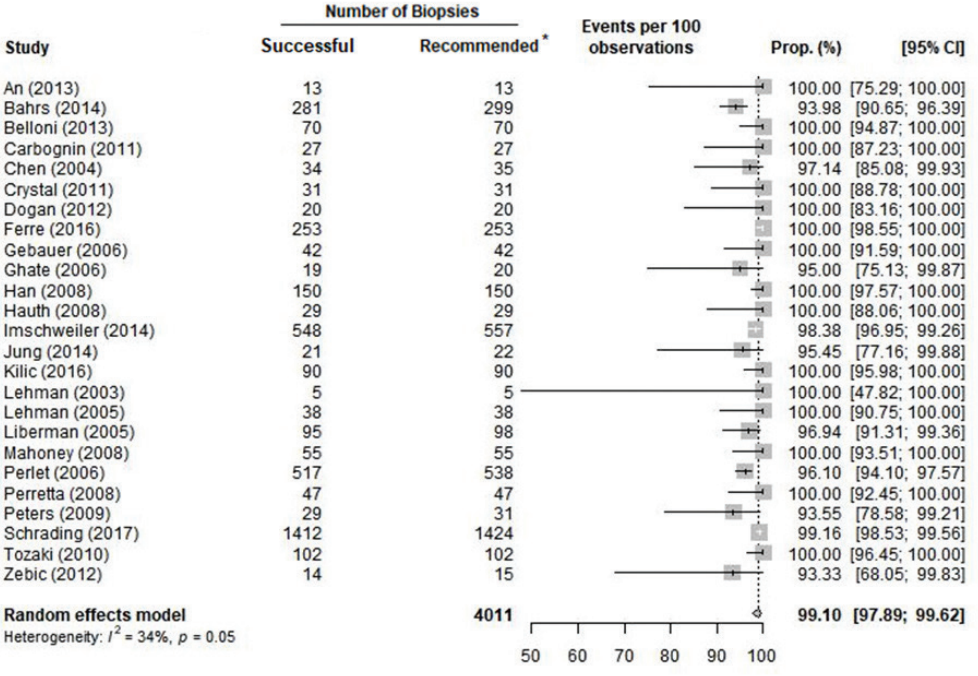

Figure 3b. Forest plot of the technical success rates in MRI-guided biopsies

Prop.: proportion; CI: confidence interval; I²: I squared (25% low heterogeneity, 25–50% medium, >50% high).

*p-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-squared statistic). A low p-value (<0.05) indicates that there is significant heterogeneity between studies. *: cancelled biopsies due to non-enhancement on the day of biopsy were excluded from the technical success analysis. Recommended biopsy number reflects that exclusion*

Histopathology results and lesion types

Of 11,087 successful biopsies, the pooled rate for histopathology results was benign in 65.06% (95% CI: 59.15–70.54%), malignant in 29.64% (95% CI: 23.58–36.52%; invasive cancer, 15.16%, 95% CI: 12.56–18.18%; DCIS, 9.51%, 95% CI: 7.63–11.80%) and high risk in 16.69% (95% CI: 9.96–26.64%; ADH, 6.33%, 95% CI: 4.24–9.36%; other high-risk lesions, 12.73%, 95% CI: 7.12–21.73%) (Supplementary Figure 2). The pooled rate for invasive cancer among the malignant results was 62.10% (95% CI: 57.09–66.87%) and it was 40.00% (95% CI: 33.48–46.89%) for DCIS (Supplementary Figure 3). Among the high-risk lesions, the ADH pooled rate was 44.56% (95% CI: 30.84–59.15%) and the pooled rate for high-risk lesions other than ADH was 63.17% (95% CI: 51.40–73.55%) (Supplementary Figure 4).

Lesion type on MRI was available in 7,440 (67.11%) biopsies [5,145 mass (44.93%), 2,152 non-mass enhancement (18.79%), 143 focus (1.25%)]. The average mass enhancement size was 10.1 mm (range: 2–60) while the average non-mass enhancement size was 22.8 mm (range: 4–140), yielding an overall average lesion size of 12.4 mm (range: 2–140). Corresponding histopathological results were missing in 1,140 masses (1,140/5,145, 22.16%), 1,571 non-mass enhancements (1,571/2,152, 73.00%) and 82 foci (82/143, 57.34%). Of the 4,005 mass lesions, 2,417 (60.35%) were benign, 1,097 (27.39%) were malignant and 491 (12.26%) were high-risk. Overall, mass lesions were more likely to yield malignancy compared to non-mass and foci lesions [27.39% vs 11.36% (non-mass) and 18.03% foci, $p<0.001$]. Table 2 shows lesion types on MRI with the corresponding histopathology results.

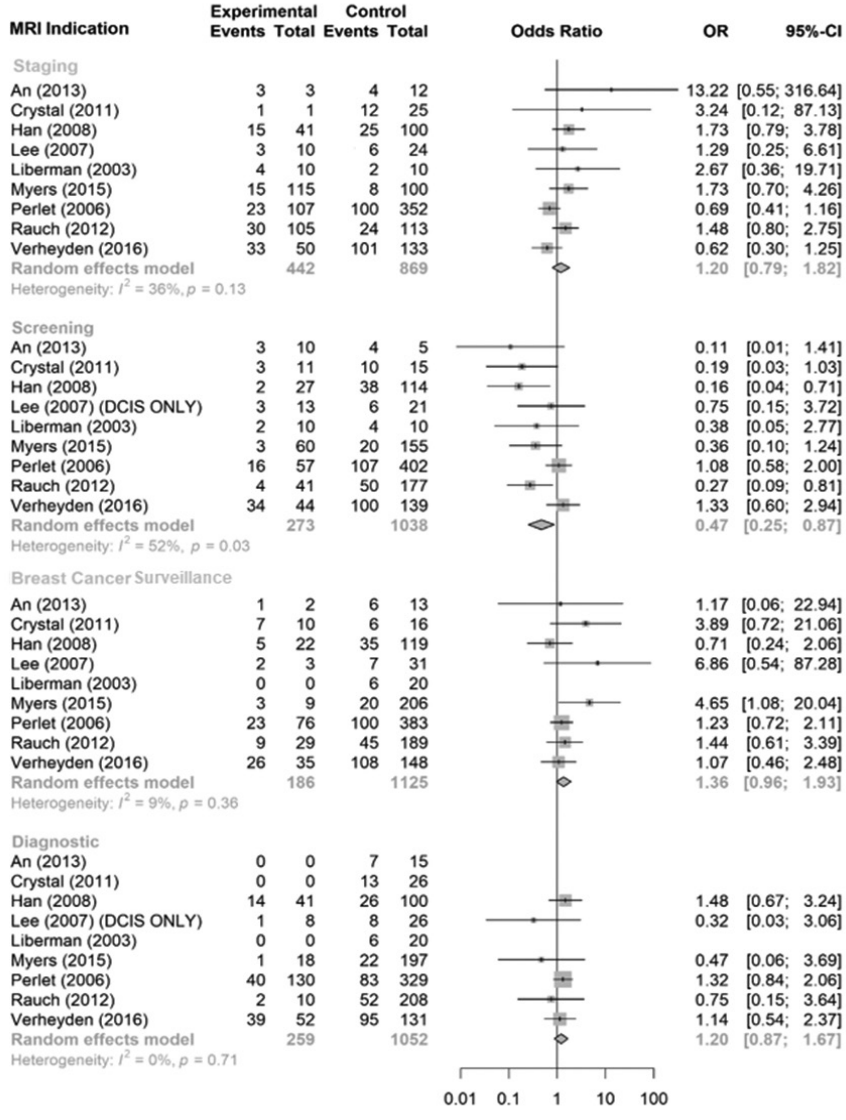

Figure 4. Forest plot showing the association of MRI indication with the likelihood of malignancy outcome in MRI-guided breast biopsy

MRI: magnetic resonance imaging; OR: odds ratio; CI: confidence interval; I²: I squared (25% low heterogeneity, 25–50% medium, >50% high); DCIS: ductal carcinoma in situ

p-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-square statistic). A low p-value (<0.05) indicates there is significant heterogeneity between studies

Upgrade Rates

Surgical upgrade to invasive cancer occurred in 12.24% of DCIS lesions (95% CI: 7.76–18.77%) (Figure 5a). The upgrade rate among all high-risk lesions was 15.14% (95% CI: 10.69–21.17%) (Figure 5b). Of 294 ADH lesions, upgrade to DCIS or invasive cancer was seen in 31.81% (95% CI: 25.57–38.77%) (Figure 5c) while a pooled upgrade rate of 6.75% (95% CI: 2.57–16.56%) (Figure 5d) was seen in high-risk lesions other than ADH (LCIS, ALH, FEA RSL/CSL). Among high-risk lesions, ADH had the highest upgrade rate to malignancy [OR 3.51 (95% CI: 2.18–5.65), p<0.001].

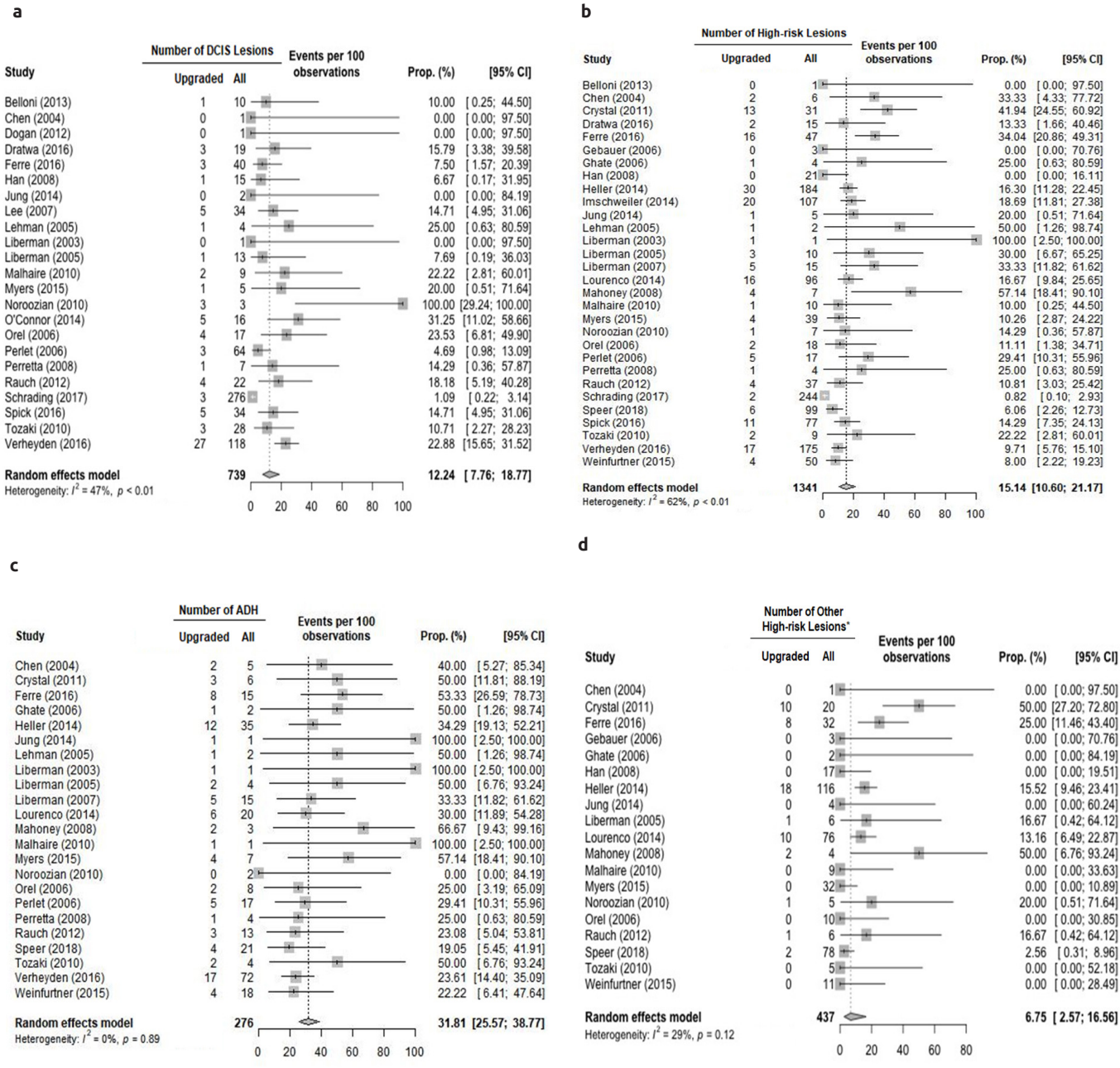

Figure 5. Forest plots of upgrade rates of ductal carcinoma *in situ* (DCIS) to invasive cancer, b.) high-risk lesions to DCIS or invasive cancer, c.) atypical ductal hyperplasia (ADH) to DCIS or invasive cancer, and d.) high-risk lesions other than ADH to DCIS or invasive cancer after MRI-guided breast biopsy

Prop.: proportion; CI: confidence interval; I^2: I squared (25% low heterogeneity, 25–50% medium, >50% high); DCIS: ductal carcinoma in situ; ADH: atypical ductal hyperplasia

p-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-squared statistic). A low p-value (<0.05) indicates that there is significant heterogeneity between studies.

**: other high-risk lesions include lobular carcinoma in situ, papillary lesions (intraductal papilloma and papilloma with atypia), atypical lobular hyperplasia, flat epithelial atypical radial scars/complex sclerosing lesions*

Benign-discordant biopsies and false negative rates

Short-term follow-up with a median of 25 months (range: 0.4–117) was performed in 1,651 (20.92%) patients. The pooled malignancy rate after the benign biopsy result was 1.64% (95% CI: 0.96–2.81%) (Figure 6a). The pooled radiology-pathology discordance rate was 2.48% (95% CI: 1.62–3.77%) (Figure 6b). When benign-discordant biopsies were excluded, the pooled false negative rate was 0.75% (95% CI: 0.34–1.62%) (Figure 6c).

When we compared studies based on the year published (before/in 2010 versus after 2010), needle size (≤11G vs >11G), the average number of cores sampled (more than 13 cores sampled vs others), and average lesion size (≤12 mm vs >12 mm), we did not find enough evidence to establish any association with the false negative rate, DCIS to invasive cancer or the high-risk lesion upgrade rate (*p*-values: 0.13–1.00). Table 3 represents the comparison results in detail.

Post-biopsy Complications

Post-biopsy complications [158 (1.42%) hematoma, 17 (0.15%) vasovagal response, 19 (0.17%) other] were rare and seen in 186 out of 7,893 patients (2.36%, 95% CI: 2.03–2.72%).

Discussion and Conclusion

MRI-guided breast biopsy is an efficient and highly accurate technique with high technical success (99.10%, 95% CI: 97.89–99.62%) and a low false-negative rate (0.75%, 95% CI: 0.34–1.62%). We found a low false-negative rate in benign-concordant lesions, which supports that there is no need to follow-up patients with MRI after a benign-concordant biopsy result (19-22).

We found that benign biopsies accounted for more than half of all MRI-guided breast biopsies (65.06%, 95% CI: 59.15–70.54%) in all lesion types (60.35% in mass, 61.96% in non-mass enhancement, 68.85% in focus). Our findings suggest that enhancing lesion type by ACR BI-RADS descriptors influenced the malignancy rate and that mass lesions were more likely to yield malignancy compared to non-mass lesions and foci (27.39% vs 11.36% non-mass and 18.03% foci, $p<0.001$). This finding is in keeping with previous studies which reported that the malignancy rate is higher for masses (34–60%) (23-25). However, our pooled malignancy rate in mass lesions was somewhat less than had been previously reported. Masses are more likely to be identified on second-look ultrasound (58–65%) than non-mass-like lesions (12–54%), and consequently were more likely to undergo ultrasound-guided needle biopsy (26-29). It was also reported that lesions which were seen on second-look ultrasound were more likely to be malignant (57.4–91.7%) (28-31). Collectively, this results in only those masses likely to be benign undergoing MRI-guided biopsy, which can be the reason why we saw a low pooled malignancy rate.

In our study, the pooled rate for malignancy was 29.64% (95% CI: 23.58–36.52%). Patients undergoing MRI for breast cancer surveillance, diagnostic indication, and breast cancer staging had a higher rate of malignant results (OR, 1.36, 1.20, and 1.20; respectively), although none of them were statistically significant (p=0.09–0.40).

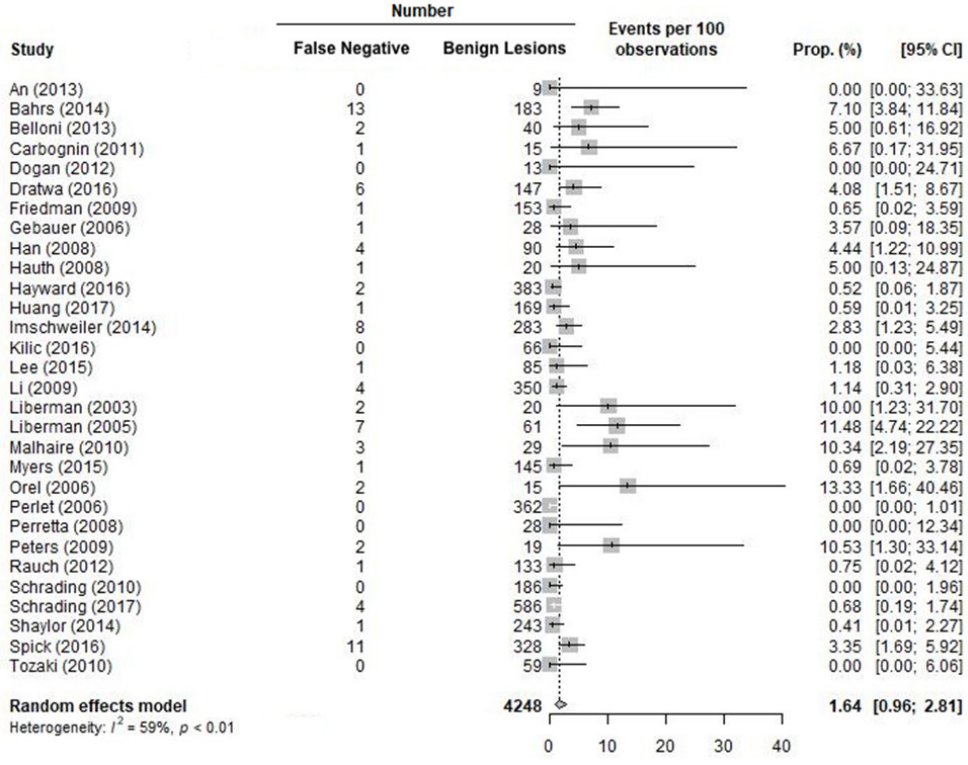

Figure 6a. Forest plots demonstrating malignancy and radiology-pathology discordance rates following a benign MRI-guided breast biopsy, pooled forest plot of overall malignancy rates after a benign MRI-guided breast biopsy

Prop.: proportion; CI: confidence interval; I²: I squared (25% low heterogeneity, 25–50% medium, >50% high).

*p-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-square statistic). A low p-value (<0.05) indicates that there is significant heterogeneity between studies; *: identified after follow-up (median, 25; range, 0.4-117 months) or immediate excision or re-biopsy*

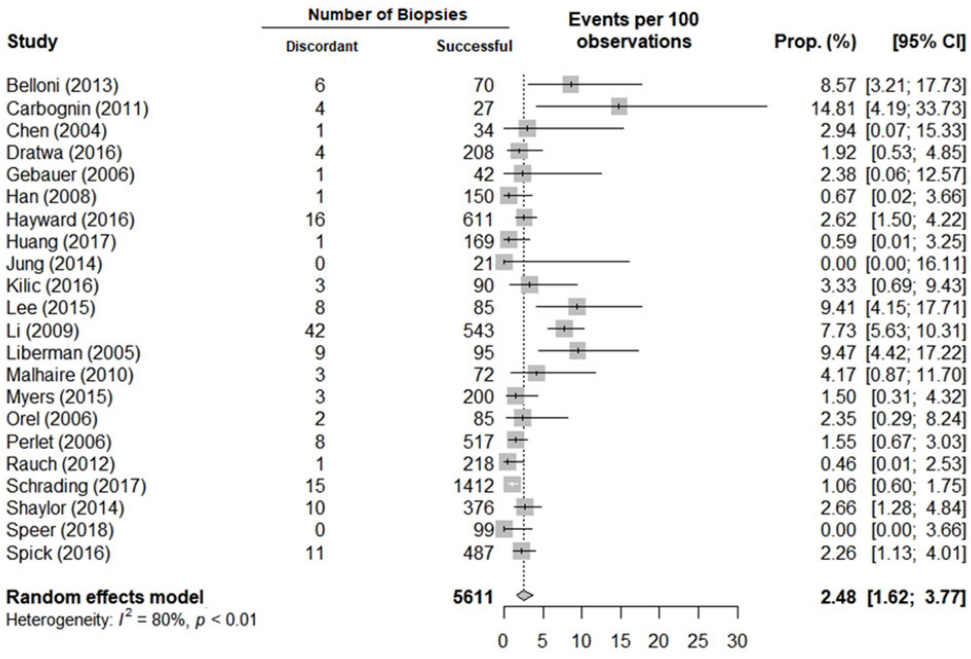

Figure 6b. Forest plots demonstrating malignancy and radiology-pathology discordance rates following a benign MRI-guided breast biopsy, radiology-pathology discordance rate after MRI-guided breast biopsy

Prop.: proportion; CI: confidence interval; I²: I squared (25% low heterogeneity, 25–50% medium, >50% high).

*p-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-square statistic). A low p-value (<0.05) indicates that there is significant heterogeneity between studies; *: identified after follow-up (median, 25; range, 0.4-117 months) or immediate excision or re-biopsy*

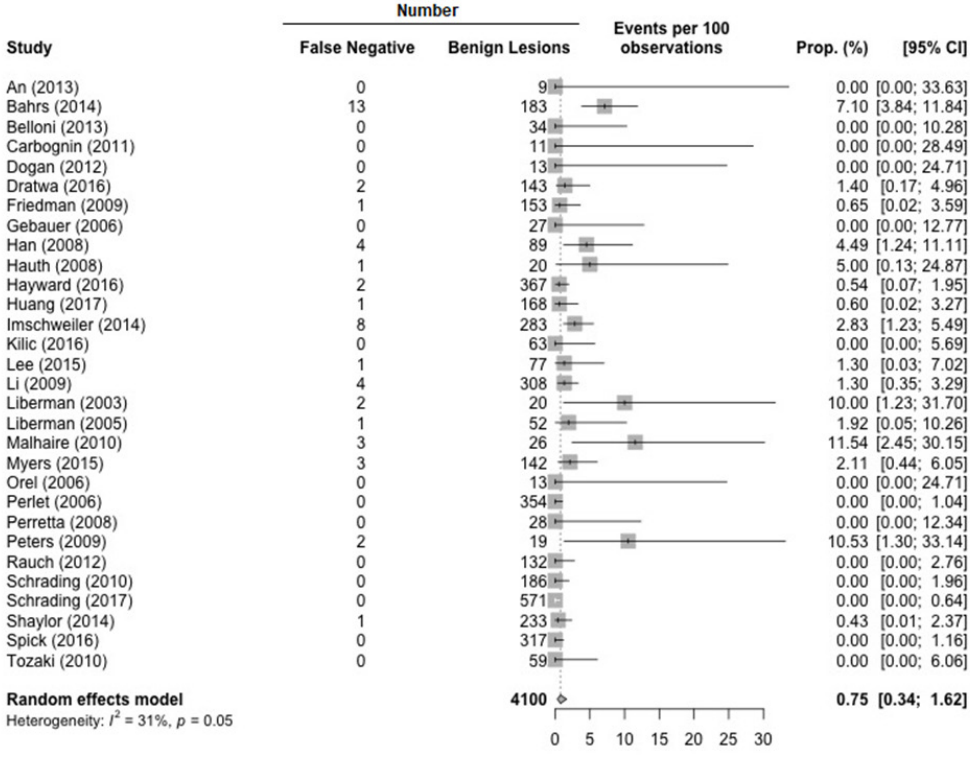

Figure 6c. Forest plots demonstrating malignancy and radiology-pathology discordance rates following a benign MRI-guided breast biopsy, malignancy identified* following a benign-concordant MRI-guided breast biopsy

Prop.: proportion; CI: confidence interval; I²: I squared (25% low heterogeneity, 25–50% medium, >50% high).

*p-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-square statistic). A low p-value (<0.05) indicates that there is significant heterogeneity between studies; *: identified after follow-up (median, 25; range, 0.4-117 months) or immediate excision or re-biopsy*

Table 3. Comparison of false negative, DCIS upgrade and high-risk lesion upgrade rates based on study characteristics

	Study year			Needle size			Number of cores sampled			Lesion size		
	Before or in 2010	After 2010	p*	≤11G	>11G	p*	≤13 cores	>13 cores	p*	≤12 mm	>12 mm	p*
False negative rate (%)	1.16 (0.4, 3.5)	0.5 (0.2, 1.5)	0.22	0.7 (0.3, 1.6)	2.5 (1.4, 4.6)	0.40	0.9 (0.2, 4.9)	1.2 (0.1, 10.2)	0.73	2.0 (0.6, 6.2)	0.1 (0, 32.2)	0.33
DCIS to Invasive cancer upgrade rate (%)	13.51 (7.8, 22.5)	10.9 (5.5, 20.5)	0.63	12.3 (7.5, 19.3)	13.3 (3.4, 40.5)	0.97	12.5 (5.7, 25.2)	6.2 (1.2, 27.1)	0.64	13.0 (7.1, 22.5)	19.8 (15.1, 25.5)	0.18
ADH upgrade rate (%)	36.8 (26.2, 48.8)	30.3 (23.1, 38.5)	0.29	31.5 (25.2, 38.5)	42.9 (14.4, 77.0)	0.53	30.2 (20.1, 42.5)	100 (0,-)	1.00	35.7 (16.1, 61.7)	27.0 (19.6, 35.8)	0.52
Other high risk lesion upgrade rate¥ (%)	3.8 (0.5, 25.7)	9.0 (3.2, 23.2)	0.39	6.9 (2.6, 16.8)	0 (0,-)	0.98	7.2 (2.7, 17.9)	0 (0,-)	1.00	3.0 (1.0, 8.9)	10.3 (0.9, 59.1)	0.13

DCIS: ductal carcinoma in situ; ADH: atypical ductal hyperplasia; G: gauge; all values are percentages. Data in parentheses are 95% confidence intervals. Upper limit of some proportions was not estimable due to small sample size. ¥: other high-risk lesions include lobular carcinoma in situ, papillary lesions (intraductal papilloma and papilloma with atypia), atypical lobular hyperplasia, flat epithelial atypical radial scars/complex sclerosing lesions; *p-values were calculated using meta-regression with mixed effects models

Detection of malignancy was significantly lower in those patients who underwent MRI for screening purposes (OR 0.47, 95% CI: 0.25, 0.87; p=0.02). When interpreting our results, it should be considered that the study results included were homogeneous in breast cancer surveillance, staging, and diagnostic indication groups whereas in the screening group, they were heterogeneous (*p*-values of the random effects models were: 0.36, 0.13, 0.71, and 0.03, respectively). In contrast to previous studies which reported the frequency of malignancy to be significantly higher in those patients presenting for diagnostic versus screening purposes (screening 10–14% vs diagnostic 28–36%; $p<0.05$) (24, 31), we did not compare individual indications with each other. Rather, with a Bayesian model, we compared whether the indication of interest affected the MRI biopsy outcome or not. This difference in analyzing methods should be considered.

ADH identified with MRI-guided biopsy was found to have a pooled underestimation rate of 31.13% (95% CI: 25.17–37.78%), slightly higher than that of stereotactic biopsy (mean 20%, range 10–27%, with 11-gauge vacuum-assisted biopsy probe) (32-37). ADH has high upgrade rates (15.0–53.3%) verified over multiple studies (31, 38-42). In a recent study by Michaels et al., it was found that ADH was more likely to upgrade to cancer at surgical excision than other high-risk lesions (22.5% vs 3.4%, p=0.005) and that larger high-risk lesions had a greater tendency for an upgrade than smaller lesions (1.8 vs 1.2 cm, p=0.073). Furthermore, Rauch et al. (31) and Heller et al. (38) reported that the risk of upgrade in MRI-detected high-risk lesions was higher if the high-risk lesion was identified in the same breast as a prior malignancy, or if the patient had had a recent diagnosis of malignancy. Our findings underscore that the surgical upgrade to malignancy is common among high-risk lesions, especially ADH. Traditionally, it has been recommended to surgically remove high-risk lesions due to their high degree of underestimation on biopsy. However, the most recent recommendations advocate a more cautious multidisciplinary approach to assess the individual risk of patients and to avoid surgical excision whenever possible (43, 44). Unfortunately, due to a lack of correlating data on patient history, we could not further investigate multivariable associations on the surgical upgrade of high-risk lesions diagnosed at MRI-guided breast biopsy to predict the individual risks of patients.

MRI-guided breast biopsy is a safe technique with low complication rates (0–6%) (3, 10, 11, 45-48). Complications are generally minor (hematomas, malaise, skin damage) and easily managed (11, 47, 48). In our systematic review, we found a complication rate of 2.36%, almost all comprising hematomas, and none of them requiring major interventions, such as surgery.

Occasionally, a finding identified as suspicious on prior breast MRI no longer enhances on the day of the biopsy. It has been hypothesized that these cancellations occur as a result of changing hormonal status (related to the menstrual cycle, menopausal status, age, hormone suppression, or replacement therapy) which can affect background parenchymal enhancement, patient positioning, or the over-compression of the breast within the MRI-biopsy coil (11, 24, 49-55). It has also been reported that non-visualization was more commonly seen in non-mass enhancement (54). In our review, 4.58% (95% CI: 1.81–11.11%) of the scheduled biopsies were canceled due to non-enhancement on the day of the biopsy, with single center reports ranging from 6.9–13% (11, 24, 49, 50, 53-55). The lower pooled cancellation rate due to non-enhancement in our study may be due to our inclusion of newer

studies performed over the last decade, which reflect the learning curve to appropriately recognize normal but variably enhancing parenchyma by radiologists, resulting in fewer biopsies recommended for benign background enhancement. Previously, it had been reported that the cancer detection rate among lesions for which biopsy was canceled due to non-enhancement was low (2–10%) (49, 53, 55). This rate could not be analyzed in our systematic review.

Careful radiologic-pathologic correlation is necessary to confirm the concordance of imaging findings with pathology. In our review, imaging-pathologic discordance occurred in 2.48% (95% CI: 1.62–3.77%) of MRI-guided biopsies. This discordance rate is similar to rates reported for stereotactic and ultrasound-guided needle biopsies (1.3–4.4%) and further validates the MRI-guided breast biopsy technique (56-60). Previously, it was found that lesions which were missed rather than sampled on MRI-guided biopsies had a higher rate of imaging discordance, and lesions with discordant imaging had a higher risk of malignancy (30–100%) (47, 56, 61). This malignancy risk was higher than had been reported for stereotactic-guided biopsy (11.7–53.8%) (58-60) and ultrasound-guided biopsy (0.1–2.4%) (57, 62, 63). This could have been caused by the MRI patient population characteristics, which includes high-risk patients, patients with newly diagnosed breast cancer or a history of breast cancer. Since a similar discordance rate was observed in MRI-guided biopsy with higher malignancy, there should be a standard reference for reporting false-negative rates in MRI-guided biopsies. We realized that there is no standard of reference and, in some studies, benign-discordant biopsies which were found to be malignant after re-biopsy or surgical excision were counted as false-negatives (64-66), while in others, those cases were excluded from the false negative cases (67). In our systematic review, we defined the false negative rate as the rate of malignancy identified after a benign-concordant MRI-guided breast biopsy, and the pooled false-negative rate for the studies included was 0.75% (95% CI: 0.34–1.62%).

The limitations of this meta-analysis include the heterogeneity between the groups and the across studies (I-squared >25%). Most studies were retrospective in design, with only three prospective studies contributing data into the pooled estimates. As a result, bias and confounding could not be fully eliminated, and the interpretation of our findings should factor in the heterogeneity between the studies.

In the series published to date, the reported false-negative rates were determined only for those cases in which follow-up or immediate excision/re-biopsy was performed. In addition to that, due to the retrospective study design, only those lesions which were successfully biopsied were reported in some of the studies included (21, 38, 68-71). Thus, the technical success rate was missing. We did not pool those studies' data in our technical success rate analysis so as not to inflate the technical success rate. However, the true false-negative and the technical success rates of MR-guided breast biopsy remain to be determined, and this was another limitation of our study.

Most of the articles lacked correlating data between histopathology and clinical indication. Hence, we had to perform our correlation analysis with 9 studies (out of 50 the studies included), which limited the statistical power of our analysis. Another limitation was inconsistent reporting of study-level data for variables such as age, number of cores sampled, lesion sizes, and follow-up times. We used the available mean or median values for those variables in our pooled analysis.

The lack of standardization in reporting the technical success rates and false negative rates made it hard to pool the available data. Despite this, we had determined our reference standards before we began our literature search and stuck to those standards. Three investigators independently extracted the relevant information in addition to reviewing and confirming the selected articles. We also applied Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) items to assess study quality and the likelihood of bias (15). Our estimates, therefore, represent the most comprehensive evidence summary on breast MRI-guided biopsy outcomes, despite the above-mentioned limitations inherent in this study-level meta-analysis.

MRI-guided breast biopsy is a highly accurate technique with a high technical success rate, and negligible false negative and complication rates. Our findings can be used to guide breast radiologist practice, to inform transparent discussion with patients on the consequences of having an MRI-guided breast biopsy, and to assist the development of evidence-based clinical guidelines on follow-up recommendations in benign-concordant breast lesions. The substantial degree of variation in performance metrics across the studies included in our analysis suggests that ongoing quality improvement efforts are needed.

Ethics Committee Approval: The requirement to obtain institutional review board approval was waived for this literature review, which involved only publicly available data.

Informed Consent: Informed consent was not needed in this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.B., B.E.D.; Design: B.B.Ö., Y.X., S.B., M.E.S., B.E.D.; Data Collection or Processing: B.B.Ö., J.Y., Y.X., S.B., B.E.D.; Analysis or Interpretation: B.B.Ö., J.Y., Y.X., S.B., M.E.S., B.E.D.; Literature Search: B.B.Ö., J.Y., Y.X., S.B., M.E.S., B.E.D.; Writing: B.B.Ö., J.Y., Y.X., S.B., M.E.S., B.E.D.

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

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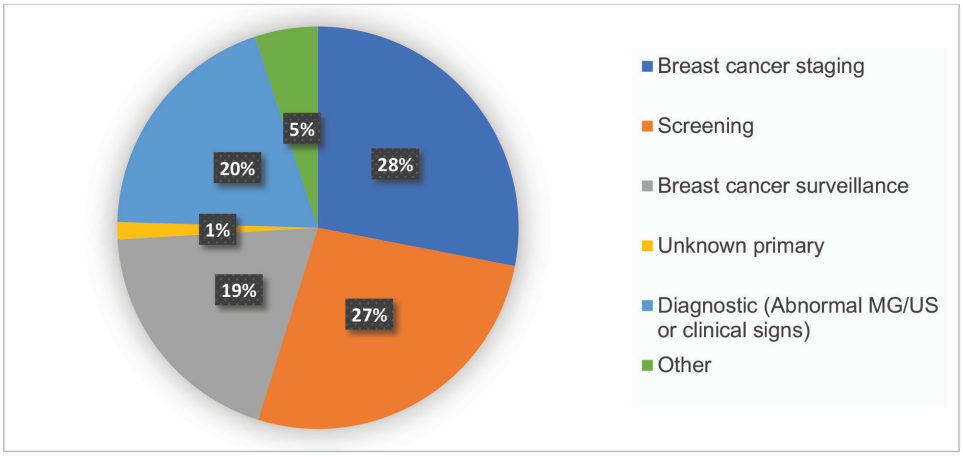
Supplementary Table 1. Databases searched and search strategies

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	exp BREAST/	35377
2	exp BREAST NEOPLASMS/	235614
3	(breast* or mammar* or mastectom*).ti,ab.	382212
4	or/1-3	421273
5	limit 4 to yr="2000 -Current"	255896
6	exp MAGNETIC RESONANCE IMAGING/	341859
7	MAGNETIC RESONANCE IMAGING, INTERVENTIONAL/	1005
8	(MRI or "magnetic resonance").ti,ab.	331892
9	(MR adj2 (guid* or direct* or detect*1 or detected or detecting or screen* or control*)).ti,ab.	3498
10	or/6-9	475519
11	5 and 10 [breast + MRI]	8477
12	exp BIOPSY/	236167
13	biops*.ti,ab.	312377
14	or/12-13	440694
15	11 and 14 [breast + MRI + biopsy]	1825
16	((MR or MRI or "magnetic resonance") adj5 (biops* or VAB or vacuum) adj5 (breast* or mammar* or mastectom*)).ti,ab.	222
17	15 and 16	197
18	exp MASS SCREENING/	106278
19	(screen* or surveillance).ti.	158825
20	or/18-19	214191
21	11 and 20 [breast + MRI + screening]	594
22	((MR or MRI or "magnetic resonance") adj5 screen* adj5 (breast* or mammar* or mastectom*)).ti,ab.	290
23	(21 and 22) not 17 [non-biopsy records]	203
24	PREDICTIVE VALUE OF TESTS/	155709
25	(PPV* or "predictive value*" or NPV).ti,ab.	81737
26	(false adj3 (positive* or negative*)).ti,ab.	60591
27	((diagnostic* or biops*) adj3 yield*).ti,ab.	8702
28	(diagnostic* adj3 (perform* or specificity or precision or value)).ti,ab.	48191
29	((cancer* or neoplas* or carcinom* or malignan*) adj3 (rate or rates or frequen*)).ti,ab.	44057
30	((patholog* or histopatholog* or histolog* or radiopatholog*) adj3 correlat*).ti,ab.	24752
31	exp *BREAST NEOPLASMS/pa and (exp *MAGNETIC RESONANCE IMAGING/mt or MAGNETIC RESONANCE IMAGING, INTERVENTIONAL/mt or exp IMAGE-GUIDED BIOPSY/)	683
32	or/24-31 [PPV & related terms]	370031
33	17 and 32 [most likely relevant biopsy]	112
34	17 not 33 [other biopsy]	85
35	23 and 32 [most likely relevant screening]	71
36	23 not 35 [other screening]	132
37	limit 17 to english language	180
38	17 not 37 [biopsy non-English]	17
39	limit 23 to english language	196
40	23 not 39 [screening non-English]	7

Supplementary Table 2. Review-tailored QUADAS-2 tool

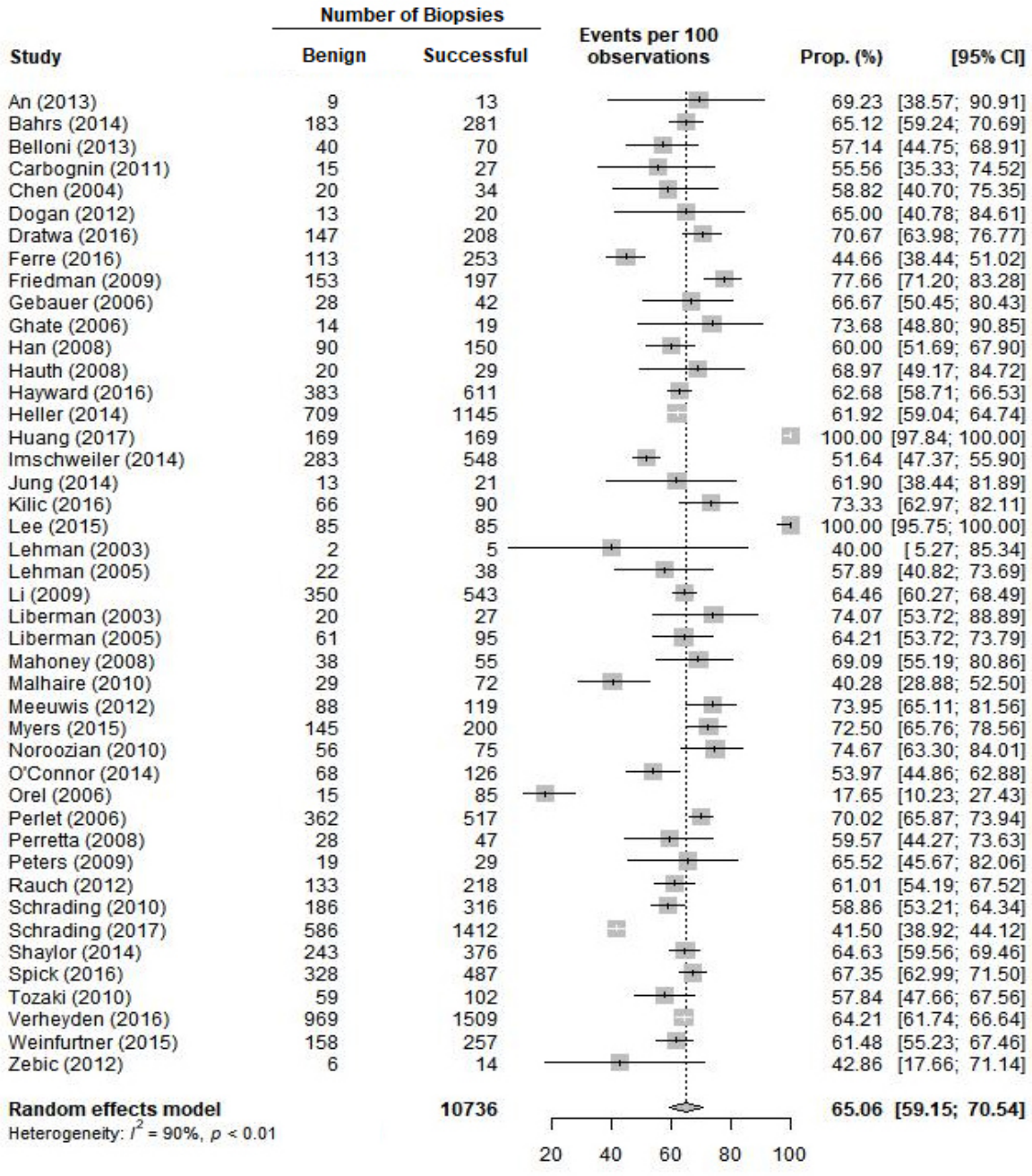
Domain	Signaling questions	Risk of bias	Concerns regarding applicability
Patient selection	Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	Could the selection of patients have introduced bias?	Are there concerns that the included patients do not match the review question?
Index Test	Were the index test results interpreted without knowledge of the results of the reference standard? Were the technical factors of the index test (Magnet strength, needle size) pre-specified?	Could the conduct or interpretation of the index test have introduced bias?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Reference standard	Is the reference standard likely to correctly classify the target condition?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Are there concerns that the target condition as defined by the reference standard does not match the review question?
Flow and timing	Was there an appropriate interval between index test(s) and reference standard? Did all patients receive a reference standard?	Could the patient flow have introduced bias?	



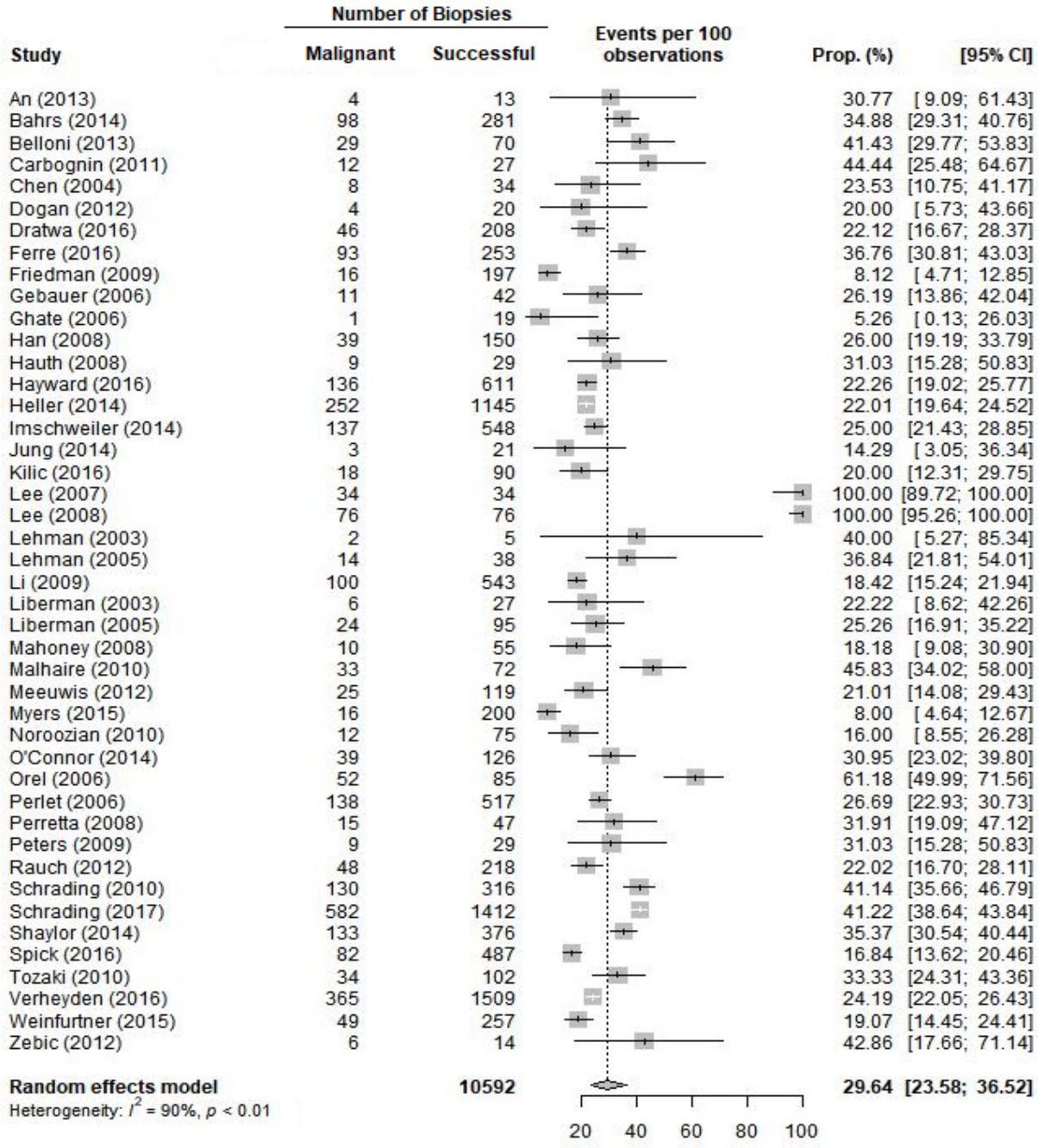
Supplementary Figure 1. Pie chart showing diagnostic indication for MRI-guided breast biopsy

MG: mammography; US: ultrasound; MRI: magnetic resonance imaging

a


Number of Biopsies
Study
Benign
Successful
Events per 100 observations
Prop. (%)
[95% CI]
An (2013) 9 13 69.23 [38.57; 90.91]
Bahrs (2014) 183 281 65.12 [59.24; 70.69]
Belloni (2013) 40 70 57.14 [44.75; 68.91]
Carbognin (2011) 15 27 55.56 [35.33; 74.52]
Chen (2004) 20 34 58.82 [40.70; 75.35]
Dogan (2012) 13 20 65.00 [40.78; 84.61]
Dratwa (2016) 147 208 70.67 [63.98; 76.77]
Ferre (2016) 113 253 44.66 [38.44; 51.02]
Friedman (2009) 153 197 77.66 [71.20; 83.28]
Gebauer (2006) 28 42 66.67 [50.45; 80.43]
Ghate (2006) 14 19 73.68 [48.80; 90.85]
Han (2008) 90 150 60.00 [51.69; 67.90]
Hauth (2008) 20 29 68.97 [49.17; 84.72]
Hayward (2016) 383 611 62.68 [58.71; 66.53]
Heller (2014) 709 1145 61.92 [59.04; 64.74]
Huang (2017) 169 169 100.00 [97.84; 100.00]
Imschweiler (2014) 283 548 51.64 [47.37; 55.90]
Jung (2014) 13 21 61.90 [38.44; 81.89]
Kilic (2016) 66 90 73.33 [62.97; 82.11]
Lee (2015) 85 85 100.00 [95.75; 100.00]
Lehman (2003) 2 5 40.00 [5.27; 85.34]
Lehman (2005) 22 38 57.89 [40.82; 73.69]
Li (2009) 350 543 64.46 [60.27; 68.49]
Liberman (2003) 20 27 74.07 [53.72; 88.89]
Liberman (2005) 61 95 64.21 [53.72; 73.79]
Mahoney (2008) 38 55 69.09 [55.19; 80.86]
Malhaire (2010) 29 72 40.28 [28.88; 52.50]
Meeuwis (2012) 88 119 73.95 [65.11; 81.56]
Myers (2015) 145 200 72.50 [65.76; 78.56]
Noroozian (2010) 56 75 74.67 [63.30; 84.01]
O'Connor (2014) 68 126 53.97 [44.86; 62.88]
Orel (2006) 15 85 17.65 [10.23; 27.43]
Perlet (2006) 362 517 70.02 [65.87; 73.94]
Perretta (2008) 28 47 59.57 [44.27; 73.63]
Peters (2009) 19 29 65.52 [45.67; 82.06]
Rauch (2012) 133 218 61.01 [54.19; 67.52]
Schrading (2010) 186 316 58.86 [53.21; 64.34]
Schrading (2017) 586 1412 41.50 [38.92; 44.12]
Shaylor (2014) 243 376 64.63 [59.56; 69.46]
Spick (2016) 328 487 67.35 [62.99; 71.50]
Tozaki (2010) 59 102 57.84 [47.66; 67.56]
Verheyden (2016) 969 1509 64.21 [61.74; 66.64]
Weinfurtner (2015) 158 257 61.48 [55.23; 67.46]
Zebic (2012) 6 14 42.86 [17.66; 71.14]
Random effects model 10736 65.06 [59.15; 70.54]
Heterogeneity: I^2 = 90%, p < 0.01
20
40
60
80
100

b


Number of Biopsies
Study
Malignant
Successful
Events per 100 observations
Prop. (%)
[95% CI]
An (2013) 4 13 30.77 [9.09; 61.43]
Bahrs (2014) 98 281 34.88 [29.31; 40.76]
Belloni (2013) 29 70 41.43 [29.77; 53.83]
Carbognin (2011) 12 27 44.44 [25.48; 64.67]
Chen (2004) 8 34 23.53 [10.75; 41.17]
Dogan (2012) 4 20 20.00 [5.73; 43.66]
Dratwa (2016) 46 208 22.12 [16.67; 28.37]
Ferre (2016) 93 253 36.76 [30.81; 43.03]
Friedman (2009) 16 197 8.12 [4.71; 12.85]
Gebauer (2006) 11 42 26.19 [13.86; 42.04]
Ghate (2006) 1 19 5.26 [0.13; 26.03]
Han (2008) 39 150 26.00 [19.19; 33.79]
Hauth (2008) 9 29 31.03 [15.28; 50.83]
Hayward (2016) 136 611 22.26 [19.02; 25.77]
Heller (2014) 252 1145 22.01 [19.64; 24.52]
Imschweiler (2014) 137 548 25.00 [21.43; 28.85]
Jung (2014) 3 21 14.29 [3.05; 36.34]
Kilic (2016) 18 90 20.00 [12.31; 29.75]
Lee (2007) 34 34 100.00 [89.72; 100.00]
Lee (2008) 76 76 100.00 [95.26; 100.00]
Lehman (2003) 2 5 40.00 [5.27; 85.34]
Lehman (2005) 14 38 36.84 [21.81; 54.01]
Li (2009) 100 543 18.42 [15.24; 21.94]
Liberman (2003) 6 27 22.22 [8.62; 42.26]
Liberman (2005) 24 95 25.26 [16.91; 35.22]
Mahoney (2008) 10 55 18.18 [9.08; 30.90]
Malhaire (2010) 33 72 45.83 [34.02; 58.00]
Meeuwis (2012) 25 119 21.01 [14.08; 29.43]
Myers (2015) 16 200 8.00 [4.64; 12.67]
Noroozian (2010) 12 75 16.00 [8.55; 26.28]
O'Connor (2014) 39 126 30.95 [23.02; 39.80]
Orel (2006) 52 85 61.18 [49.99; 71.56]
Perlet (2006) 138 517 26.69 [22.93; 30.73]
Perretta (2008) 15 47 31.91 [19.09; 47.12]
Peters (2009) 9 29 31.03 [15.28; 50.83]
Rauch (2012) 48 218 22.02 [16.70; 28.11]
Schrading (2010) 130 316 41.14 [35.66; 46.79]
Schrading (2017) 582 1412 41.22 [38.64; 43.84]
Shaylor (2014) 133 376 35.37 [30.54; 40.44]
Spick (2016) 82 487 16.84 [13.62; 20.46]
Tozaki (2010) 34 102 33.33 [24.31; 43.36]
Verheyden (2016) 365 1509 24.19 [22.05; 26.43]
Weinfurtner (2015) 49 257 19.07 [14.45; 24.41]
Zebic (2012) 6 14 42.86 [17.66; 71.14]
Random effects model 10592 29.64 [23.58; 36.52]
Heterogeneity: I^2 = 90%, p < 0.01
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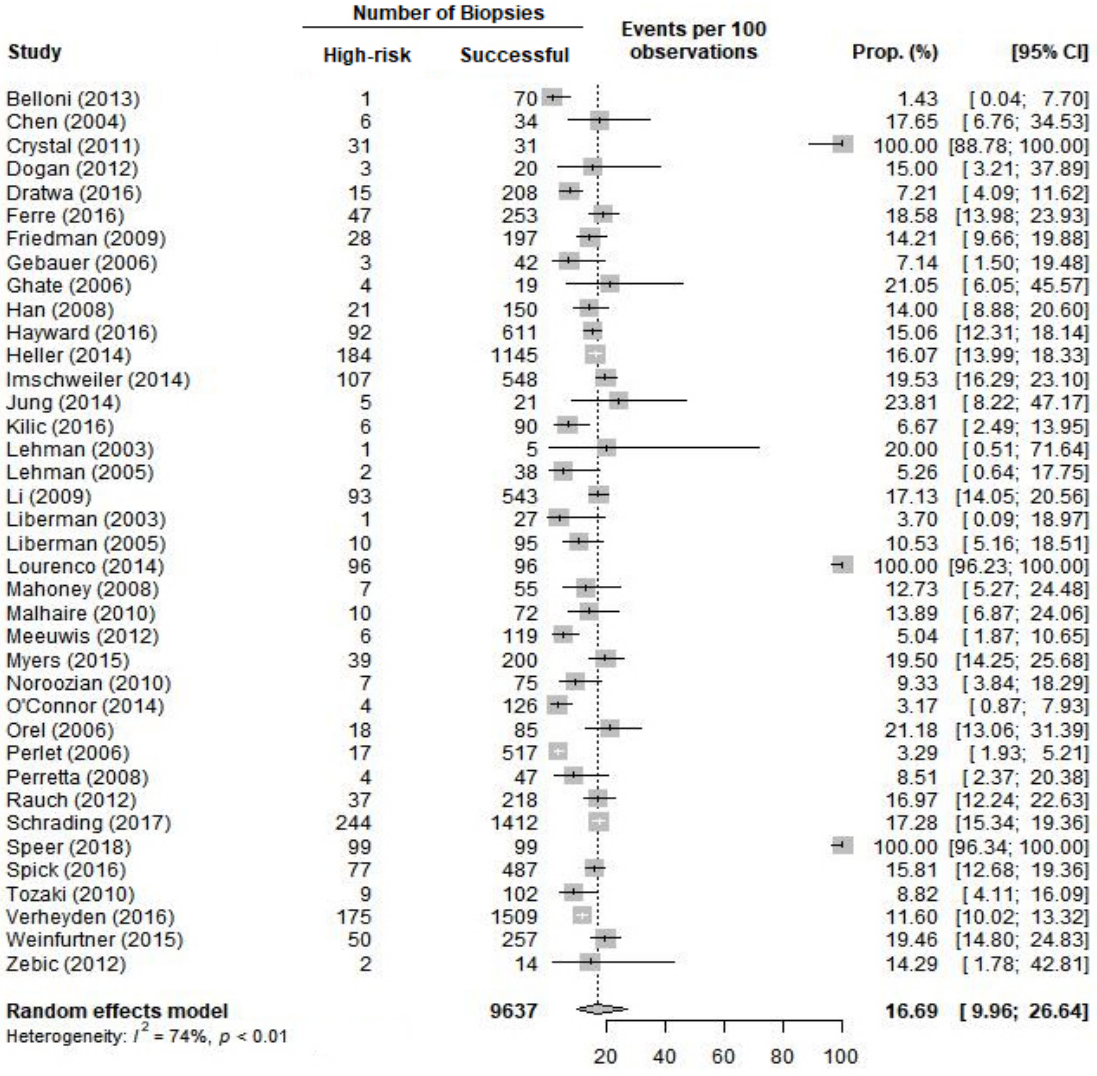
40
60
80
100

c

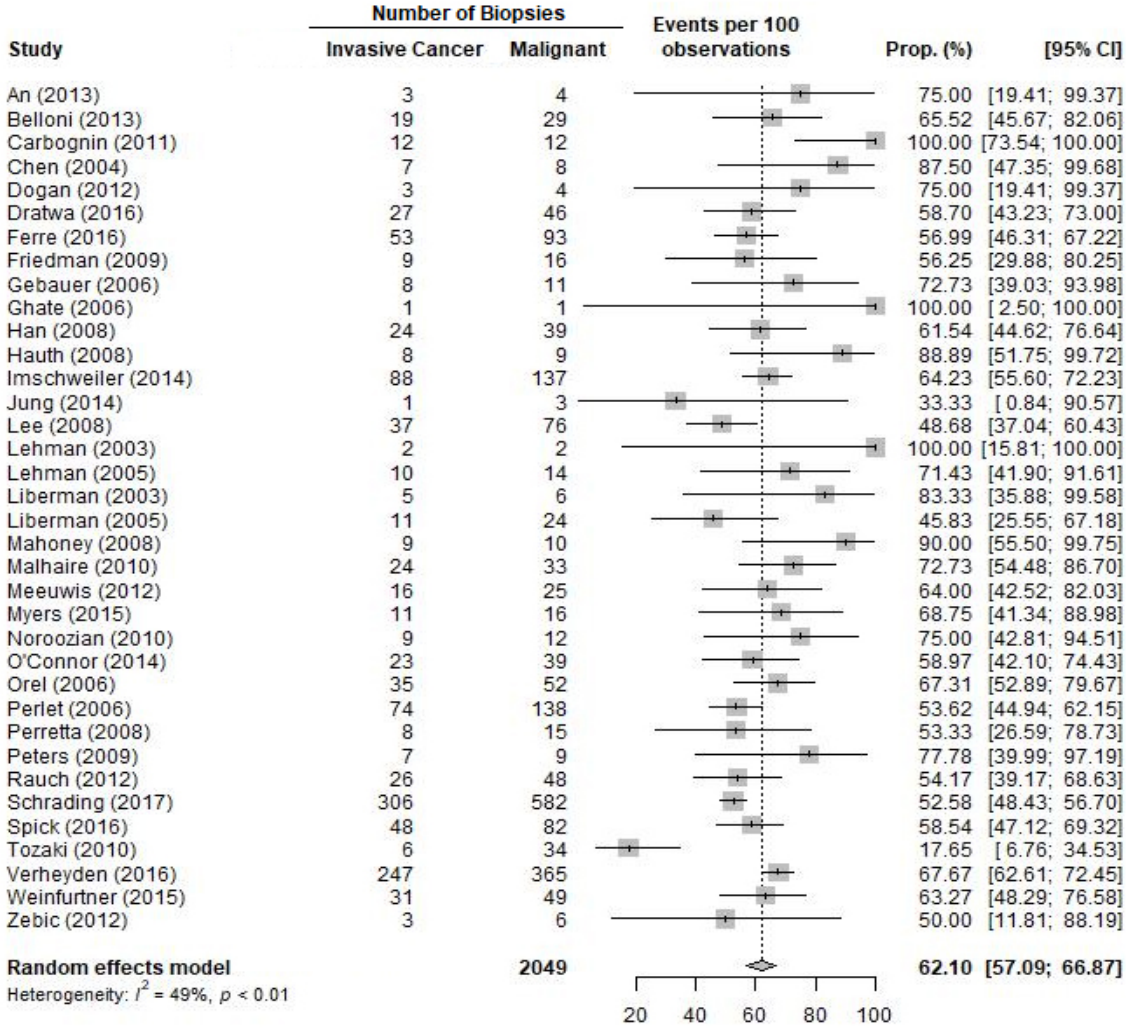


Supplementary Figure 2. Forest plot of **(a)** benign **(b)** malignant **(c)** high-risk lesion rates in successfully performed MRI-guided breast biopsies

MRI: magnetic resonance imaging; Prop.: proportion; CI: confidence interval; I^2: I square (25% low heterogeneity, 25–50% medium, >50% high); p-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-square statistic). A low p-value (<0.05) indicates there is significant heterogeneity between studies.

High-risk lesions include atypical ductal hyperplasia, lobular carcinoma in situ, papillary lesions (intraductal papilloma and papilloma with atypia), atypical lobular hyperplasia (ALH), flat epithelial atypical radial scars/complex sclerosing lesions

a


Number of Biopsies
Study
Invasive Cancer
Malignant
Events per 100 observations
Prop. (%)
[95% CI]
An (2013) 3 4 75.00 [19.41; 99.37]
Belloni (2013) 19 29 65.52 [45.67; 82.06]
Carbognin (2011) 12 12 100.00 [73.54; 100.00]
Chen (2004) 7 8 87.50 [47.35; 99.68]
Dogan (2012) 3 4 75.00 [19.41; 99.37]
Dratwa (2016) 27 46 58.70 [43.23; 73.00]
Ferre (2016) 53 93 56.99 [46.31; 67.22]
Friedman (2009) 9 16 56.25 [29.88; 80.25]
Gebauer (2006) 8 11 72.73 [39.03; 93.98]
Ghate (2006) 1 1 100.00 [2.50; 100.00]
Han (2008) 24 39 61.54 [44.62; 76.64]
Hauth (2008) 8 9 88.89 [51.75; 99.72]
Imschweiler (2014) 88 137 64.23 [55.60; 72.23]
Jung (2014) 1 3 33.33 [0.84; 90.57]
Lee (2008) 37 76 48.68 [37.04; 60.43]
Lehman (2003) 2 2 100.00 [15.81; 100.00]
Lehman (2005) 10 14 71.43 [41.90; 91.61]
Liberman (2003) 5 6 83.33 [35.88; 99.58]
Liberman (2005) 11 24 45.83 [25.55; 67.18]
Mahoney (2008) 9 10 90.00 [55.50; 99.75]
Malhaire (2010) 24 33 72.73 [54.48; 86.70]
Meeuwis (2012) 16 25 64.00 [42.52; 82.03]
Myers (2015) 11 16 68.75 [41.34; 88.98]
Noroozian (2010) 9 12 75.00 [42.81; 94.51]
O'Connor (2014) 23 39 58.97 [42.10; 74.43]
Orel (2006) 35 52 67.31 [52.89; 79.67]
Perlet (2006) 74 138 53.62 [44.94; 62.15]
Perretta (2008) 8 15 53.33 [26.59; 78.73]
Peters (2009) 7 9 77.78 [39.99; 97.19]
Rauch (2012) 26 48 54.17 [39.17; 68.63]
Schrading (2017) 306 582 52.58 [48.43; 56.70]
Spick (2016) 48 82 58.54 [47.12; 69.32]
Tozaki (2010) 6 34 17.65 [6.76; 34.53]
Verheyden (2016) 247 365 67.67 [62.61; 72.45]
Weinfurtner (2015) 31 49 63.27 [48.29; 76.58]
Zebic (2012) 3 6 50.00 [11.81; 88.19]
Random effects model 2049 62.10 [57.09; 66.87]
Heterogeneity: I^2 = 49%, p < 0.01
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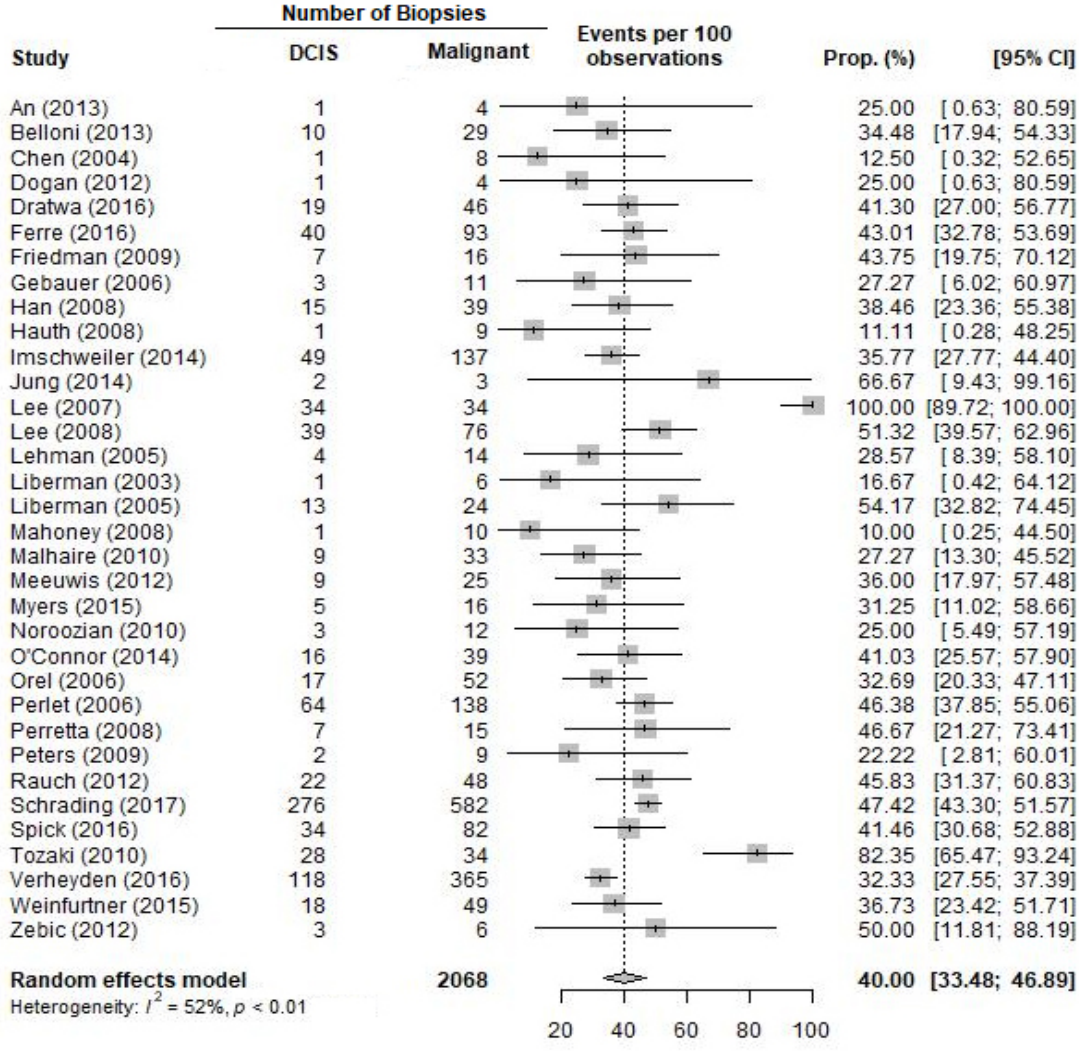
40
60
80
100

b

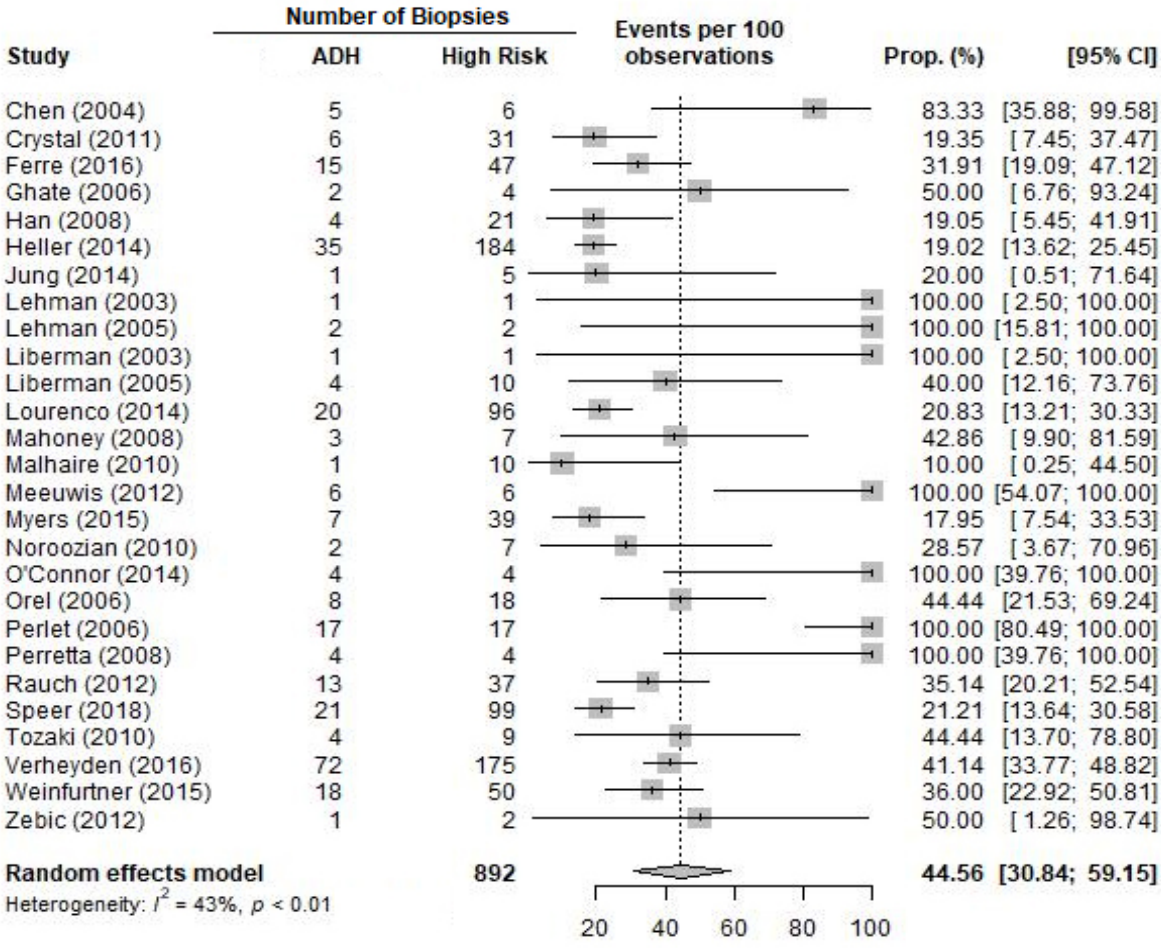


Supplementary Figure 3. Forest plot of **(a)** invasive cancer, and **(b)** ductal carcinoma *in situ* (DCIS) rates among malignant MRI-guided breast biopsies.

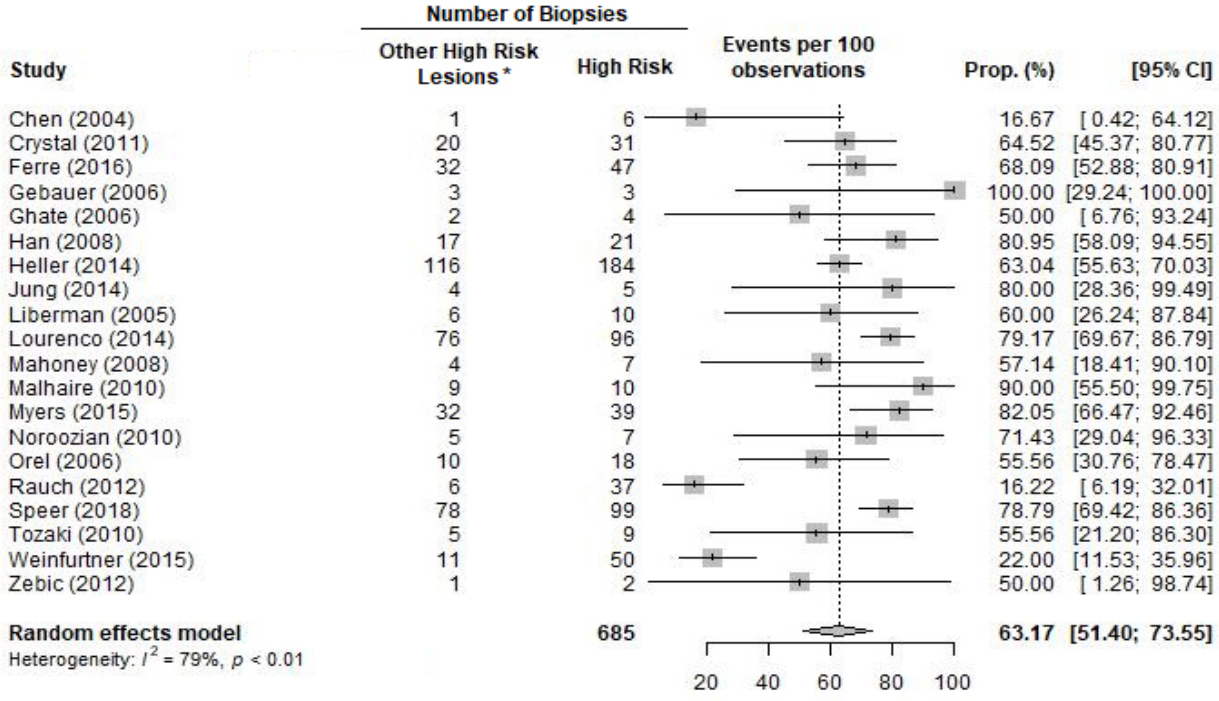
Prop.: proportion; CI: confidence interval; DCIS: ductal carcinoma in situ, I2: I square (25% low heterogeneity, 25–50% medium, >50% high).

P-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-square statistic). A low p-value (<0.05) indicates there is significant heterogeneity between studies

a


Number of Biopsies
Study
ADH
High Risk
Events per 100 observations
Prop. (%)
[95% CI]
Chen (2004) 5 6 83.33 [35.88; 99.58]
Crystal (2011) 6 31 19.35 [7.45; 37.47]
Ferre (2016) 15 47 31.91 [19.09; 47.12]
Ghate (2006) 2 4 50.00 [6.76; 93.24]
Han (2008) 4 21 19.05 [5.45; 41.91]
Heller (2014) 35 184 19.02 [13.62; 25.45]
Jung (2014) 1 5 20.00 [0.51; 71.64]
Lehman (2003) 1 1 100.00 [2.50; 100.00]
Lehman (2005) 2 2 100.00 [15.81; 100.00]
Liberman (2003) 1 1 100.00 [2.50; 100.00]
Liberman (2005) 4 10 40.00 [12.16; 73.76]
Lourenco (2014) 20 96 20.83 [13.21; 30.33]
Mahoney (2008) 3 7 42.86 [9.90; 81.59]
Malhaire (2010) 1 10 10.00 [0.25; 44.50]
Meeuwis (2012) 6 6 100.00 [54.07; 100.00]
Myers (2015) 7 39 17.95 [7.54; 33.53]
Noroozian (2010) 2 7 28.57 [3.67; 70.96]
O'Connor (2014) 4 4 100.00 [39.76; 100.00]
Orel (2006) 8 18 44.44 [21.53; 69.24]
Perlet (2006) 17 17 100.00 [80.49; 100.00]
Perretta (2008) 4 4 100.00 [39.76; 100.00]
Rauch (2012) 13 37 35.14 [20.21; 52.54]
Speer (2018) 21 99 21.21 [13.64; 30.58]
Tozaki (2010) 4 9 44.44 [13.70; 78.80]
Verheyden (2016) 72 175 41.14 [33.77; 48.82]
Weinfurtner (2015) 18 50 36.00 [22.92; 50.81]
Zebic (2012) 1 2 50.00 [1.26; 98.74]
Random effects model 892 44.56 [30.84; 59.15]
Heterogeneity: I^2 = 43%, p < 0.01
20
40
60
80
100

b



Supplementary Figure 4. Forest plot of **(a)** atypical ductal hyperplasia, and **(b)** other high-risk lesions* rates among high-risk MRI-guided breast biopsies

Prop: proportion; CI: confidence interval; I2: I square (25% low heterogeneity, 25–50% medium, >50% high), ADH: atypical ductal hyperplasia.

P-values belong to between-study heterogeneity test (the Higgin's & Thompson's I-square statistic). A low p-value (<0.05) indicates there is significant heterogeneity between studies.

**Other high-risk lesions include lobular carcinoma in situ (LCIS), papillary lesions (intraductal papilloma and papilloma with atypia), atypical lobular hyperplasia (ALH), flat epithelial atypical (FEA) radial scars (RSL)/complex sclerosing lesions (CSL)*

Original Article

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The Importance of Culturally Relevant Breast Clinic Navigation in Improving Breast Cancer Care in Africa

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ABSTRACT

Objective: Cultural norms, community-specific cultural or religious beliefs, and resultant patient health-belief models are known to pose a significant but imperceptible barrier to breast cancer care. However, there is a paucity of data addressing the need for culturally relevant breast clinic navigation in the context of culturally diverse regions. Thus, this study aimed to assess the benefit of culturally similar breast clinic navigators in facilitating treatment adherence and improving overall care in patients.

Materials and Methods: This study was a retrospective qualitative study. It included breast cancer patients who attended our clinic from January, 2017 to December, 2017 and whose management plan included neoadjuvant chemotherapy. These patients were assigned culturally similar breast clinic navigators who counselled them from diagnosis, to treatment, to survivorship. Additionally, navigation concerns were grouped into the following: Navigating the neighbourhood, navigating hostile hospital environments, and navigating medical consultations.

Results: Through counselling sessions and regular telephone follow-up, breast clinic navigators were able to address navigation concerns, provide support for the patient as well as inform the multidisciplinary team (MDT) on the patient's thought process and potential barriers for care. Thus, treatment plans were personalised, resulting in improved, holistic care.

Conclusion: The role of culturally relevant patient navigators within the MDT is not well-described in the current literature. However, this role is useful where a gap exists between medical professionals and patients from varied backgrounds. Thus, navigators from the same/similar backgrounds help improve the healthcare worker's understanding of the patient's thought process, ensuring good quality and holistic breast cancer care.

Keywords: Breast cancer; navigation; patient care; Africa

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Key Points

- Cultural barriers to care are significant but intangible barriers to breast cancer care.
- Healthcare workers must accept belief in non-biomedical models of health.
- In turn, patient cooperation is important in their own medical care.
- Navigators can help bridge the gap between the patient, the community, and the specialist.
- Thus, culturally relevant navigation improves patient adherence and overall patient care.

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Introduction

Geographical Context

The Helen Joseph Breast Care Clinic (HJBCC), based in a public hospital in Johannesburg, South Africa, has been operating as a multidisciplinary unit since 2000. Treatment is provided for patients who do not have health insurance, which accounts for approximately 84% of the population (1). Patients are means-assessed and 60% of patients have a consultation and in-patient management for free or for less than US$4.

The clinic manages between 500–700 patients each month, with approximately 350 new cancer diagnoses per year. The ethnic mix of patients reflects the Johannesburg urban population with 65% black, 17% white, 11% coloured/mixed-race and 7% Asian (2, 3). Locally advanced disease accounts for the majority of the unit's breast cancer diagnoses (62%). Referral to neoadjuvant chemotherapy prior to breast surgery (with or without reconstruction) and then radiation, is the typical treatment pathway.

The clinic also raises awareness of the importance of breast health through media and government initiatives. Education and training of healthcare professionals is provided in Johannesburg, Gauteng province, and also other African countries. The education of healthcare providers includes dialogue with traditional healers in the local community, thus promoting collaborative working relationships.

Breast clinic navigators are breast cancer survivors from different cultural backgrounds, ages and racial groups who function as clinical coordinators and counsellors. This promotes adherence to treatment and survivorship programs. Navigators translate medical systems and aid patients in traversing the multi-disciplinary practice of healthcare which involves different hospitals, doctors, and treatment plans. Navigators in the Breast Clinic also guide patients from diagnosis and through treatment by providing support from initial diagnosis through to survivorship. Additionally, navigation is both vertical (from patient to doctor) and horizontal (along different medical pathways), as personalised cancer treatment is offered via the multidisciplinary team (MDT).

Breast clinic navigators also work within their own communities whilst sharing insights into a patient's health-belief system and their shared cultural understanding with the MDT. They have, therefore, provided awareness of numerous unseen barriers which compromise patient care. This spans issues of failed clinician communication to fears and logistical concerns around hospital environments. Hence, navigator involvement is crucial in breast cancer care as advocating for access to treatment at different geographical locations whilst negotiating diverse health belief models requires a unique and specific skill set.

Background

The benefit of a breast clinic navigator in a high-resource setting is well understood (4). However, the use of navigation in countries with minimal screening or health awareness initiatives, different cultural backgrounds, and barriers to access of quality care has not been adequately researched to date. In fact, there is a paucity of published data on navigating systems that require communication across different languages and different cultural backgrounds (5). Moreover, although a patient's health-belief model and cultural context may create significant barriers to healthcare, there are few studies addressing how the lack of culturally relevant breast clinic navigation may result in an equally important but less tangible barriers to breast cancer care (6).

Navigators in the HJBCC are from patient-specific communities. They highlight obstacles experienced by the patient, thereby aiding clinicians to adapt treatment pathways whilst addressing barriers of culturally based health beliefs. To the best of our knowledge, there are three identifiable cross-cultural barriers to care. These include, 1) inadequate communication due to language barriers, 2) delays in accepting treatment suggestions due to differing beliefs in disease and healing that may result from conflict between traditional medicine, cultural belief, and conventional medicine as well as, 3) rejection of the biomedical model due to patient mistrust or failures in communication and understanding between the healthcare professional and the patient. Thus, breast clinic navigators should be well-versed in both the clinical nuances of care as well as the cultural background of the patients. This is to facilitate a better dialogue between the healthcare providers, the surrounding community, and the individual patients; thereby, enhancing adherence to prescribed treatment regimens and improving overall care. Therefore, the aim of this study was to assess the benefits of culturally similar breast clinic navigators in facilitating treatment adherence and improving overall care in patients. The focus was on community-specific cultural and religious beliefs as well as patient health-belief models.

Materials and Methods

Study Design

The study was a retrospective, qualitative observational analysis of breast cancer patients who attended the HJBCC. Data pertaining to the benefits of breast health navigators in understanding a patient's cultural context were collected through observation of current practices at the HJBCC. Patients were assigned culturally similar clinic navigators upon their breast cancer diagnosis. Following diagnosis, patients answered seven questions as per a template already provided to the clinic navigators, namely:

1. What has the doctor told you?

2. Did you understand what the doctor told you?

3. Did you expect this diagnosis?

4. How are you feeling about your diagnosis?

5. Do you have a family history of cancer?

6. What is your biggest concern?

7. Are you on any chronic medication?

These were administered as part of the first navigator counselling session. Following these questions and discussion, there was a focus on the patient's perception of their disease, health-seeking behaviours, family support and dynamics as well as their counselling experience with a navigator and doctor. Navigators also consolidated what breast cancer is, the type of breast cancer that the patient has, the next step of treatment and potential side effects. Notable, unique, and community-specific psychosocial and contextual issues were then recorded and collated upon consultation for the MDT's knowledge

and/or intervention. This was to ensure an individualised and complete understanding as possible for both the patient and the navigator as well as to ensure effective transfer of medical and logistic information from the clinician to the patient and vice versa.

Study Population

A total of 300 patients were included in this study. They were seen by three breast clinic navigators of different cultural identities and ages. The study comprised 178 (59.3%) patients who self-identified as Black, 86 (28.7%) patients who self-identified as White, 17 (6%) patients who self-identified as Coloured/Mixed-Race, and 19 (6%) self-identified Indian/Asian patients.

Inclusion Criteria

All newly diagnosed breast cancer patients seen at the HJBCC from January, 2017 to December, 2017 whose management plan included neoadjuvant chemotherapy were included.

Exclusion Criteria

Patients who received any treatment at other facilities were excluded. Patients diagnosed with breast cancer before the study start-period were also excluded.

Navigator Selection and Training

Navigators are individuals who have previously had breast cancer. They were recruited through the Breast Health Foundation in Johannesburg, South Africa. Candidates go through a rigorous training process, completing both a clinical breast cancer course and a lifeline-counselling course before being selected as full-time clinic navigators. Once selected, they work within their communities of origin or are assigned patients from culturally similar backgrounds.

Culturally Relevant Navigation

Newly diagnosed breast cancer patients were assigned culturally similar clinic navigators upon discussion with the MDT. Patients were assigned by virtue of their race (Black/White/Mixed/Asian), language preference or cultural background. Hence, patients were able to discuss their fears and concerns with their navigators as well as address their culturally based beliefs about their illnesses. Navigators then relayed pertinent information to the MDT and highlighted any obstacles to patient care in meetings. Moreover, after a treatment plan was decided upon, the patient was contacted on a monthly basis, by telephone, to assess their concerns (logistical and medical) being experienced so as to facilitate adherence to their treatment.

Low-resource environments are those in which healthcare resources are limited. In South Africa, the public health sector is understaffed and overworked (1). Resource limitation is further aggravated by the unequal distribution in the "per capita expenditure" between South Africa's public and private health sectors. Two-thirds of the GDP allocated to health (approximately 5.2% of the total GDP) is assigned to the private sector with the per capita expenditure on healthcare ranging from US$140 in the public sector to US$1,400 in the private sector (1). Conceptualising issues into three specific navigational barriers centred around cultural beliefs has contributed to a successful patient care model for such environments to ensure better patient adherence, and therefore, better patient outcomes. Thus, navigational concerns were grouped into the following:

1. Navigating the neighbourhood

2. Navigating hospital environments

3. Navigating medical consultations.

Navigating the neighbourhood

Perceptions of breast cancer have changed over the last 30 years, with the realisation that it occurs in any race, age, or culture. Awareness in South Africa has involved both successful and failed community education projects, mainly led by media-directed public health campaigns, and breast cancer advocacy and support groups (7). Thus, navigators were tasked with determining the reasons behind some projects' failures and how to make breast health awareness more relatable for people living in their surrounding communities.

Navigating hostile hospital environments

Insights into the perception of a "hostile hospital environment" need to be re-addressed in both patients and communities. The financial and social cost associated with breast cancer treatment needed to be better understood and addressed in order to improve patient care.

Navigating medical consultations

Misinformation around treatments or perceived complications around clinical modalities of care may not always be addressed by the treating physician. Additionally, the patient's cultural and/or spiritual beliefs about their illness may not be adequately engaged with. Thus, the navigator's role after the medical consultation was to address any treatment hesitation that may have stemmed from a lack of information as well as help accommodate the patient's cultural or spiritual norms within their breast cancer management.

Results

Unique/Community-specific Cultural Barriers Identified

• The concept of disease as a familial issue. Thus, the conversation surrounding diagnosis and treatment must be directed at the familial patriarch/matriarch as is noted in predominantly Indian/Asian as well as some Black communities.

• The concept of disease as a spiritual phenomenon which requires ancestral/spiritual intervention as seen in some Black or non-race specific religious communities.

Navigating the Divide of Breast Healthcare

1. Navigating the neighbourhood

Listening to patient navigators from the community who highlighted the reasons for failure of these projects and redirected information based on local cultural belief systems resulted in an increase in patient attendance to treatment centres. Initial problems such as the diversity of languages spoken, poor literacy in English, and an inherent suspicion of accepting advice from women of a different cultural background were corrected by the involvement of the navigator, through provision of personalised information and training within the community. This training included understanding preconceptions and beliefs around the cause of cancer, which were resulting in symptomatic women not accessing care.

2. Navigating hostile hospital environments

The role of the breast care navigator in this regard was critical, as he or she interfaced with the patient, the community, and medical personnel working in regional clinics. The above-mentioned barriers were, therefore, addressed to ensure personalized patient care.

The navigator also provided a more successful conduit to answering questions about hospital treatment misconceptions such as hair growth after chemotherapy, or abandonment post-mastectomy. Additionally, navigators discussed non-surgical management options with patients, including a trial of endocrine therapy in endocrine-sensitive breast cancer which could allow for time to deal with medical fears of treatment or perceived imminent death by both the patient and their family.

3. Navigating medical consultations

Breast clinic navigators ensured that patients were well-informed on both breast-conserving surgery and mastectomies. Moreover, navigators with similar belief structures to the patients could successfully support and aid newly diagnosed women in accepting an inclusive rather than exclusive approach to their treatment options. Thus, the role of the navigator in asking relevant questions about other treatment regimes, as well as in understanding a patient's thought processes around treatments, aided better compliance, and avoided late presentation of advanced disease due to alternative treatment seeking behaviour.

Lastly, phenomena that had an effect on help-seeking behaviour included a lack of knowledge about what a symptom means in addition to the fear of both management strategies and outcomes of the disease or the treatment process. There was also a sense of disconnect regarding formal health systems and a lack of confidence in such systems.

Discussion and Conclusion

Beliefs around breast cancer differ amongst different racial and cultural groups (8). While little has been studied on the beliefs of cancer in South Africa, studies into adherence of antiretroviral treatment for HIV/AIDS indicate some potential cultural barriers, which can also be extrapolated to cancer care (9). Cultural barriers to care are important albeit intangible barriers which if appropriately addressed could improve patient adherence and the overall experience from diagnosis to survivorship. Understanding the perceived cause of the disease, including concepts of curses and spiritual punishments (current and generational), could help explain reluctance to confront the disease. Additionally, misinformation may breed misconceptions about the disease and so it is necessary to address false or negative beliefs associated with conventional medical treatment as well (10, 11).

Generally, misinformation around treatments or perceived complications around clinical modalities of care may not always be addressed by the treating physician. Furthermore, accepting conventional breast cancer treatment poses more culturally specific dilemmas which may not be noticeable during the patient-doctor interaction. An example of such a dilemma, taken directly from this study, is that some cultures do not have a model of patient autonomy. Therefore, it is important to ascertain to whom news of diagnosis should be directed. This may be further complicated by distance and presence of the family patriarch/matriarch (decision-maker). However, the need for consent from the husband or family elders, who may not reside locally, delays treatment. Hence, travel to non-urban areas, with concomitant seeking of traditional healing advice or treatment, may be necessary but is often perceived as favouring no treatment. The result is that the patient may default or be seen as a "defaulter" on the determined treatment plan. Thus, a culturally aware navigator was often required to visit the home, or to have repeated telephone follow-ups with the patient to ensure that this was not the case.

Moreover, patients with a belief in a higher power may often wish to embark on a trial of prayer. Medical practitioners are sometimes perceived to be spiritual sceptics and as not being able to understand the importance of faith in spiritual powers. Patients may also believe that seeking medical treatment is a sign of weakness in religious faith and an indication of doubt in the healing power of "God". This view may be further propagated by charismatic leaders encouraging patients to seek only religious healing, with fatalism in God's punishment taking priority over conventional care. Strong beliefs in chance or fatalism may, therefore, lead women to recognise the presence of the disease but be disinclined to remedy it (12).

A breast cancer diagnosis may also be seen as a part of a curse or disapproval of ancestral powers. Hence, the resultant cure cannot be found in a medical model but in appeasing the ancestors prior to seeking medical treatment. Navigators in our environment were able to bridge this divide between faith and medical management by virtue of their training and individual life-experience. In fact, navigators with similar belief structures as the patient, who have had breast cancer and likely wrestled with similar thought processes, could successfully support newly diagnosed women in accepting an inclusive rather than exclusive approach to treatment options.

Additionally, fear of breast cancer treatment is widely described (13, 14). Many studies have shown that concerns around the concept of a mastectomy are not a phenomenon unique to non-westernised cultures (14). However, these concerns are often managed insensitively by medical practitioners who have been blunted by the attitude of life over limb. Increasingly, breast-conserving surgery is offered in most specialist units either pre- or post-neoadjuvant chemotherapy and comes with obligatory radiation. However, women may be unaware of advances such as breast-conserving surgery and would, therefore, delay treatment because of the fear of mastectomy and lack of information provided by the doctor. Thus, breast clinic navigators are crucial in providing information and ensuring patients are well-informed about all treatment options available to them.

In addition to interpreting and explaining treatment misconceptions and fears to both the physicians and the patients, breast clinic navigators expedite access to multidisciplinary breast units. This is through their engagement with local primary healthcare professionals, which facilitates earlier diagnoses and detection of non-adherence to treatment. Furthermore, navigators not only work with patients in the hospital, but also visit women in the community. This allows them to share their experiences and wisdom as well as encourage co-operative community détente within the communities they are from or familiar with. As a result, these navigators can prove essential in improving the dialogue between the patient, the community, and the specialist.

Regrettably, access to breast cancer care may be limited by a patient's financial constraints (10, 15). Accessing chemotherapy facilities and hospital admissions for breast cancer surgery when salaries or pensions need to be collected would often result in a perceived non-arrival for care. Lack of easily accessible transport would also prevent patients from attending clinics, receiving medication (endocrine therapy) and/or daily radiation sessions. Moreover, monthly payments of repeat

medication prescription collections would further impair adherence in financially burdened patients. Thus, navigators engaged with the patients about their finances as the patients can feel comfortable to relay such financial issues to someone whom they feel would understand them. In turn, navigators conveyed these issues to the MDT so that treatment can be individualised and tailored to the patient's social context.

Therefore, one of the primary solutions to overcoming cultural barriers to care is knowledge (16). There is a duality of awareness which must take place both with the healthcare professional and the patient. Healthcare professionals must accept belief in non-biomedical models of health, and work with the patients (via navigators) to find acceptable solutions and treatment plans (17). Conversely, patients and the community can be educated by navigators about the importance of co-operative medical care. As pointed out by Meara et al. (18) in the Lancet Commission on global health: "Although healthcare has improved in the last 25 years, the development is not uniform, with the most noticeable deficiencies in the system seen in the developing world" (18). Part of the improvement of global healthcare can be achieved through navigation-based education which encompasses a biopsychosocial approach to patient care. That is, successful patient navigation involves the provision of individualised healthcare by understanding the community background of a patient, including the racial, cultural, and educational influences which affect access to healthcare and adherence to treatment. Such understanding is optimised when a breast clinic navigator is chosen from a similar racial and/or cultural background as the patient population of the community in which they operate.

Cultural barriers to healthcare, and specifically, to breast cancer care exist. These barriers are intangible but should be acknowledged to ensure well-rounded patient care from diagnosis to survivorship. Furthermore, the interplay between medicine, culture and beliefs about breast cancer diagnoses underline the importance of holistic, culturally aware patient navigators in the MDT. These navigators should have diverse medical and cultural areas of expertise, ensuring optimal communication between the treating physicians, the patients, their families as well as the surrounding communities. Furthermore, understanding the possible disparities between culture, patient health-beliefs and conventional medical practices promotes adherence to treatment and, therefore, improves the efficacy of care. Currently, the formal incorporation of culturally relevant patient navigators within the MDT is not routinely described. However, this role is useful where a gap exists between medical professionals and patients from varied backgrounds. Learning from this in our shrinking global village, where access to information may encourage divergence from current medical "gold standards", is also essential. Thus, further research into the role of culturally relevant patient navigators in breast cancer care in Africa, and beyond, is also necessary as navigators, today, play a vital role in the daily practice of breast care units. More so, navigators who are culturally similar to the patients whom they counsel help improve the healthcare worker's understanding of the patient's thought process and thereby help improve overall patient care.

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Authorship Contributions

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

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Original Article

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The Randomized Controlled Study of Low-Level Laser Therapy, Kinesio-Taping and Manual Lymphatic Drainage in Patients With Stage II Breast Cancer-Related Lymphedema

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ABSTRACT

Objective: To compare the effects of low-level laser therapy, kinesio-taping and manual lymphatic drainage (MLD) on the affected arm volume, quality of life, arm function, neuropathic pain and shoulder mobility in patients with stage II breast cancer-related lymphedema.

Materials and Methods: Forty-five breast cancer patients with stage II lymphedema were included. The patients were randomized to three groups and treated with MLD, kinesio-taping or low-level laser therapy. After these different therapeutic modalities, all patients received multilayer compression bandaging, lymphedema remedial exercises, skin care, and a patient education program by the same lymphedema therapist. All treatments were applied 5-days a week for three weeks. The lymphedema compression garments were prescribed to all patients and follow-up visits were planned at the end of the treatment, and at four and 12 weeks. The efficacy of the treatments was evaluated by volumetric calculations based on circumferential measurements using the formula for a truncated cone, in addition to goniometric assessments for shoulder joint ROM, and questionnaires: Quick-disability of arm, shoulder and hand for arm disability; pain-detect for neuropathic pain; and quality of life for arm lymphedema (LYMQOL-arm).

Results: The baseline patient and disease characteristics, and outcome measures were similar between groups. All treatment modalities were found to be effective in decreasing arm volume, and improving quality of life, upper extremity disability and neuropathic pain. The percentage of decreased arm volume or treatment success was better in kinesio-taping group than in the MLD group at the end of the treatment, and at four and 12 weeks after treatment (p = 0.009, p = 0.039, and p = 0.042, respectively).

Conclusion: Kinesio-taping led to better results than MLD and was similarly effective compared with low-level laser in stage II breast cancer-related lymphedema at the twelfth week of follow-up. Kinesio-taping and low-level laser should be considered as alternative treatments in early-moderate stages of lymphedema. After these modalities, multi-layer compression and compression bandaging remain cornerstones of lymphedema treatment.

Keywords: Lymphedema; breast cancer; low level laser therapy; kinesio-taping; manual lymphatic drainage; complex decongestive treatment

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Key Points

- Lymphedema is chronic, progressive and disabling disease needed self-management including skin care, self-manual lymphatic drainage massage, compressive garments, and exercises. Since manual lymphatic drain age is time-consuming and tiresome technique, alternative treatments such as kinesio-taping and LLLT should be considered because of similar effectivity in early stage of lymphedema.

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Introduction

Lymphedema is a chronic, progressive and sometimes disabling disease if it has been not treated until end stage. Breast cancer (BC) related lymphedema (BCRL) is the most common cause of lymphedema in developed countries with an incidence ranging from 6–30% (1-4).

The main risk factors for BCRL are the number of removed axillary lymph nodes, the number of metastatic lymph nodes, axillary radiotherapy, taxane type chemotherapy, obesity, advanced age, lack of physical activity, and the presence of hematoma, seroma or infection in the affected quadrant (4-6).

Lymphedema patients need life-long care, medical and psychosocial support (2). For optimal benefits, it is important to diagnose early, start treatment early and customize the treatment (2). Complex decongestive therapy (CDT) is the internationally accepted gold standard treatment method consisting of two-phases (2). The first phase of CDT is intensive and is performed by health professionals; this phase includes skin care, manual lymphatic drainage (MLD), compression therapies, such as multi-layer low-stretch bandaging, and specialized exercises (2). The second phase is for maintenance and is performed by the patient, caregiver, or family and consists of the same components, and compression garments.

MLD is a unique gentle massage technique intended to increase lymphatic circulation using lymphatic anastomoses and territories in addition to diaphragmatic breathing. MLD can be applied by health professionals or by patients themselves (self MLD). Since MLD is a time-consuming technique and costly to implement, there were some recent studies that investigated the effectiveness of combining alternative techniques. However, there were a limited number of randomized controlled studies investigating the efficacies of MLD (7, 8), low-level laser therapy (LLLT) (9-11), and kinesio-taping (12-14). Moreover, there was no direct comparative study of these treatment modalities.

There were also some controlled studies including intermittent pneumatic compression devices (15), low-level laser treatment (9-11), electrotherapy (16), extra-corporal shock wave therapy (17), and kinesio-taping (2, 7).

The aim of this study was to compare the effectiveness and tolerability of LLLT, and kinesio-taping, as alternative treatment options for MLD, in patients with stage II BCRL.

Materials and Methods

Patients with BCRL attending the University of Health Sciences Turkey, Ankara Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Division of Oncological Rehabilitation and Lymphedema were evaluated in this study. Ethical approval was obtained to conduct this study from the Institutional Review Board for Human Subjects (approval number: E-18-2025, date: 26.06.2018).

Patients were eligible if they had unilateral, stage I-III BC, unilateral stage II arm lymphedema and arm volume difference of 5–20% on the affected side after BC surgery. Exclusion criteria were: Patients with stage IV BC; bilateral BC; bilateral lymphedema; stage I (spontaneous reversible), late stage II (spontaneous irreversible with fibrotic changes) or stage III lymphedema; skin infection or lesion in the arms; diseases of the cardiovascular, pulmonary, renal, hepatic, other skin and allergic diseases; and patients who had received lymphedema treatment in the last six months. Patients were also excluded if there was a history of band-aid or skin allergy.

The study was performed with 60 patients who reed to participate in the study. Six of the patients did not meet the study criteria, the other 6 patients were not included in the study due to transportation problems. The participating patients were randomly divided into three groups using numbered envelopes with the shooting method. The patients were divided into groups of 15, 18 and 15 people according to the treatment protocol in the envelope they took. Before the treatment of patients in the kinesio-taping group, a 4x1 cm-sized kinesio-tape was applied to the volar surface of the forearm to test for kinesio-tape allergy. After the tape was removed the next day, the skin was examined and three patients with allergic skin reactions were excluded from the study. The flowchart of the study was shown in Figure 1.

Each physical therapy session was performed by the same therapist, for five days a week for three weeks. All patients were educated about self-massage, skin care and precautions for lymphedema using both face-to-face information and printed materials. At the end of the each physical therapy session, multi-layer bandaging was performed in all groups (Figure 2). Patients were informed about wearing bandages for 23–24 hours daily. After bandaging, supervised lymphedema exercises, including hand squeezing using green egg soft-ball (Erlegen, Turkey), and active resistive exercises for shoulder, elbow and wrist joints using green resistance tape (Thera-band®, Germany) were administered to all patients.

In the MLD group, MLD using Vodder's massage technique was applied to the patients approximately 30–45 minutes by the same certified lymphedema therapist (18). After MLD, multi-layer bandaging was applied to these patients.

Kinesio-taping and multilayer bandaging was performed in the second group of patients. Diagonal direction of fan-cut kinesio-tape was applied from proximal to distal using the lymphedema kinesio-taping technique of paper-off tension (19-21). The anchor for the first kinesio-tape on the volar arm was placed to front side of the shoulder. The fan-like ends of the first kinesio-tape were directed to the elbow towards the lateral epicondyle. The rear of the shoulder was used as the anchor point for the second kinesio-tape for the dorsal arm. After the anchor was positioned, the arm kinesio-tape was fixed to the back of the shoulder, the fan-like ends were directed towards the medial epicondyle. The third kinesio-tape for the forearm was anchored to the end of the first kinesio-tape, that is, the lateral epicondyle, and the fan-like ends were directed towards the dorsal forearm and adhered to the medial side of the wrist. Then, the fourth kinesio-tape for the forearm was applied with the anchor starting from the medial epicondyle, with the fan-like ends directed towards the volar forearm to the lateral side of the wrist. Finally, the fifth and sixth kinesio-tapes for the hand were started on the ulnar and radial side of the wrist and the fan-like ends were terminated through the dorsum of the hand to between the fingers. The kinesio-taping applications of the patients were performed by the same therapist and were renewed twice a week (Figure 3a and 3b). After kinesio-taping, multilayer bandaging was also applied to the patients in the kinesio-tape group.

Patients in the low-level laser group received LLLT and multilayer bandaging by the same therapist. A power density of 30 mW/cm^2 and a square centimeter density of 1.5 J/cm^2 for 1 minute Gallium-Aluminum-Arsenid laser (Ga-Al-As) (BTL-5000®, BTL industries

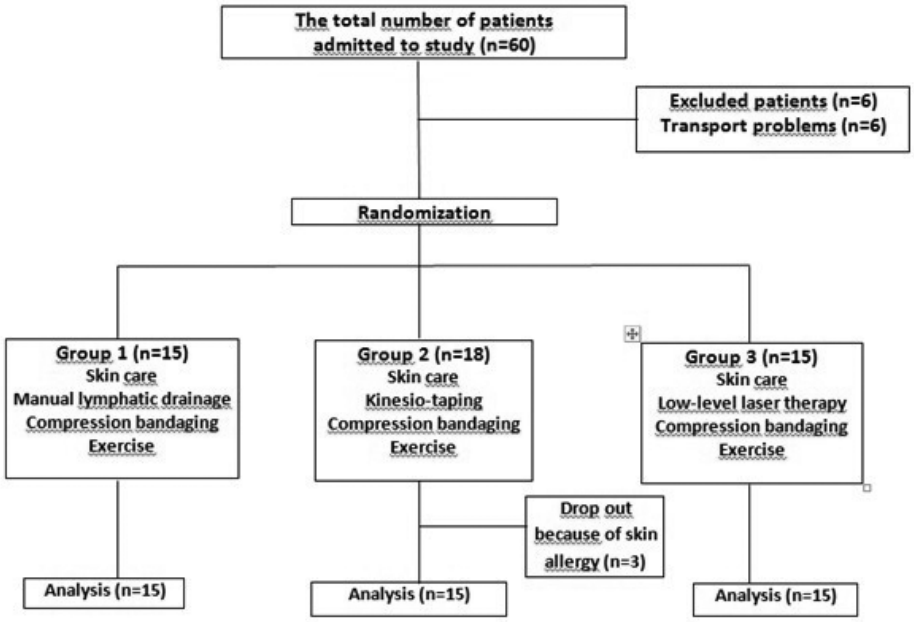

Figure 1. The flowchart of the study

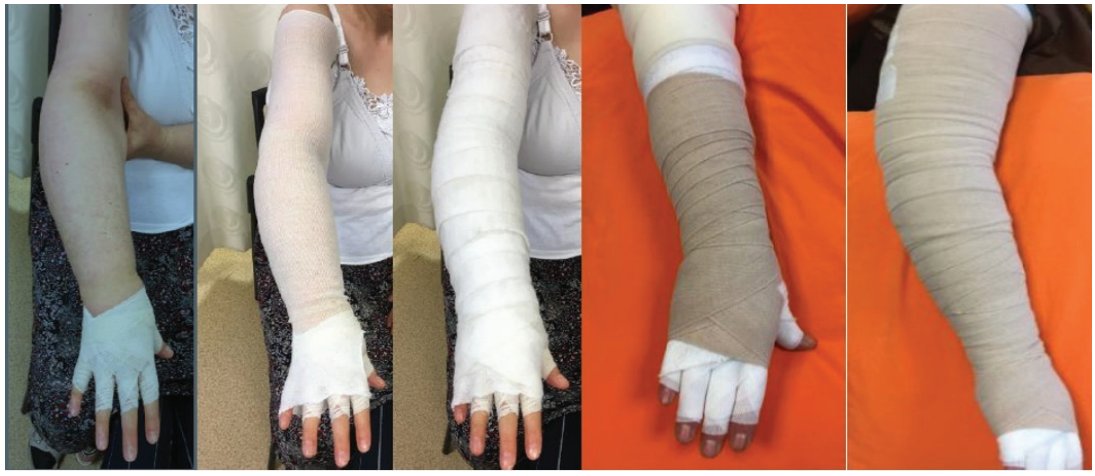

Figure 2. Finger wrap, tubular stockinette, cotton wrap, forearmshort-stretch

Bandage, arm short-stretch bandage of multi-layer bandaging were applied to all groups

Ltd. Hertfordshire, UK) was applied directly using a grid technique. Patients were placed in the supine position with the arm in 90 degrees abduction. LLLT was applied to a total of 12 points in the axillary lymphatics or armpit region and eight points in the cubital lymphatics or volar elbow area, to be applied to each point for one minute, the whole procedure taking 20 minutes (22, 23). After LLLT, multilayer bandaging was also applied to the patients in LLLT group.

After 15 sessions of the different treatments detailed, flat-knitted lymphedema garments with pressure level of CCL2 (30–40 mmHg) (Medi GmbH®, Bayreuth, Germany) were prescribed to all patients for the maintenance phase. Patients regularly performed skin care, self-massage, day-worn compression garments and lymphedema exercises in the maintenance phase.

Patients

Demographic data of the patients, including personal information, such as age, sex, height (m), weight (kg), body-mass index (kg/m^2), occupation, marital status, education level, caregiver support, and co-morbidities, and disease characteristics and lymphedema history were recorded.

Outcomes

Patients were evaluated at four time-points: Baseline; end of the treatment; and four and 12 weeks after the end of the treatment by the same physician. Volumetric measurements of arms were calculated from circumferential measurements using the formula for a truncated cone. Patients completed three questionnaires: Lymphedema Quality of Life Tool (LYM-QoL ARM); Quick DASH for assessment of upper extremity disability; and neuropathic pain was assessed with the

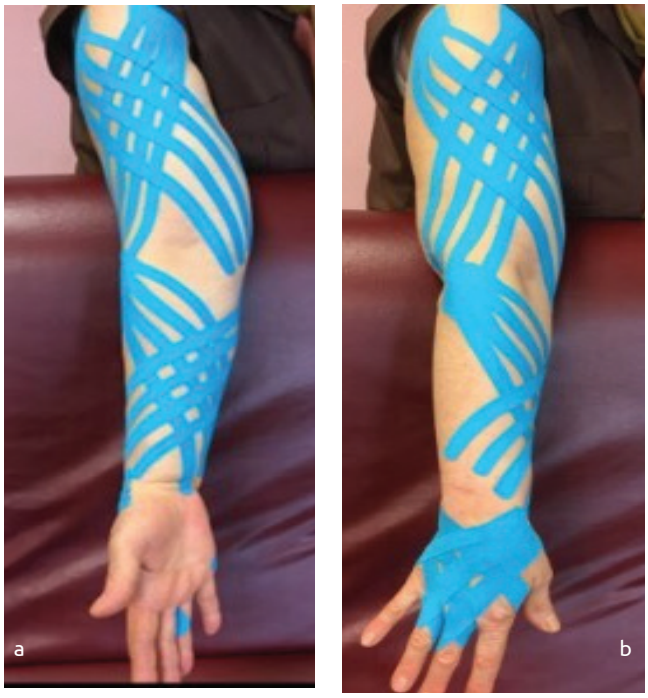

Figure 3. Kinesio-taping with lymphedema teqnique

pain detect questionnaire (PDQ). Joint range of motion (ROM) was assessed using plastic goniometer in shoulder joint.

Circumferential Measurement and Volume Calculation

Circumferential tape measurements of both arms were taken in 4-cm intervals starting from the ulnar styloid to the axilla while the patient was sitting in a sturdy chair with shoulder flexed at 90 degrees by a single physician. Circumferential measurements were made at every point with zero tension and without compression using non-flexible measuring tape.

The circumference measurement of both arms was recorded in each examination for volumetric calculations using the truncated cone formula. This technique is a valid and reliable method correlated with volumetric measurements (24, 25). Excess volume was defined as the difference between pre-treatment lymphedematous arm volume (LV) and pre-treatment healthy arm volume (HV) and the percentage of volume difference was preferred in evaluating the severity of lymphedema because the percentage of volume difference (PVD) showed the severity of lymphedema better than volume excess (24). The PVD formula was used to calculate the percentage of volume difference, which is an indicator of lymphedema severity (24, 25).

PVD = 100 x (LV-HV)/HV

(PVD: The percentage of volume difference or the severity of lymphedema) (24). The treatment success or response to lymphedema treatment was evaluated with the PDV as summarized below: PDV = 100 x (Pre-treatment arm volume – Post-treatment arm volume)/(Pre-treatment arm volume)

[PDV: The percentage of decreased volume (PDV) or the treatment success]

Functional Status of the Upper Extremity

In order to determine the functional level of the upper extremity, the 11-item Quick-DASH (disability of arm, shoulder and hand) questionnaire, which measures physical function and symptoms and is self-completed, was used. Each item offers can be scored on a5-point scale and at least 10 out of 11 questions must be answered in order to calculate the Quick DASH score (26, 27).

Quality of Life

LYM-QoL-Arm questions are grouped under four areas: Function, appearance, symptom and mood. It consists of 21 questions and the last question consists of the "general quality of life" scale (QoL). The item scoring in each area is: Nothing = 1, a little = 2, much = 3, a lot = 4. The total score for each area is calculated by adding all scores together and dividing by the total number of questions answered. Higher scores indicate lower quality of life. The final question on general quality of life (QoL) is scored between 0 and 10. Higher scores for the final question indicate a better overall quality of life (28, 29).

Neuropathic Pain

The PDQ is a patient-based, easy-to-use, 4-item questionnaire originally developed in German. The final score is scored between 0 and 38 points. Below 13 means no neuropathic pain, between 13 and 19 indicates uncertainty for neuropathic pain, and a score of more than 19 indicates possible neuropathic pain component (30, 31).

Shoulder Range of Motion

A standard plastic goniometer was used to measure ROMs for active shoulder flexion, abduction, and external rotation. The measurement was made on the examination table while the patient was lying down in the supine position. The reliability of the goniometric measurement technique for evaluating shoulder ROM has been previously demonstrated (32).

Power Analysis

After the criteria of the study were determined, the change in power analysis using G-power 3.1 version was taken as 5%, 6%, and 7% for each group, respectively, and the effect size was 0.56. In a study comparing the difference between three independent averages using the ANOVA test when the alpha error rate was 0.05 and the power was 0.91 (1-beta), the size of the groups was determined as 15 (33). A total of 60 patients with upper extremity lymphedema were included in the study by calculating 30% more than the specified group size.

Statistical Analysis

The data collected from the patients were entered into the SPSS 21.0 package program (IBM Inc., Armonk, NY, USA), a data set was created and statistical analysis was performed. Descriptive statistics [frequency, percentages, means ± standard deviations, median (range between quarters)] of the variables were indicated with tables. Conformity to normal distribution was determined by Kolmogorov–Smirnov and Shapiro–Wilk tests in order to determine whether the variables met the parametric test assumptions.

After determining that the variables fit the normal distribution, for pairs Student's t–test and ANOVA test were used for more than two groups. ANOVA test if the difference between the groups was found to be significant after the post-hoc comparisons were made in order to determine that it originated from the group Bonferoni

paired comparison test was continued. Repeated measures ANOVA test was performed for repeated measures for parametric variables. If significance was found after performing the ANOVA test in repeated measurements Bonferoni to determine at what time the difference is due to the measurement corrected Bonferoni corrected paired Sample t–test was performed.

After determining that the variables do not fit the normal distribution binary groups the Mann–Whitney U test was used for each group, and the Kruskal–Wallis H test for more than two groups. If the difference between the groups was found to be significant after the Kruskal–Wallis H test, Pairwise comparisons were made to determine which group the difference originated from. Dunn–Bonferoni pairwise comparison test was used.

Friedman test was used for non-parametric repeated variables. Significance after Friedman test determined, to determine at what time the difference was due to measurement. Wilcoxon test with Bonferoni correction was performed. The chi-square test was used for the comparison of categorical variables. A p value of <0.05 was considered statistically significant.

Results

Demographic characteristics of patients are shown in Table 1. There were no significant differences between groups in terms of age (p = 0.297) and body mass index (BMI) (p = 0.144). Distribution of obese, overweight, and normal BMI patients were different between groups (p = 0.043). The frequency of obese patients was n = 11 (73.3%) in the MLD Group, n = 3 (20%) in the kinesio-taping group, and n = 9 (60%) in the LLLT group. This was significantly different between the kinesio-tape and the MLD groups (p = 0.01).

There was no difference between the treatment groups in terms of regarding lymphedema characteristics, BC surgery and BC-related treatments (see Table 2 and Table 3).

The improvement in the lymphedema arm volume or treatment success was determined by calculating the percentage of decreased volume (PDV). The percentage of improvement and subsequent change in the lymphedema arms of patients is summarized in Table 4. Compared the three groups, the PDV or treatment success was significantly higher in the kinesio-taping group than the MLD group at the end of the treatment, and four weeks and 12 weeks after treatment (p = 0.009, p = 0.039, and p = 0.042, respectively).

All LYM-QoL measures at follow-up showed significant improvement in the kinesio-taping group (p = 0.007, p = 0.005, and p = 0.002, respectively). Change in LYM-QoL values showed a significant decrease at the end of the treatment and 4 weeks after treatment (p = 0.022 and p = 0.043, respectively) in the MLD group. A significant decrease was found only at the end of treatment when compared to before treatment in the LLLT group (p = 0.043).

No significant differences were found in intergroup comparisons of LymQoL values at the end of the treatment, and at the fourth and twelfth weeks after treatment (p = 0.650, p = 0.874, and p = 0.326, respectively) (Table 5).

There were significant improvement in Quick-DASH scores in both the kinesio-taping and LLLT groups at the end of the treatment, and at the fourth and twelfth weeks after treatment (p = 0.003, p = 0.016, respectively). A significant decrease was found at the end of the treatment in quick-DASH scores in the MLD group (p = 0.008).

No statistically significant intra-group and inter-group differences were found in the improvement of Quick DASH scores between

Table 1. The comparison of demographics of patients in the three treatment groups. Data are given as n (%) unless otherwise stated

		MLD (a)	Kinesio (b)	LLLT (c)	*p*-value
Age (years)	Mean ± SD (min–max)	57.6±9.5 (35–70)	51.4±10.7 (27–67)	55.3±12.1 (33–78)	0.297[w]
Body mass index (BMI)(kg/cm²)	Mean ± SD (min–max)	31.5±4.1 (24.5–37.4)	28±4.2 (22.2–36.4)	31.1±7 (19.6–46.7)	0.144[w]
BMI classification	Obese*	11 (73.3)	3 (20)	9 (60)	0.043[x]
	Normal	1 (6.7)	4 (26.7)	3 (20)	
	Overweight	3 (20)	8 (53.3)	3 (20)	
Occupation	Housewives*	15 (100)	12 (80)	15 (100)	0.043[x]
	Office workers	0 (0)	3 (20)	0 (0)	
Education level	Literate	5 (33.3)	1 (6.7)	2 (13.3)	0.522[x]
	Primary school	6 (40)	7 (46.7)	7 (46.7)	
	Middle school	1 (6.7)	1 (6.7)	2 (13.3)	
	High school	2 (13.3)	2 (13.3)	3 (20)	
	University	1 (6.7)	4 (26.7)	1 (6.7)	

SD: standard deviation; Min–max: minimum – maximum; *: statistically significant difference between the kinesio-taping and MLD groups; [x]: chi-square test; [w]: ANOVA test for normal distribution; MLD: manual lymphatic drainage; LLLT: low-level laser theraphy

Table 2. Lymphedema characteristics of patients

		MLD (a)	Kinesio (b)	LLLT (c)	*p*-value	*p*-value
Affected extremity	Right	6 (40)	7 (46.7)	6 (40)	0.913	
	Left	9 (60)	8 (53.3)	9 (60)		
Affected extremity	Dominant	10 (66.7)	8 (53.3)	7 (46.7)	0.533	
	Non-dominant	5 (33.3)	7 (46.7)	8 (53.3)		
Duration of lymphedema (months)	Mean ± SD	70.9±54.8	24±26.7	53.4±58		*a vs b=0.011
	Median (25-75 CI)	54 (35–112)	13 (6–26)	31 (13–80)	0.014	a vs c=0.852
	Min–max	4–200	1–95	6–215		b vs c=0.205
Postoperative time (months)	Mean ± SD	81.3±52.4	81.3±128.8	67.1±54.7		
	Median (25-75 CI)	64 (50–122)	32.1(18–72)	49 (30–86)	0.197	
	Min–max	6–180	6–480	19–216		
Postoperative time to diagnosis of lymphedema (months)	Mean ± SD	29.3±30.6	59.7±127.3	14.5±17.7		
	Median (25-75 CI)	24 (4–46)	12 (5–34)	12 (6–13)	0.286	
	Min–max	1–121	1–454	1–64		
Caregiver support	No	10 (66.7)	2 (13.3)*	4 (26.7)	0.020	a vs b=0.017 a vs c=0.753 b vs c=0.214
	Yes	5 (33.3)	13 (86.7)	11 (73.3)		
Caregiver support of spouse		2 (13.3)	10 (66.7)*	8 (53.3)		a vs b=0.012 a vs c=0.841 b vs c=0.209
Caregiver support of daughter		0 (0)	1 (6.7)	2 (13.3)		
Caregiver support of sister		1 (6.7)	2 (13.3)	1 (6.7)		
Health professional		2 (13.3)	0 (0)	0 (0)		
Garment non-adherence	Yes	1 (6.7)	3 (20)	1 (6.7)	0.407	
	No	14 (93.3)	12 (80)	14 (93.3)		

SD: standard deviation, Median (25–75% CI): median (1st Quarter – 3rd Quarter value)
Min–max: minimum – maximum; *: significantly different from the MLD group; MLD: manual lymphatic drainage; CI: confidence interval; LLLT: low-level laser theraphy

groups at follow-up periods including end of the treatment, and fourth and twelfth weeks after treatment (p = 0.872, p = 0.720, p = 0.422, respectively) (Table 6).

PDQ scores at baseline were 17±13.9 in the MLD group, 18.5±11.6 in the kinesio-taping group, and 16±13.1 in the LLLT group (p = 0.871). When the groups were evaluated within themselves, a significant decrease was found in all three groups only end of the treatment compared to baseline (p = 0.011, p = 0.028, p = 0.007, respectively).

No significant differences were found in the improvement in PDQ scores of groups at the end of the treatment, and fourth and twelfth weeks after treatment between groups (p = 0.475, p = 0.600, p = 0.601, respectively).

No significant limitation was found in shoulder ROM both at the beginning and follow-up in any patients.

Discussion and Conclusion

The results showed that all treatment modalities, including MLD, kinesio-taping and LLLT, were safe and effective in the treatment of stage II breast-cancer related lymphedema at follow-up until 12 weeks after treatment. Kinesio-taping was similarly effective as LLLT and more effective on PDV compared to MLD in the present study. All of these treatment methods were similarly effective on quality of life, upper extremity disability and neuropathic pain. In addition, we observed that the treatment success was greater in patients who did not receive adjuvant chemotherapy compared to those who received it.

Table 3. Breast ca surgery and related treatment characteristics of patients

		MLD (a)	Kinesio (b)	LLLT(c)	*p*-value
Breast ca pathology	Invasive ductal cancer	15 (100)	13 (86.7)	14 (93.3)	0.343
	Invasive lobular cancer	0 (0)	2 (13.3)	1 (6.7)	
Breast ca stage	Stage 1	1 (6.7)	2 (13.3)	4 (26.7)	0.591
	Stage 2	10 (66.7)	8 (53.3)	8 (53.3)	
	Stage 3	4 (26.7)	5 (33.3)	3 (20)	
Breast ca surgery	Breast conserving surgery	3 (20)	9 (60)	5 (33.3)	0.071
	Modified radical mastectomy	12 (80)	6 (40)	10 (66.7)	
Axillary surgery type	Axillary lymph node dissection	14 (93.3)	15 (100)	15 (100)	0.360
	Sentinel lymph node biopsy	1 (6.7)	0 (0)	0 (0)	
Dissected lymph node (n)	Mean ± SD	18.5±7.1	19.5±10.9	20±6.3	
	Median (25–75 CI)	18 (16–23)	16 (12–23)	20 (14–23)	0.745
	Min–max	1–33	5–41	12–31	
Metastatic lymph node (n)	Mean ± SD	6.3±9.6	4.8±7.6	2.9±4.2	
	Median (25–75 CI)	2 (0–10)	2 (0–7)	2 (0–3)	0.961
	Min-max	0–31	0–25	0–17	
Radiation therapy	n (%)				0.207
	No	0 (0)	2 (13.3)	3 (20)	
	Yes	15 (100)	13 (86.7)	12 (80)	
Axillary radiation	n (%)				0.164
	No	2 (13.3)	6 (42.9)	6 (40)	
	Yes	13 (86.7)	8 (57.1)	9 (60)	
Radiation dose (centigray)	Mean ± SD	6173.3±2505.8	5123.1±1094	5083.3±1083.6	
	Median (25–75 CI)	6000 (5000-6000)	5000 (5000-6000)	5000 (5000-6000)	0.388
	Min–max	5000/15000	3000/6600	3000/6000	
Chemotherapy	No	2 (13.3)	1 (6.7)	0 (0)	0.343
	Yes	13 (86.7)	14 (93.3)	15 (100)	
Adjuvant chemotherapy	Mean ± SD	6.8±2.4	7.1±3.2	7.5±4	
	Median (25–75 CI)	8 (4/8)	6.5 (4/8.3)	6 (4/8)	0.995
	Min-max	4/12	4/16	4/17	
Neo-adjuvant chemotherapy	No	13 (86.7)	12 (80)	13 (86.7)	0.844
	Yes	2 (13.3)	3 (20)	2 (13.3)	
Type of chemotherapy	AC	1 (7.7)	5 (35.7)	5 (33.3)	0.405
	ACT	6 (46.2)	6 (42.9)	6 (40)	
	CAF	6 (46.2)	3 (21.4)	4 (26.7)	
Endocrine therapy	No	5 (33.3)	6 (40)	5 (33.3)	0.908
	Yes	10 (66.7)	9 (60)	10 (66.7)	
Type of endocrine therapy	Tamoxifen	4 (40)	8 (80)	8 (80)	0.091
	Aromatase inhibitors	6 (60)	2 (20)	2 (20)	

AC: doxorubicin + cyclophosphamide, ACT: doxorubusin + cyclophosphamide + docetaxel,
CAF: cyclophosphamide + doxorubicin + fluoro-uracil, SD: standart deviation, median (25–75% CI): (1st quartile-3rd quartile), Min–max: minimum – maximum; CI: confidence interval; MLD: manual lymphatic drainage; ; LLLT: low-level laser theraphy

Table 4. Percentage of decreased volume (PDV) and subsequent changesat follow-up of end of the treatment (1), 4th weeks (2) and 12th weeks (3)

	Percentage of decreased volume	MLD (a)	Kinesio (b)	LLLT (c)	*p*-value	*p*-value
PDV (1)	Mean ± SD	2.9±8.7	10.3±5.2	8.7±4.7	0.008[w]	a vs b=0.009[q]
	Median (25–75 CI)	2 (-3/9)	10 (5/14)	9 (5/12)		a vs c=0.059[q]
	Min–max	-14/17	4/21	1/18		b vs c≥0.999[q]
PDV (2)	Mean ± SD	0±12.3	8.2±8	4.9±8.4	0.04[x]	a vs b=0.039[y]
	Median (25–75 CI)	-1 (-1/4)	9 (3/14)	7 (2/10)		a vs c=0.284[y]
	Min–max	-33/24	-8/21	-15/16		b vs c≥0.999[y]
PDV (3)	Mean ± SD	4.1±11.9	9.4±8.3	7.4±5.8	0.042[x]	a vs b=0.042[y]
	Median (25–75 CI)	2 (0/6)	11 (5/15)	8 (5/10)		a vs c=0.238[y]
	Min–max	-23/27	-12/22	-7/18		b vs c≥0.999[y]
	p-value	0.175z	0.945z	0.111z		

PDV (1): decreased volume percentage after treatment; PDV (2): decreased volume percentage 4 weeks after treatment; AVY (3): decreased volume percentage 12 weeks after treatment;
SD: standard deviation; Median (25–75% CI): median (1st Quarter value/3rd Quarter value); Min–max: minimum – maximum; [w]: ANOVA test; [x]: Kruskal–Wallis test; [q]: post–hoc Bonferoni test; [z]: Friedman test; [y]:Dunn–Bonferoni Pairwise comparison test; CI: confidence interval; MLD: manual lymphatic drainage; ; LLLT: low-level laser theraphy

Table 5. Inter- and intra-group comparisons for LymQoL change (%)

	LymQoL	MLD(a)	Kinesio (b)	LLLT (c)	*p*-value
End of the treatment	Mean ± SD	-9.14±7.87	-11.97±10.95	-11.06±16.27	
	Median (25–75 CI)	-8.57 (-13.39-0)	-11.63 (-16.97/-5.88)	-3.85 (-17.39/0)	0.650[w]
	Min–max	-21.74/0	-44.83/0	-61.29/0	
4th weeks after treatment	Mean ± SD	-8.83±8.33	-13.77±16.99	-11.06±16.62	
	Median (25–75 CI)	-11.43 (-13.39/0)	-9.28 (-21.21/-1.64)	-11.61(-23.24/0)	0.874[w]
	Min–max	-21.74/2.86	-56.12/5	-44.52/16.75	
12th weeks after treatment	Mean ± SD	-7.78±7.49	-14.58±13.11	-11.02±13.33	
	Median (25-75 CI)	-10 (-13.39/0)	-12.69 (-21,51/-5.88)	-8.39 (-17.39/0)	0.326[w]
	Min–max	-20/2.86	-49.25/0	-41.94/0	
	p-value	0.368 x	0.180 x	0.223 x	

SD: standard deviation, Median (25–75% CI): median (1st Quarter value/3rd Quarter value), Min–max: minimum–maximum, [w]: Kruskal–Wallis testi; x: Friedman test; CI: confidence interval; MLD: manual lymphatic drainage; ; LLLT: low-level laser theraphy

There is no head-to-head comparison study for these three treatment methods in the literature. However, there are some studies evaluating the effectiveness of each treatment methods (7-14). In a cochrane review, it was shown that compression therapies (multilayer bandaging, compression garments, intermittant pneumatic compression) should be used in all stages of lymphedema treatment (34). It was reported that MLD contributed 7% to compression treatments in this review. In another systematic review conducted in 2018, it was stated that the effects of MLD on the quality of life were not clear but it was effective in volume reduction (35).

The kinesio-taping technique used to support lymphatic drainage is a relatively new option in the field of physical therapy (14). Although kinesio-taping is a relatively new treatment modality, its use for lymphedema control is becoming more common. Kinesio-tape has some physiological effects, such as reducing pain and

Table 6. Inter-group comparison of Quick DASH changes (%)

	Quick DASH	MLD (a)	Kinesio (b)	LLLT (c)	*p*-value
End of the treatment	Mean ± SD	-19.57±26.37	-18.24±14.82	-18.66±21.64	
	Median (25–75 CI)	-12 (-26.67/0)	-23.53 (-29.17/0)	-12.5 (-36.36/0)	0.872[w]
	Min–max	-100/0	-42.11/0	-60/0	
4th weeks after treatment	Mean ± SD	-12.07±14.74	-16.51±19.01	-19.4±24.1	
	Median (25–75 CI)	-10.53 (-25/0)	-14.29 (-29.17/0)	-12.5 (-45.45/0)	0.720[w]
	Min–max	-45/6.67	-62.96/0	-60/16.67	
12th weeks after treatment	Mean ± SD	-9.18±13.91	-15.98±19.97	-16.6±19.4	
	Median (25–75 CI)	0 (-15.79/0)	-8.33 (-25/0)	-8.7 (-36.36/0)	0.422[w]
	Min–max	-45/0	-70.26/0	-50/0	
	p-value	0.175x	0.945x	0.111x	

SD: standart deviation; Median (25–75% CI): median (1st Quarter value / 3rd Quarter value); Min–max: minimum–maximum; [w]: Kruskal–Wallis testi; [x]: Friedman test; CI: confidence interval; MLD: manual lymphatic drainage; ; LLLT: low-level laser theraphy

abnormal sensory sensitivity, supporting the movement of muscles, and preventing congestion of lymphatic fluid or hemorrhages under the skin. After kinesiotape is applied, the kinesio-taped area creates convolutions and increases the space between the skin and muscles (36). With the lymphatic application technique of kinesio-taping, the skin is removed and the area between the dermis and fascia is opened, so that the lymphatic drainage effect continues for 24 hours (13). When the physiological effects, such as capillary filtration reduction are analyzed, it has been suggested that kinesio-taping is more similar to compression therapy (13). In our study, it was seen that kinesio-taping was obviously effective in volume reduction. When we look at the treatment success measured by PDV in the affected limb, it was found to be significantly more effective than MLD, causing improvement immediate after treatment, and at four and twelve weeks after treatment. However, the patient characteristics, such as longer duration of lymphedema, lesser spouse support, more obesity and more houewive profiles in the MLD group compared to the those of kinesio-taping group are confounders and might explain the worse response to treatment.

In a meta-analysis examining the effectiveness of kinesiotape in BCRL, studies conducted between 2009 and 2016 were evaluated. In total, seven studies met the criteria and it was stated that kinesio-taping was effective in the treatment of lymphedema due to breast cancer, but it was not superior to other treatments (37).

A meta-analysis investigating the effectiveness and safety of kinesio-taping in cancer-related lymphedema reported that the frequency of kinesio-tape related skin reactions was between 10% and 21%. It has been stated that the quality of life is better and kinesio-taping is not more comfortable in those who have made multilayer short-stretch bandaging (38). In our study, skin reaction due to kinesio-tape was observed in 3 (16.6%) of 18 patients. This relatively common occurrence of skin reactions in patients is in keeping with previous reports. This type of common reaction might limit the use of kinesio-taping for treatment of BCRL.

LLLT has been used worldwide since 1995 and was approved by the FDA in 2007. Laser therapy is believed to increase the contractility of lymphatics, which allows the transport of lymph fluid by stimulating lymphangiogenesis and lymphatic motoricity, softening fibrotic tissues, and increasing macrophage activity. By these mechanisms, it allows the flow of fluid into the extracellular space (10, 11). Its effects are considered to be chronic rather than short term (39).

In a meta-analysis published in 2017, where the effectiveness of LLLT in BCRL was investigated, it was reported that LLLT is more effective than sham laser treatment in reducing the limb volume and its effect on pain is also greater than sham laser therapy, in the short term (23). Another meta-analysis of LLLT in BCRL reported that the decrease in the limb volume was statistically and clinically significant in the groups in which low-dose laser therapy was added, and there was a some decrease in pain with low-dose laser therapy, but the evidence that it provided an additional effect to other treatments was not sufficient (40). A systematic review showed that LLLT may offer additional benefits compared to compression therapies (pneumatic compression or compression bandage), a placebo laser, or no treatment for patients with BCRL. However, LLLT did not appear to significantly improve outcomes when compared to with other types of active interventions (11).

Although there are some studies in the literature comparing the components of CDT, the standard treatment method in lymphedema, to the best of our knowledge, there is no study comparing LLLT, kinesio-taping and MLD in a single study. Thus we belive this is the first published study to directly compare kinesio-taping, MLD and LLLT.

The strengths of our study are the similarities of age, education level, diagnosis and treatment characteristics of the breast cancer, dominant extremity involvement, compression garment compliance, baseline lymphedematous extremity volumes and stage of lymphedema in all patients.

Limitations include the relatively low number of patients, and short follow-up of this study. Further limitations are the heterogeneity of some group characteristics including rates of obesity and housewife occupations, more chronic cases and less care-giver support in the MLD group.

Lymphedema is a chronic, progressive and disabling disease that needs self-management, including skin care, self-MLD massage, compressive garments, and exercises. Since MLD is time-consuming and tiresome, alternative treatments, such as kinesio-taping and LLLT should be considered. This study has demonstrated a similar effectiveness in treatment of early stage lymphedema.

Ethics Committee Approval: Ethical approval was obtained to conduct this study from the Institutional Review Board for Human Subjects (approval number: E-18-2025, date: 26.06.2018).

Informed Consent: Informed consent was obtained.

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Authorship Contributions

Surgical and Medical Practices: S.S.Y., F.F.A.; Concept: S.S.Y., F.F.A.; Design: S.S.Y., F.F.A.; Data Collection and/or Processing: S.S.Y., F.F.A.; Analysis and/or Interpretation: S.S.Y., F.F.A.; Literature Search: S.S.Y., F.F.A.; Writing: S.S.Y., F.F.A.

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Original Article

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SCUBE2 as a Marker of Resistance to Taxane-based Neoadjuvant Chemotherapy and a Potential Therapeutic Target in Breast Cancer

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ABSTRACT

Objective: Taxane-based neoadjuvant chemotherapy is the most common neoadjuvant approach in breast cancer, especially in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative subtypes. However, chemoresistance is a problem in many patients, and success rates are low in estrogen receptor (ER)-positive breast cancer. The aim of this study was to identify predictive markers for resistance to taxane-based therapy, which may have a potential as therapeutic targets in breast cancer.

Materials and Methods: Three comprehensive breast cancer Gene Expression Omnibus datasets were analyzed to identify differentially expressed genes (DEGs) in breast cancer patients resistant to taxane-based neoadjuvant chemotherapy. Functional annotation clustering and enrichment analysis were performed on the DEGs list. A protein-protein interaction network was established with the upregulated genes. The predictive value and the differential expression of the central genes were validated in the extensive ROC Plotter database.

Results: Seventeen upregulated genes were found which were associated with resistance to taxane-based neoadjuvant therapy and high connectivity in the network analysis. *ESR1*, *CCND1*, and *SCUBE2* emerged as the top three key genes associated with resistance. *SCUBE2* displayed a high predictive power comparable to *ESR1*, and better than *CCND1*, the two commonly accepted markers. The predictive ability of *SCUBE2* was higher in ER-positive and HER2-positive breast cancers.

Conclusion: These results suggest that *SCUBE2* may be used as a predictive marker to guide decisions on neoadjuvant therapy. Emerging evidence about the role of *SCUBE2* as a coreceptor involved in tumor progression and angiogenesis also suggests *SCUBE2* as a potential therapeutic target. These points should be investigated in further studies.

Keywords: Breast cancer; neoadjuvant chemotherapy; chemoresistance; biomarkers; bioinformatics; *SCUBE2*

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Key Points

- Seventeen upregulated genes, *ESR1*, *CCND1*, *SCUBE2*, *PGR*, *ERBB4*, *THBS1*, *GATA3*, *BCL2*, *TBC1D9*, *THSD4*, *STC2*, *CCDC170*, *STK32B*, *NBEA*, *PLAT*, *IL6ST*, and *NAT1* were identified as the genes associated with resistance and connected with other nodes in the network analysis.
- *ESR1*, *CCND1*, and *SCUBE2* emerged as the top three key genes associated with resistance to taxane-based neoadjuvant therapy.
- *SCUBE2* displayed a high predictive power comparable to *ESR1*, and better than *CCND1*, the two commonly accepted markers in breast cancer.
- The predictive ability of *SCUBE2* was significantly high in estrogen receptor-positive and human epidermal growth factor receptor 2-positive breast cancers.

Introduction

Breast cancer is the most common cancer in the world and the leading cause of death from cancer in women (1). The most common histopathologic subtypes of breast cancer are invasive ductal carcinoma, invasive lobular carcinoma, and mixed ductal/lobular carcinomas. Increased knowledge on the expression status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) allowed molecular classification of breast cancer into molecular subtypes: hormone receptor-positive, HER2 positive, and triple-negative breast cancer (TNBC) (2, 3).

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Chemotherapy, radiotherapy, and surgery are the mainstays of treatment for breast cancer. Neoadjuvant chemotherapy became the standard of care in early breast cancer, increasing the chances of breast-conserving surgery and allowing total tumor resection in locally advanced breast cancer. Neoadjuvant chemotherapy also introduces the possibility to tailor the adjuvant chemotherapy regimens based on the response to the regimes used in the neoadjuvant setting (2, 3).

The molecular classification of breast cancer enabled tailoring of the neoadjuvant chemotherapy, based on the expression status of receptors and improving treatment outcomes. Today, endocrine therapy is an important contributor to therapeutic success in hormone receptor-positive breast cancer, and the incorporation of anti-HER2 antibody trastuzumab improved treatment outcomes substantially in HER2-positive breast cancers. Despite that, taxane-based chemotherapy is still critical in the initial management of breast cancer patients (2, 3).

Taxanes, such as paclitaxel or docetaxel, are the main components of taxane-based neoadjuvant chemotherapy in breast cancer. They act by blocking the depolimerization of microtubules, thus inhibiting cell proliferation (4). Different chemotherapeutics were adopted into the taxane-based neoadjuvant regimens over the years. Usually, three months of taxane chemotherapy is followed or preceded by anthracycline-based therapy. Formerly, the general practice was to combine 5-fluorouracil and cyclophosphamide with an anthracycline (adriamycin or epirubicin) in anthracycline-based chemotherapy (3, 5). However, current guidelines mostly recommend adriamycin/cyclophosphamide or epirubicin/cyclophosphamide, since 5-fluorouracil does not increase the therapeutic efficacy significantly (6).

The success of taxane-based neoadjuvant chemotherapy is high in HER2-positive and TNBCs. However, the number of ER+/HER2- breast cancer patients that benefit from taxane-based neoadjuvant chemotherapy are limited. Moreover, the annualized recurrence rate in breast cancer for the first 5 years was calculated as 10.4%, and the risk of recurrence continues beyond 20 years, despite the combination of high-efficacy chemotherapeutics with distinct mechanisms of action in chemotherapy (7). Therefore, further investigation of the molecular markers responsible for chemoresistance is critical in breast cancer. Such investigations may offer new drug targets for overcoming resistance to taxane-based chemotherapy.

A great interest to identify predictive markers for chemotherapy and endocrine therapy led to the development of several risk score tests, such as the Oncotype DX Breast Recurrence Score test of 21 genes, MammaPrint 70-gene assay, and EndoPredict 12-gene Molecular Score. These risk score tests were validated as predictors of response to neoadjuvant therapy in ER+/HER2- negative breast cancers (8, 9). They were proven to be successful in selecting patients who will benefit from neoadjuvant chemotherapy and decreased the cost of breast cancer management in countries including the United Kingdom and Germany, where these tests are reimbursed by public health insurance (10, 11). Despite that, these tests are not incorporated into the routine management and health insurance systems in many developing countries, which limits their use (12). Moreover, the therapeutic potential of targeting the genes included in these scoring tests has not been completely addressed.

The aim of this study was to identify markers of resistance to taxane-based neoadjuvant therapy, with predictive power and therapeutic potential comparable to ER, the most reliable marker in breast cancer. Such markers may guide therapeutic decision making, especially in countries where risk score tests are not incorporated into routine care. To this end, we analyzed three comprehensive breast cancer cohorts with gene expression profiling data by robust bioinformatics tools. We included studies which utilized pathological complete response (pCR) as the surrogate of responsiveness to taxane-based neoadjuvant chemotherapy, since the number of patients in studies which utilized relapse free survival as the surrogate of responsiveness to taxane-based neoadjuvant chemotherapy was significantly lower.

Materials and Methods

Patient Data and Identification of Differentially Expressed Genes

Three GEO expression profiling datasets (GSE20194, GSE25066, GSE32646) (13-15), which include gene profiling data for breast cancer patients that have undergone taxane-based neoadjuvant chemotherapy were analyzed in the study (https://www.ncbi.nlm.nih.gov/geo/). Affymetrix Human Genome U133A Array was utilized in GSE20194, and GSE25066 datasets, and Affymetrix Human Genome U133 Plus 2.0 Array was utilized in GSE32646. To determine genes associated with chemoresistance to taxane-based chemotherapy, the patients were stratified into pCR and residual disease (RD) groups. Pathological complete response denoted patients without residual cancer in the breast and lymph nodes. Only patients for which information on the pathological response was available were included in the analysis.

In the GSE20194 dataset, the patients received paclitaxel for three months followed by 5-fluorouracil, cyclophosphamide, and adriamycin before surgery (13). The GSE25066 dataset included samples from patients who received a taxane for three months followed by 5-fluorouracil, adriamycin, and cyclophosphamide (FAC), or 5-fluorouracil, epirubicin, and cyclophosphamide (FEC); or received four cycles of adriamycin and cyclophosphamide followed by four cycles of taxane (14). In the GSE32646 dataset, the samples were from primary breast cancer patients who had undergone neoadjuvant chemotherapy with weekly paclitaxel for three months followed by FEC every three weeks for three months (15). The neoadjuvant treatment protocols and distribution of the patients based on the ER/HER2 and pCR/RD status in each dataset are listed in Table 1.

From the GSE20194 dataset, we included 261 samples from patients who received taxane-based neoadjuvant chemotherapy followed or preceded by anthracycline-based therapy (FEC or FAC). In this dataset, eight patients received anti-HER2 therapy, and three patients received endocrine therapy in the neoadjuvant setting in addition to taxane-based neoadjuvant chemotherapy. These patients were not included in our analysis. Additionally, four patients who received only FEC or FAC, one patient who received only taxol and one patient for which information was not available about therapy, were excluded from the analysis. The patients in the GSE25066 dataset all received taxane and anthracycline based neoadjuvant chemotherapy. ER positive patients received endocrine therapy in the adjuvant setting but not in the neoadjuvant setting. GSE32646 dataset included patients who all received taxane and anthracycline based neoadjuvant chemotherapy. The authors did not mention any use of anti-HER2 therapy or endocrine therapy in these patients. The three datasets did not include patients who received any platinum chemotherapeutics.

Table 1. The distribution of the patients based on the ER/ HER2 or pCR/RD status, and neoadjuvant treatment protocols in each dataset

Dataset	GSE20194	GSE25066	GSE32646
Estrogen receptor			
ER +	140	296	77
ER-	90	205	46
Human epidermal growth factor receptor			
HER2+	40	6	35
HER2-	189	483	88
Taxane-based NAC	261	488	115
pCR	52	99	27
RD	209	389	88
NAC regimen	Weekly T × 12 + FAC × 4 or 3-Weekly T × 4 + FAC × 4	Weekly T × 12 + FAC × 4 or 3-Weekly T × 4 + FEC × 4 or AC x 4 + T x 4	Weekly T x 12 + FEC x 4

T: taxanes (either paclitaxel or docetaxel); FEC: fluorouracil / epirubicin / cyclophosphamide; FAC: fluorouracil / adriamycin / cyclophosphamide; AC: Adriamycin / cyclophosphamide; NAC: neoadjuvant chemotherapy; pCR: Pathological complete response; RD: residual disease

The differentially expressed genes (DEGs) in the RD group were identified using the GEO2R web tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/). Log transformation and force normalization were applied to the data. The Benjamini & Hochberg (False discovery rate) method was used to adjust the p-values (adjusted *p*-value significance cut-off = 0.05). The genes were filtered based on their log2-fold change (logFC) values. The genes with the log FC value >0.5 were accepted as the upregulated genes and with the log FC value <-0.5 were accepted as the downregulated genes. Then Venn Analysis was performed on jvenn (an interactive Venn diagram viewer) (http://jvenn.toulouse.inra.fr/app/index.html) to detect DEGs common to all three datasets.

Functional Annotation and Enrichment Analysis

To identify the gene ontologies and pathways that the DEGs were enriched, the upregulated or downregulated gene lists in non-responsive patients were analyzed on The Database for Annotation, Visualization, and Integrated Discovery (DAVID) (Version 6.8) (16) (https://david.ncifcrf.gov/). To understand the gene ontologies (GO-CC: Cellular compartments, GO-MF: Molecular functions, and GO-BP: Biological processes) and pathways at which the DEGs enriched, gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed on DAVID (*p*-value significance cut-off = 0.05).

Protein-protein Interaction Network Analysis

To identify the key markers associated with chemoresistance to taxane-based chemotherapy, the protein-protein interaction (PPI) network of the protein products of the DEGs was constructed on The Search Tool for the Retrieval of Interacting Genes (STRING Version 11.0) (17) (https://string-db.org/). The minimum required interaction score was set as medium confidence (0.4). The resulting PPI network was analyzed in Cytoscape (Version 3.8.2) and the topological parameters of each protein were extracted (18) (https://cytoscape.org/).

Gene Expression Profiling and Receiver Operating Characteristic Curve Analysis

To validate the upregulation of key genes in breast cancer patients who did not respond to taxane-based therapy, the gene expression profiles of breast cancer patients were analyzed on the ROC-plotter (19). Mann–Whitney test was used for statistical analysis. To validate the value of the key markers in predicting resistance to taxane-based chemotherapy, the receiver operating characteristic (ROC) curves of the key genes were analyzed in ROC-plotter (19). A total of 872 breast cancer patients (228 responders and 644 non-responders) who received taxane-based chemotherapy were included in both analysis types. To exclude the confounding effects that may be caused by other therapies, we did not include patients who received endocrine therapy, anti-HER2 therapy or carboplatin but only included patients who received taxane-based chemotherapy in ROC curve analysis. Pathological complete response was considered as the criteria for responsiveness or non-responsiveness in both analysis types.

Results

Identification of Genes Associated with Resistance to Taxane-Based Neoadjuvant Chemotherapy

To identify the genes associated with resistance to taxane-based neoadjuvant chemotherapy in breast cancer patients, we analyzed GSE20194, GSE25066, and GSE32646 datasets in GEO2R. In total, 182 samples from patients with the pCR and 699 samples from patients with the RD were analyzed. Table 1 lists the number of samples with pCR or RD in each dataset.

First, we investigated the genes differentially expressed in primary breast tumors from patients unresponsive to taxane-based neoadjuvant chemotherapy compared with the patients that responded to therapy (Figure 1a-c). We identified 60 common genes differentially expressed in unresponsive patients in all three datasets (Figure 1d). Among these,

39 DEGs were upregulated and 21 DEGs were downregulated in patients with RD (Figure 1e-f).

Functionally Enriched Pathways and Gene Ontologies Associated with Resistance to Taxane-Based Neoadjuvant Chemotherapy

To identify the pathways and gene ontologies at which the DEGs were enriched, we analyzed the gene lists for commonly upregulated genes and downregulated genes in DAVID. The 39 genes upregulated in all three datasets generated eight statistically significant clusters. *ADCY1, APBB2, BCL2, CCND1, ESR1, GATA3, IL6ST, NBEA, PGR,* and *TSPAN1* were the constituents of the top cluster among these eight clusters (Table 2). These genes were enriched in four KEGG pathways (chemical carcinogenesis-receptor activation, endocrine resistance, estrogen signaling pathway, and pathways in cancer) and two biological processes (response to xenobiotic stimulus and response to drug). The 21 genes downregulated in all three datasets did not generate clusters in functional enrichment analysis. Therefore, we continued further investigation with the upregulated genes list.

Determining The Key Hub Genes Associated with Chemoresistance

To determine the key players in resistance to taxane-based neoadjuvant chemotherapy in breast cancer, we analyzed the PPI network of the 39 common genes upregulated in resistant breast tumors at all datasets on Cytoscape (Figure 2). Among the protein products of the 39 upregulated genes, 17 proteins exhibited connectivity with at least one other protein in the PPI network. The topological parameters for these 17 connected proteins in the network are listed in Table 3. Analysis of the network with Cytoscape revealed *ESR1* (estrogen receptor 1), *CCND1* (cyclin D1), and *SCUBE2* (signal peptide-CUB-epidermal growth factor–like domain-containing protein 2), as the top three central genes associated with resistance.

Validating The Predictive Power of Key Hub Genes as Markers of Resistance to Taxane-Based Neoadjuvant Chemotherapy

Among the three markers identified in our analysis, *ESR1* and *CCND1* are already known to be associated with resistance to anthracycline-taxane-based neoadjuvant chemotherapy, endocrine therapy, and immune checkpoint inhibitors (20, 21). However, there are contradictory findings on the role of *SCUBE2* in breast cancer, and its predictive capacity for chemoresistance in breast cancer is not clear (22-24).

To compare the predictive power of *SCUBE2* with that of *ESR1,* and *CCND1* in breast cancer patients who underwent taxane-based neoadjuvant chemotherapy, we analyzed the differential expression of these genes in non-responders versus responders and the ROC plots in a validation set of 228 responders and 644 non-responders (Figure 3). All three genes were upregulated in breast cancer patients, who did not respond to taxane-based chemotherapy. *SCUBE2* displayed the highest fold increase in non-responders compared to *ESR1* and *CCND1*. The ROC analysis of these genes indicated that the predictive power of *SCUBE2* can be as high as *ESR1* and better than *CCND1*, as a marker of resistance to taxane-based chemotherapy.

A recent study detected *SCUBE2* as one of the four drug resistance markers in ER-positive breast cancers (25). However, the authors have not limited their test cohort to patients who received taxane-based neoadjuvant therapy but included patients treated with any neoadjuvant modality. To assess whether *SCUBE2* has different predictive power for taxane-based therapy resistance in distinct subtypes of breast cancer, we investigated the differential expression and ROC plots of *SCUBE2* in non-responders versus responders who had different molecular subtypes of breast cancer. In our analysis, *SCUBE2* displayed the

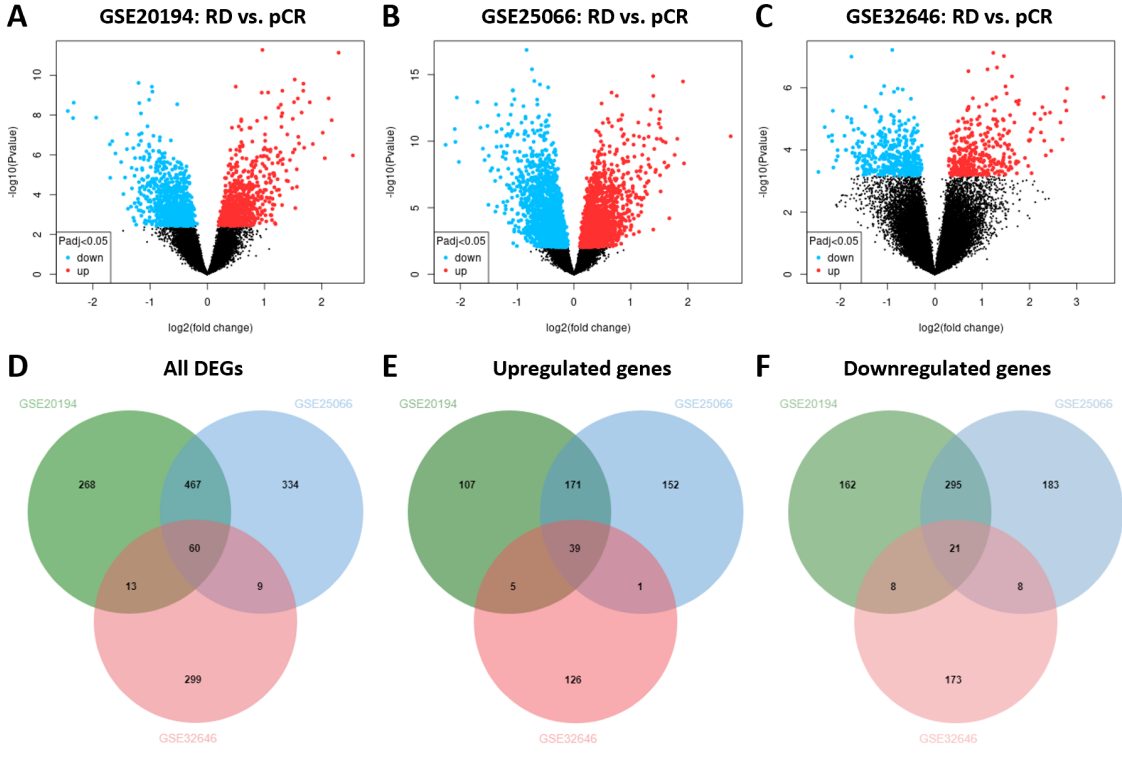

Figure 1. Identification of differentially expressed genes in resistant breast tumors. Volcano plots of differentially expressed genes (DEGs) in **A)** GSE20194, **B)** GSE25066, and **C)** GSE32646 datasets. Venn analysis of **D)** all DEGs, **E)** upregulated genes, and **F)** downregulated genes in three GEO datasets

highest fold change in HER2-positive breast cancers, compared to ER-positive/HER2-negative and TNBC subtypes, being insignificant in TNBC (Figure 4). However, the sensitivity of *SCUBE2* as a marker for resistance to taxane-based therapy was highest in ER-positive/HER2-negative breast cancer. These findings suggested that *SCUBE2* can be used as a novel marker with predictive strength comparable to *ESR1* in ER-positive/HER2-negative and HER2-positive breast cancers.

Table 2. The genes, pathways, and ontologies enriched in the top cluster of upregulated genes associated with chemoresistance

Annotation cluster 1	Enrichment score: 2.2	Count	Genes	*p*-value
GOTERM BP DIRECT	Response to xenobiotic stimulus	5	*CCND1, BCL2, GATA3, ADCY1, THBS1*	9.2E-4
KEGG Pathway	Chemical carcinogenesis-receptor activation	5	*CCND1, BCL2, PGR, ADCY1, ESR1*	1.0.E-3
KEGG Pathway	Endocrine resistance	4	*CCND1, BCL2, ADCY1, ESR1*	1.2E-3
GOTERM BP DIRECT	Response to drug	5	*CCND1, BCL2, GATA3, ADCY1, THBS1*	1.9E-3
KEGG Pathway	Estrogen signaling pathway	4	*BCL2, PGR, ADCY1, ESR1*	3.2E-3
KEGG Pathway	Pathways in cancer	5	*CCND1, BCL2, ADCY1, IL6ST, ESR1*	2.6E-2
GOTERM MF DIRECT	Sequence-specific DNA binding	3	*BCL2, PGR, ESR1*	1.2E-1
GOTERM MF DIRECT	Membrane	8	*NBEA, CCND1, BCL2, APBB2, ADCY1, IL6ST, ESR1, TSPAN1*	1.2E-1

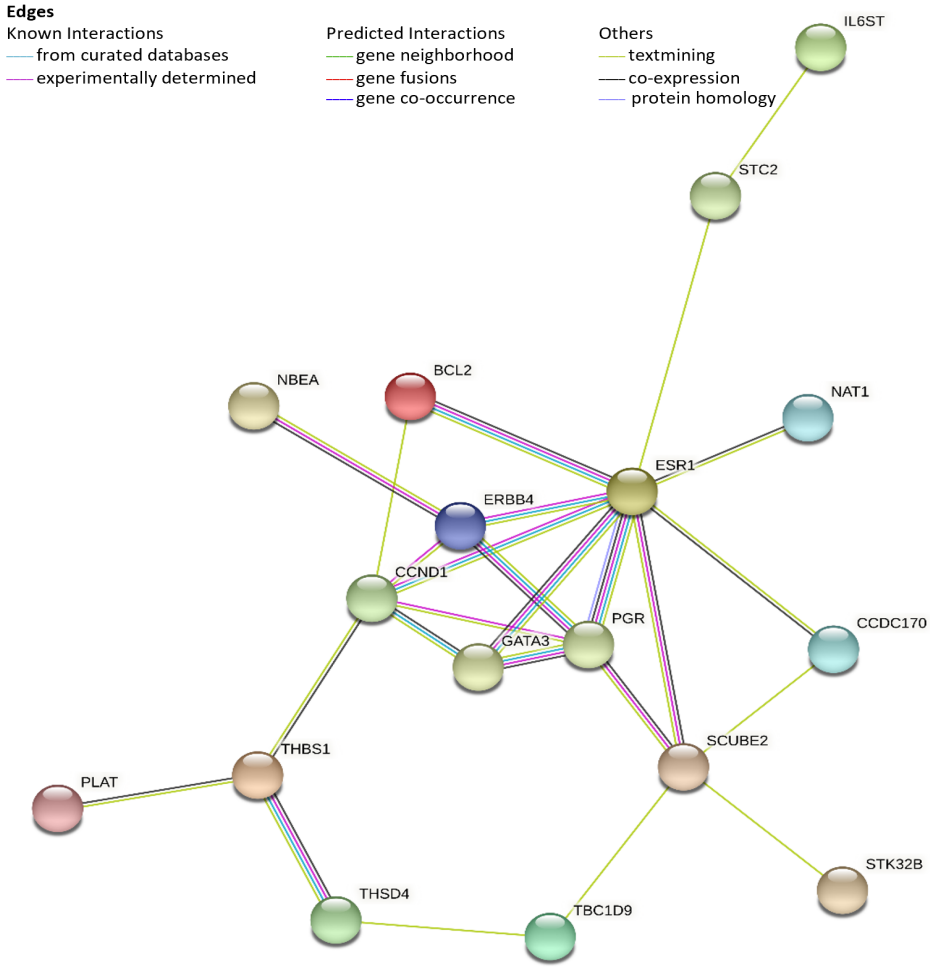

Figure 2. The PPI network of the 39 common genes upregulated in resistant breast tumors in all datasets. The network was constructed on STRING. Disconnected nodes were hidden in the network

Discussion and Conclusion

Advancements in the molecular dissection of cancers pave the way for personalized medicine in cancer therapy. Evidence on the key role of ER and HER2 in breast cancer progression enabled the incorporation of endocrine and anti-HER2 therapies with chemotherapy regimens in breast cancer management (2, 3). Despite these approaches improving treatment outcomes significantly, nearly 30% of breast cancer patients experience recurrence due to resistance to chemotherapy (26). Therefore, further dissection of the molecular markers responsible for chemoresistance is of critical importance in breast cancer.

In this study, we analyzed three breast cancer cohorts with gene expression profiling data, using up-to-date bioinformatics tools to identify key markers of resistance to taxane-based neoadjuvant therapy, which is the standard of care in early breast cancer patients. We identified 39 genes upregulated in breast cancer patients who did not respond to taxane-based neoadjuvant therapy. These genes were highly enriched in gene ontologies and KEGG pathways such as "response to xenobiotic stimulus", "chemical-carcinogenesis-receptor activation", and "endocrine resistance, confirming that the genes we identified are associated with resistance to therapy. Among these genes, *CCND1, BCL2, ADCY1, ESR1,* and *PGR* were also enriched in "endocrine resistance" and "estrogen receptor signaling" suggesting them as markers of resistance to both chemotherapy and endocrine therapy.

In network analysis, we detected that the protein products of 17 upregulated genes, namely *ESR1, CCND1, SCUBE2, PGR, ERBB4, THBS1, GATA3, BCL2, TBC1D9, THSD4, STC2, CCDC170, STK32B, NBEA, PLAT, IL6ST,* and *NAT1* displayed connectivity with others. *ESR1, PGR, BCL2*, and *SCUBE2* are being tested as a part of the 21-gene OncotypeDx Risk score test and 41-gene Biomark Assay (27). Despite that, the remaining 13 genes also have a high potential as markers of resistance to taxane-based neoadjuvant therapy in breast cancer. This should be addressed in future studies. Since we aimed to identify markers with a predictive power comparable to ER, in this study we focused on the top three genes with the highest degree and centrality in the network analysis. The most central gene was *ESR1*, the gene coding for ER, as expected. The other two central genes were *CCND1* and *SCUBE2*.

ESR1 is a key marker for prognosis and responsiveness to therapy in breast cancer. ER-positive and ER-negative breast cancers display distinct gene expression profiles. ER-positive breast cancer is known to be more resistant to chemotherapy compared to ER-negative breast cancers. This knowledge of the impact of ESR1 on poor response to chemotherapy lead to the incorporation of endocrine therapy into the neoadjuvant setting in ER-positive early breast cancer, which improved treatment outcomes substantially (20).

Table 3. Topological parameters for the upregulated genes associated with chemoresistance in breast cancer

Gene symbol	Gene	Degree	Closeness of centrality	Clustering coefficient	Average shortest path length	Neighborhood connectivity
ESR1	Estrogen Receptor 1	9	0.64	0.22	1.56	3.33
CCND1	Cyclin D1	6	0.55	0.40	1.81	4.33
SCUBE2	Signal Peptide, CUB Domain, and EGF Like Domain Containing 2	5	0.50	0.20	2.00	3.80
PGR	Progesterone Receptor	5	0.53	0.60	1.88	5.40
ERBB4	Erb-B2 Receptor Tyrosine Kinase 4	4	0.48	0.50	2.06	5.25
THBS1	Thrombospondin 1	3	0.42	0.00	2.38	3.00
GATA3	GATA Binding Protein 3	3	0.46	1.00	2.19	6.67
BCL2	B-cell lymphoma 2	2	0.44	1.00	2.25	7.50
TBC1D9	TBC1 Domain Family Member 9B	2	0.39	0.00	2.56	3.50
THSD4	Thrombospondin Type 1 Domain Containing 4	2	0.35	0.00	2.88	2.50
STC2	Stanniocalcin 2	2	0.42	0.00	2.38	5.00
CCDC170	Coiled-Coil Domain Containing 170	2	0.44	1.00	2.25	7.00
STK32B	Serine/Threonine Kinase 32B	1	0.34	0.00	2.94	5.00
NBEA	Neurobeachin	1	0.33	0.00	3.00	4.00
PLAT	Plasminogen Activator	1	0.30	0.00	3.31	3.00
IL6ST	Interleukin 6 Cytokine Family Signal Transducer	1	0.30	0.00	3.31	2.00
NAT1	N-Acetyltransferase 1	1	0.40	0.00	2.50	9.00

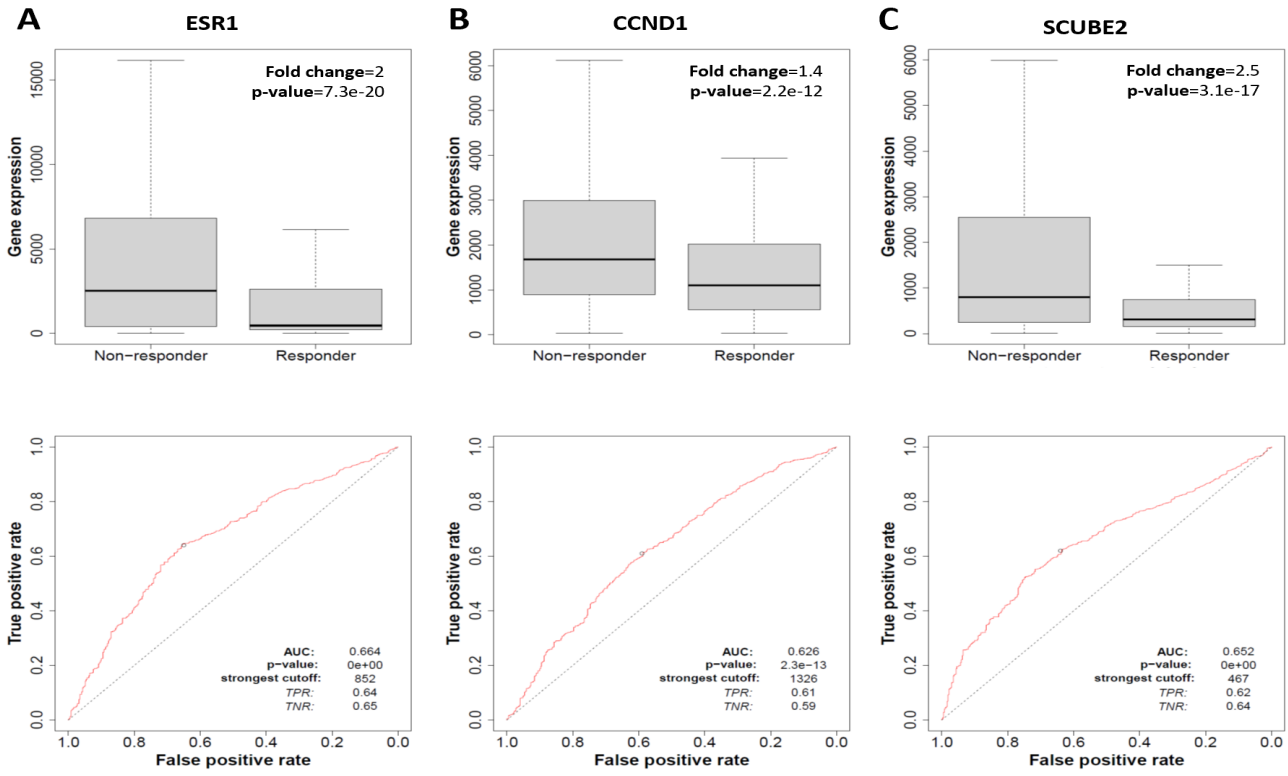

Figure 3. The differential expression (up) and ROC plots (down) for **A)** *ESR1*, **B)** *CCND1*, and **C)** *SCUBE2* in a validation set of 228 responders and 644 non-responder breast cancer patients who undergone taxane-based chemotherapy

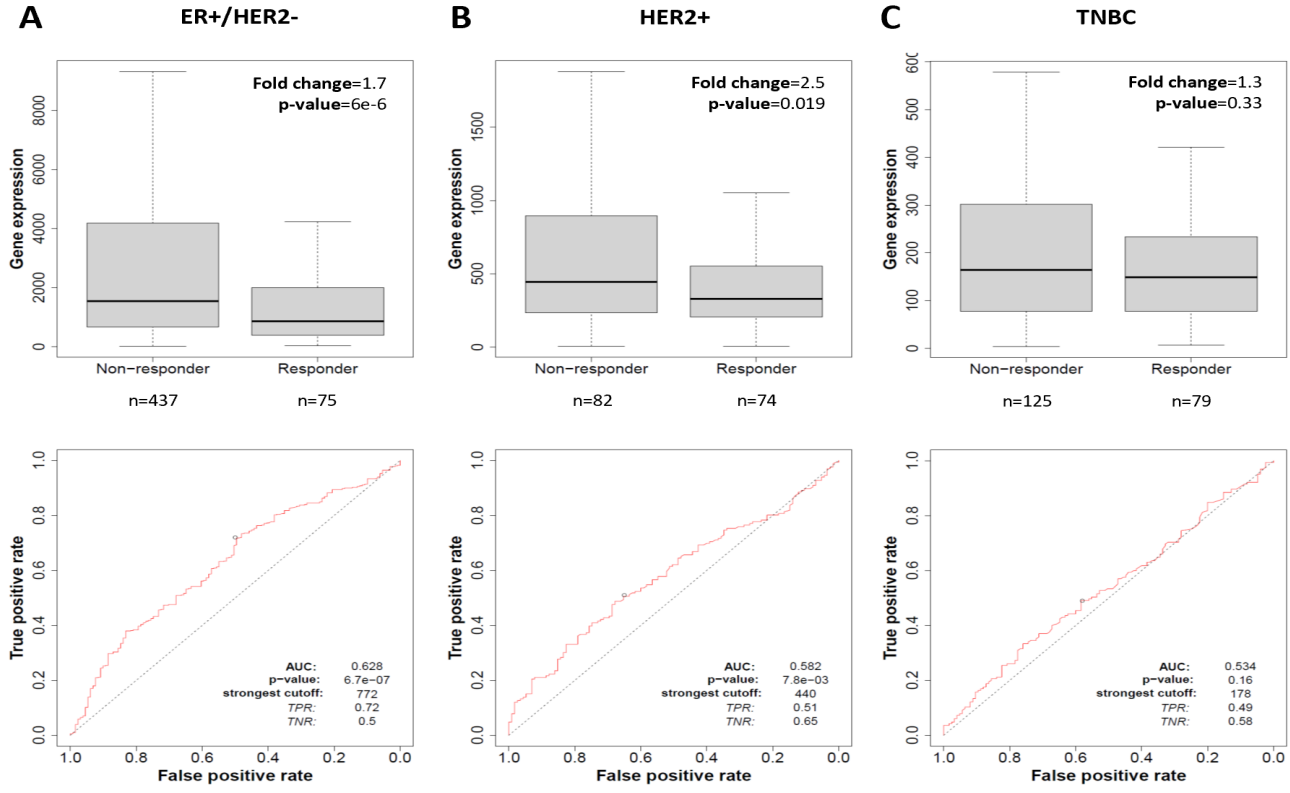

Figure 4. The differential expression (up) and ROC plots (down) for *SCUBE2* in **A)** ER+/HER2-, **B)** HER2+, and **C)** triple-negative breast cancer (TNBC) subtypes in a validation set of 228 responders and 644 non-responder breast cancer patients which undergone taxane-based chemotherapy

CCND1 (cyclin D1) is a cell cycle protein that activates cyclin-dependent kinases (CDK4 and CDK6) and promotes the transition from G1 to S. *CCND1* is overexpressed in almost half of breast cancer cases and is associated with poor prognosis, especially in ER-positive breast cancers (28). High *CCND1* expression was also correlated with a poor response to anthracycline-taxane-based neoadjuvant chemotherapy, endocrine therapy, and immune checkpoint inhibitors (21). Since *CCND1* is also a positive regulator of ER, both direct and ER-mediated actions of *CCND1* can contribute to chemoresistance. In parallel to the growing evidence on the significance of *CCND1* mediated activation of CDK4 and CDK6, several CDK inhibitors such as Ribociclib, and Abemaciclib are approved for breast cancer treatment (29).

Our study confirmed the association of *ESR1* and *CCND1* with resistance to taxane-based therapy in breast cancer. However, the most important contribution of our study is the identification of *SCUBE2* as a relatively novel marker for taxane-based neoadjuvant therapy and a potential drug target. Our analysis suggested that *SCUBE2* may be used as a predictive marker, especially in ER-positive/HER2- negative and HER2-positive breast cancers with a sensitivity and specificity similar to *ESR1*.

SCUBE2 encodes a secreted glycoprotein with epidermal growth factor-like repeats and a CUB domain (CUB: complement C1r/C1s, Uegf, Bmp1), which interacts with the cell surface (30). It is involved in the regulation of different molecules altered in cancer, such as sonic Hedgehog, and GRB7. *SCUBE2* is used as a biomarker in various cancers, namely endometrium cancer, non-small cell lung carcinoma, colorectal cancer, glioma, and breast cancer. Genetic alterations in *SCUBE2* were observed in uterine carcinomas, gastric cancer, melanoma, glioma, colorectal cancer, and many other cancers. *SCUBE2* exhibited tumor suppressor function in glioma, non-small cell lung cancer and colorectal carcinoma. However, several reports suggest that *SCUBE2* may display tumor suppressor or oncogenic effects in breast cancer in a context-dependent manner (31).

SCUBE2 was suggested to suppress the proliferation of breast cancer cells via inhibition of BMP, an inducer of cell proliferation in the MCF-7 metastatic breast cancer cell model and a mouse xenograft model (22). *SCUBE2* induced an epithelial phenotype, suppressing epithelial-mesenchymal transition, invasion, and migration of MDA-MB-231 invasive ductal breast carcinoma cell line (23). Additionally, *SCUBE2* positivity was associated with better disease-free survival in breast cancer patients with primary invasive ductal carcinoma (22). Despite these findings, a more recent study in MDA-MB-231 cells and *in vivo* models reported that increased expression of *SCUBE2* in breast cancer stem cells induces epithelial-mesenchymal transition, increased tumor growth, and metastasis via activation of Notch signaling. Additionally, ectopic overexpression of *SCUBE2* led to resistance to paclitaxel in TNBC cells (24).

Although there is a discrepancy about the exact molecular role of *SCUBE2* in breast cancer, our analysis demonstrated that *SCUBE2* may be a key marker for chemoresistance to taxane-based neoadjuvant therapy in breast cancer. Its predictive specificity and sensitivity were as high as *ESR1*, a well-established marker for chemoresistance in breast cancer. Ruey-Bing Yang's group demonstrated that *SCUBE2* acts as a coreceptor for vascular endothelial growth factor receptor 2 (VEGFR2), potentiating angiogenesis (32). The group demonstrated that knock out of *SCUBE2* suppressed angiogenesis and tumor growth in melanoma and Lewis Lung carcinoma xenograft models, and an anti-*SCUBE2* antibody displayed synergistic action with the anti-VEGF antibody in an orthotopic pancreas cancer model (33). Further research in breast cancer may reveal the molecular mechanisms by which *SCUBE2* contributes to resistance to taxane-based chemotherapy and provide further insight into its molecular functions. Such insight may open the door for the development of novel molecular targeted agents against *SCUBE2*.

In our study, we analyzed breast cancer samples from all receptor subtypes as a pool to identify markers of resistance to taxane-based therapy, that can be utilized as a predictor and a new therapeutic target in large groups of patients. Despite that, a more detailed analysis of breast cancer subtype-specific cohorts, and a comparison of the markers for different subtypes would improve the efforts to predict responsiveness and personalize therapy in distinct breast cancer subtypes. This will be addressed in our future studies.

Another limitation of the study is the use of pCR as the surrogate of sensitivity to taxane-based neoadjuvant chemotherapy, since the number of patients in studies that utilized relapse free survival as the surrogate was much lower. pCR is mostly preferred in clinical trials to speed up the drug registry process. However, there are controversies about the efficiency of pCR as a surrogate of survival, and there seems to be differences in its surrogacy in different breast cancer subtypes (34-36). Therefore, the value of *SCUBE2* to predict resistance to taxane-based therapy should also be validated in large cohorts using overall survival as the surrogate.

In conclusion, our study identified *SCUBE2* as a novel marker for resistance to taxane-based therapy with a predictive power comparable to *ESR1* and even better than *CCND1* in breast cancer. Further investigations into the molecular functions of *SCUBE2* in specific breast cancer subtypes may provide the opportunity to develop new, targeted therapies that can overcome resistance to taxane-based therapy in breast cancer.

Availability of Data and Materials

The GSE20194, GSE25066, and GSE32646 datasets we analyzed during the current study are available in Gene Expression Omnibus (GEO) repository (https://www.ncbi.nlm.nih.gov/geo/geo2r/).

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Original Article

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Genetic, Surgical and Oncological Approach to Breast Cancer, with *BRCA1, BRCA2, CDH1, PALB2, PTEN* and *TP53* Variants

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ABSTRACT

Objective: The aim of this study was to determine the frequency of germline variants in *BRCA1, BRCA2, CDH1, PALB2, PTEN* and *TP53* in patients admitted to a medical genetics clinic with breast cancer and to assess these identified variants according to published genetic, surgical and oncological perspectives.

Materials and Methods: Medical history, and cancer diagnosis information for 195 independent probands with operated breast cancer were collected from requisition forms and medical records. The exonic regions and exon-intron junctions in *BRCA1, BRCA2, CDH1, PALB2, PTEN* and *TP53* genes were sequenced. Analysis of fastq files was performed on the Qiagen Clinical Insight-Analyse Universal with panel-specific pipeline and vcf files were interpreted clinically using Qiagen Clinical Insight-Interpret.

Results: Gene variants (pathogenic, likely pathogenic and variants of unknown significance) were detected in 53 (27.2%). Detailed information about the patients (age of diagnosis, family history, gender), cancer stage, tumour characteristics (ER, PR, human epidermal growth factor receptor 2 status) and all information related to the detected variants (gene, location, nucleotide and amino acid change, exon number, impact, mutation classification, dbSNP number and HGMD variant class) were assessed. In total, 58 mutations were identified including 14 novel, previously unreported variants.

Conclusion: Molecular characterization and identification of mutations have important implications for predictive, preventive, and personalized medicine, including genetic counseling and development of specific treatment protocols. We emphasize variants of unknown significance (VUS) as the clinical significance of VUS changes over time and variant classification is important for clinical molecular genetic testing and clinical guidance. This study may provide new insights into risk assessment for variants in *CDH1, PALB2, PTEN* and *TP53*, in addition to *BRCA1* and *BRCA2*, which may prove useful for clinical management of breast cancer patients. Further studies are needed to identify the common gene variants in the Turkish population and evaluate the pathogenity of VUS.

Keywords: *BRCA1/2*; breast cancer; *CDH1/PALB2*; genetic testing; *TP53/PTEN*

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Key Point

- The purpose of this study was to determine the frequency of germline variants in *BRCA1, BRCA2, CDH1, PALB2, PTEN* and *TP53* in a population of Turkish patients admitted to a medical genetics clinic with breast cancer. In addition, the identified variants were assessed in the light of published genetic, surgical and oncological perspectives.

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Introduction

Breast cancer is the most prevalent cancer and the leading cause of death among women worldwide, accounting for approximately 12% of all new cancer cases diagnosed in recent years (1). The etiology of breast cancer is multifactorial and complex, and most cases are sporadic, although genetic factors play an important role. The most common cause of hereditary breast cancer is because of inherited germline mutations in the high-penetrant cancer predisposition genes *BRCA1* and *BRCA2*. Beside these genes, advances in DNA sequencing techniques, such as next generation sequencing, have helped to identify additional breast cancer susceptibility genes, including *TP53, CDH1, PALB2* and *PTEN* and various rare gene variants have also been reported to increase the risk of developing breast cancer. The prevalence of *BRCA1* and *BRCA2* pathogenic variants is estimated to be 1/400 to 1/500 in the general population and is increased in some populations due to the founder effect (2). It is estimated that the risk of developing breast cancer by age of 80 is 72% for *BRCA1* mutation carriers and 69% for *BRCA2* mutation carriers, respectively. According to the literature, the risk for contralateral breast cancer 20 years after first breast cancer diagnosis is 40% for *BRCA1* and 26% for *BRCA2* carriers (3).

Tumor protein p53 (*TP53*) is one of the most mutated genes in cancer, including breast cancer. *TP53* is a tumor suppressor gene that encodes tumor protein p53, a transcription factor. Germline *TP53* mutations are associated with Li-Fraumeni syndrome, a rare autosomal dominant genetic disorder. In Li-Fraumeni syndrome, in addition to breast cancer, brain tumors, adrenocortical carcinoma, leukemia, and germ cell tumors have been reported. Although germline *TP53* mutations are rare and seen in approximately 1% of all breast cancers, the lifetime risk of breast cancer in *TP53* mutation carriers is nearly 80–90%, considerably greater than for other genes (4).

The *CDH1* gene encodes E-cadherin, a calcium ion-dependent cell-cell adhesion protein, and it is known that germline *CDH1* pathogenic variants predispose the individuals to both diffuse gastric cancer and lobular breast cancer (LBC). Studies have shown that estimated cumulative risk of LBC for women is 42% by age 80 years (5, 6). Partner and localizer *BRCA2* (*PALB2*) is one of the important DNA repair genes that co-localizes with *BRCA2* in nuclear foci. *PALB2* has functions in homologous recombination, recombinational repair and checkpoint mechanisms. Several studies showed the increased risk of breast cancer in *PALB2* mutation carriers. In a large cohort, *PALB2* mutations were found in approximately 1% of the *BRCA1/2* negative patients with breast cancer and in 0.19% of healthy controls (7). Phosphatase and tensin homolog (*PTEN*) is one of the most common tumor suppressor genes. It is known that germline *PTEN* mutations predispose to the development of Cowden syndrome, an autosomal dominant inherited cancer syndrome characterized by multiple hamartomas and malignancies, including breast, thyroid, and endometrial cancer. Studies have shown that the prevalence of Cowden syndrome to about 1:200,000 patients and women with Cowden syndrome have a 20% to 50% lifetime risk of developing breast cancer (8).

Patients with suspected hereditary breast cancer should obtain genetic counseling and be informed about the risk factors. The National Comprehensive Cancer Network (NCCN) has published recommendations to guide healthcare providers in identifying individuals with hereditary cancer syndrome (Table 1) (9). In the presence of any of the criteria, there is an indication for genetic testing for hereditary breast cancer as there is high lifetime risk for mutation

Table 1. Testing criteria for breast cancer susceptibility genes (summarized from ref. 9)

1.	Individuals with any blood relative with a known pathogenic or likely pathogenic variant in a cancer susceptibility gene		
2.	Personal history of cancer		
	a. Breast cancer with at least one of the following	*Diagnosed at age ≤45 y; or	
		*Diagnosed at age 46-50 y with	• Unknown or limited family history, • A second breast cancer diagnosed at any age, • ≥1 close blood relative with breast, ovarian, pancreatic or prostate cancer at any age
		*Diagnosed at age ≤60 y with triple-negative breast cancer	
		*Diagnosed at any age with;	• Ashkenazi Jewish ancestry, • ≥1 close blood relative with breast cancer at age ≤50 y ovarian, pancreatic, metastatic, intraductal/ cribriform histology or high-risk group prostate cancer at any age, • ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
		*Diagnosed at any age with male breast cancer	
	b. A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline		
	c. Individuals who meet Li-Fraumeni syndrome testing criteria or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria		
	d. To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer		
3.	Family history of cancer	• An individual with a first- or second-degree blood relative with any of these criteria An individual who does not meet the criteria but has a probability ≥5% of a *BRCA1/2* pathogenic variant based on probability models	

PTEN: phosphatase and tensin homolog; HER2: human epidermal growth factor receptor 2

carriers (Table 2) (10). Detection of germline mutations may lead to the improvement of diagnostics and selection of patients sensitive to targeted therapeutics. Therefore it may help the development of familial screening strategies and may also have important implications for development of specific treatment and prevention protocols in mutation carriers.

Materials and Methods

A total of 195 operated breast cancer patients who attended a Medical Genetics Department between 2019 and 2022 were included. According to the NCCN guideline criteria, in the 195 patients selected for this study, the age and the family history of the patients were the main criteria (Table 1). The study was conducted in accordance with the Declaration of Helsinki and was approved by İzmir Katip Çelebi Non-Interventional Clinical Studies Institutional Review Board (0028/20.01.2022). Medical history was collected from requisition forms and medical records. Written informed consent forms were obtained from all patients. In this study, the exonic regions and exon-intron junctions in *BRCA1, BRCA2, CDH1, PALB2, PTEN* and *TP53* genes were analyzed. The workflow included sample extraction, library preparation, sequencing and bioinformatics steps. In the sample extraction step, DNA from blood samples was extracted using EZ1 DSP DNA Blood Kit (Qiagen, Hilden, Germany). Qubit dsDNA HS, Thermo kit with Qubit 3 Fluorometer were performed to measure and optimize DNA concentration. QIAseq Targeted DNA Human *BRCA1* and *BRCA2* Plus Panel, Qiagen (333505) were used according to manufacturer instructions for Illumina sequencers. The genomic DNA was fragmented and all fragmented DNA was barcoded with unique molecular indices to track the original DNA molecule; hence, high sensitivity detection was obtained. Additionally, targeted genes were amplified with single primer extension technology and a bead clean-up step was performed to discard unwanted fragments. The concentration optimization of libraries was performed using Qiaseq Quant Assay Kit (Qiagen), and all libraries were diluted to 4 nM. Libraries with different sample indices were combined in equimolar amounts in a final pool. As a next step, the final pool was sequenced in a Miseq System, (Illumina Inc., San Diego, CA, USA), according to manufacturer's guide. The secondary analysis of fastq files was performed using Qiagen Clinical Insight-Analyse Universal with a panel-specific pipeline. Finally, the vcf files were clinically interpreted using Qiagen Clinical Insight-Interpret. Pathogenic, likely pathogenic variants and VUS in *BRCA1, BRCA2, CDH1, PALB2, PTEN* and *TP53* genes were identified, reported and assessed in light of published evidence.

Results

Gene variants (pathogenic, likely pathogenic and VUS) in *BRCA1, BRCA2, CDH1, PALB2, PTEN* and *TP53* genes were found in 53 (27.2%) of 195 patients. Of the cohort, 122 (62.6%) attended clinic with a positive family history. Furthermore, 121 (62.05%) were under 45 years of age and 48 (24.6%) met both family history and age criteria. In total, 58 mutations were identified with four patients having more than one mutation, while 14 novel previously unreported variants were detected. Of 53 patients, 20 had pathogenic variants, three had likely pathogenic variants and 35 had VUS.

Of the nine patient with *BRCA1* variants, eight had different variants, three had the same mutation and one had two *BRCA1* variants. Of the eight different *BRCA1* variants, four were considered pathogenic and four were VUS.

There were 26 different *BRCA2* variants identified in 32 patients, and of these 10 were pathogenic, one likely pathogenic and 15 were VUS.

Three different *TP53* variants were detected in three patients, of which two were pathogenic and one was VUS. Eight different *PALB2* variants were detected in eight patients, including two pathogenic, two likely pathogenic and four VUS. Five different *CDH1* variants were identified in five patients, all of which were VUS. In this cohort, no variant was found in the *PTEN* gene. Detailed information about the patients (age of diagnosis, family history, gender), cancer stage, tumour characteristics [ER, PR, and human epidermal growth factor receptor 2 (HER2) status] and all information related with the detected variants (gene, location, nucleotide and amino acid change, exon number, impact, mutation classification, dbSNP number and HGMD variant class) can be seen in Tables 3–7 and Figures 1–3.

Table 2. *BRCA1, BRCA2, TP53, CDH1, PALB2* and *PTEN* genes and lifetime risks for breast cancer (10)

Gene and transcript	Cytogenetic location	Genomic coordinates (GRCh38)	Tumor age (years)	Risk (%)	Incidence (birth incidence of pathogenic variants)	Life expectancy
BRCA1 NM_007294.4/	CHR 17q21.31	17:43,044,294-43,125,363	>18	50–90	1 in 400–800	62 years
BRCA2 NM_000059.4/	CHR 13q13.1	13:32,315,507-32,400,267	>18	40–90	1 in 800	68 years
TP53 NM_000546.6/	CHR 17p13.1	17:7,668,420-7,687,489	>18	80–95	1 in 5000	Severely reduced
CDH1 NM_004360.5/	CHR 16q22.1,	16:68,737,291-68,835,536	>18	70–80	Very rare	Reduced
PALB2 NM_024675.4	CHR 16p12.2	16:23,603,164-23,641,309	>18	40–60	<1 in 1000	Normal
PTEN NM_000314.8	CHR 10q23.31	10:87,863,624-87,971,929	>18	60	1 in 10000–250000	Reduced

Table 3. Detailed information about the patients and detected variants in the *BRCA1* gene. In total, nine patient had eight different *BRCA1* mutations, three of them had the same mutation and one (P2) had two *BRCA1* variants

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotide/ amino acid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class/evidence
1	S133	38	+	Female	BRCA1 NM_007294.4/ CHR 17: 41,276,047	c.66dupA p.E23fs*18	2	Frameshift	Pathogenic	rs80357783	Disease causing mutation
					CDH1 NM_004360.5/ CHR 16: 68,847,232	c.1154C>G p.P385R	9	Missense	Variant of uncertain significance	No dbSNP ID found	Not reported
2	S69	50	+	Female	BRCA1 NM_007294.4/ CHR 17: 41,243,715	c.3833A>C p.K1278T	10	Missense	Variant of uncertain significance	No dbSNP ID found	Not reported
					BRCA1 NM_007294.4/ CHR 17: 41,244,466	c.3082C>T p.R1028C	10	Missense	Variant of uncertain significance	rs80357049	Disease causing mutation?
3	S366	28	+	Female	BRCA1 NM_007294.4/ CHR 17: 41,246,489	c.1059G>A p.W353*	10	Stop gain	Pathogenic	rs80356935	Disease causing mutation
4	S109	39		Female	BRCA1 NM_007294.4/ CHR 17: 41,244,748	c.2800C>T p.Q934*	10	Stop gain	Pathogenic	rs80357223	Disease causing mutation
5	S539	55	+	Female	BRCA1 NM_007294.4/ CHR 17: 41,245,664	c.1884T>G p.S628R	10	Missense	Variant of uncertain significance	rs80357495	Not mentioned as a disease causing mutation
6	S1512	45		Female	BRCA1 NM_007294.4/ CHR 17: 41,228,634	c.4358-3A>G	Intron 12	Splicing	Variant of uncertain significance	No dbSNP ID found	Disease causing mutation?
7	S425	69	+	Female	BRCA1 NM_007294.4/ CHR 17: 41,209,079	c.5266dupC p.Q1756fs*74	19	Frameshift	Pathogenic	rs80357906	Disease causing mutation
8	S1408	49	+	Female	BRCA1 NM_007294.4/ CHR 17: 41,209,079	c.5266dupC p.Q1756fs*74	19	Frameshift	Pathogenic	rs80357906	Disease causing mutation
9	S809	65	+	Female	BRCA1 NM_007294.4/ CHR 17: 41,209,079	c.5266dupC p.Q1756fs*74	19	Frameshift	Pathogenic	rs80357906	Disease causing mutation

Table 4. Detailed information about the patients and detected variants in the *BRCA2* gene. Twenty-six different *BRCA2* variants were detected in 31 patients; 10 were considered pathologic, 1 likely pathologic and 15 were considered variant of uncertain significance (VUS)

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotide/amino acid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class/evidence
1	S374	52		Female	BRCA2 NM_000059.4/ CHR 13: 32,899,249	c.353G>A p.R118H	4	Missense	Variant of uncertain significance	rs80358603	Disease causing mutation?
2	S1538	37		Female	BRCA2 NM_000059.4/ CHR 13: 32,905,066	c.692G>C p.S231T	9	Missense	Variant of uncertain significance	rs1064793498	Disease causing mutation
3	S2101	29		Female	BRCA2 NM_000059.4/ CHR 13: 32,906,669	c.1055dupA p.Y352*	10	Frameshift Insertion	Pathogenic	rs886038060	Not reported
4	S1012	53	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,907,376	c.1763_1766delATAA p.N588fs*25	10	Frameshift	Pathogenic	rs80359303	Disease causing mutation
5	S231	42		Female	BRCA2 NM_000059.4/ CHR 13: 32,911,100	c.2608A>G p.I870V	11	Missense	Variant of uncertain significance	No dbSNP ID found	Not reported
6	S1754	35		Female	BRCA2 NM_000059.4/ CHR 13: 32,911,418	c.2926_2927delTCinsAT p.S976I	11	Missense	Variant of uncertain significance	No dbSNP ID found	Not mentioned as a disease causing mutation
7	S1579	39	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,911,802	c.3310A>C p.T1104P	11	Missense	Variant of uncertain significance	rs80358577	Disease causing mutation?
					BRCA2 NM_000059.4/ CHR 13: 32,911,995	c.3503T>A p.M1168K	11	Missense	Variant of uncertain significance	rs80358598	Not mentioned as a disease causing mutation
					CDH1 NM_004360.5/ CHR 16: 68,867,348	c.2595G>C p.W865C	16	Missense	Variant of uncertain significance	rs778019174	Not reported
8	S144	28	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,912,525	c.4033G>T p.D1345Y	11	Missense	Variant of uncertain significance	No dbSNP ID found	Not mentioned as a disease causing mutation

Table 4. continued

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotide/amino acid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class/evidence
9	**S111**	**60**	**+**	**Male**	**BRCA2 NM_000059.4 / CHR 13: 32,912,962**	**c.4471_4474delCTGA p.L1491fs*12**	**11**	**Frameshift**	Pathogenic	rs80359451	Disease causing mutation
10	**S183**	**39**		**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,913,118**	**c.4631dupA p.N1544fs*4**	**11**	**Frameshift**	Pathogenic	rs80359460	Disease causing mutation
11	S2090	52	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,913,696	c.5206_5208delCAA p.Q1736del	11	In-frame deletion	Likely Pathogenic	No dbSNP ID found	Not reported
12	**S1526**	**37**		**Female**	**BRCA2NM_000059.4/ CHR 13:32,914,066**	**c.5576_5579delTTAA p.I1859fs*3**	**11**	**Frameshift**	Pathogenic	rs80359521	Disease causing mutation
13	**S1727**	**75**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,914,283**	**c.5791C>T p.Q1931***	**11**	**Stop gain**	Pathogenic	rs80358807	Disease causing mutation
14	**S125**	**28**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,914,919**	**c.6427_6428delTCinsAT p.S2143I**	**11**	**Missense**	**Variant of uncertain significance**	No dbSNP ID found	Disease causing mutation?
15	**S89**	**38**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,914,919**	**c.6427_6428delTCinsAT p.S2143I**	**11**	**Missense**	**Variant of uncertain significance**	No dbSNP ID found	Disease causing mutation?
16	**S429**	**33**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,915,118**	**c.6626T>C p.I2209T**	**11**	**Missense**	**Variant of uncertain significance**	rs431825344	Not mentioned as a disease causing mutation
17	**S1820**	**43**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,921,033**	**c.7007G>A p.R2336H**	**13**	**Splicing**	Pathogenic	rs28897743	Disease causing mutation
18	**S1038**	**80**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,953,960**	**c.7481G>A p.R2494Q**	**15**	**Missense**	**Variant of uncertain significance**	rs80358973	Disease causing mutation?

Table 4. continued

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotide/amino acid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class/evidence
19	S1547	45	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,944,552	c.8345G>A p.S2782N	19	Missense	Variant of uncertain significance	No dbSNP ID found	Not mentioned as a disease causing mutation
20	S959	58	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,944,558	c.8351G>A p.R2784Q	19	Missense	Pathogenic	rs80359076	Disease causing mutation
					PALB2 NM_024675.4/ CHR 16: 23,614,913	c.3428T>A p.L1143H	13	Missense	Variant of uncertain significance	No dbSNP ID found	Disease causing mutation
21	S2047	52	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,944,638	c.8431G>A p.D2811N	19	Missense	Uncertain significance	No dbSNP ID found	Not reported
22	S956	40	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,945,189	c.8585dupT p.E2863fs*6	20	Frameshift	Pathogenic	rs80359720	Disease causing mutation
23	S639	42	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,950,845	c.8671A>G p.T2891A	21	Missense	Variant of uncertain significance	No dbSNP ID found	Not mentioned as a disease causing mutation
24	S143	39	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,950,845	c.8671A>G p.T2891A	21	Missense	Variant of uncertain significance	No dbSNP ID found	Not mentioned as a disease causing mutation
25	S1751	52		Female	BRCA2 NM_000059.4/ CHR 13: 32,953,603	c.8904C>T p.T2968T	22	Synonymous	Variant of uncertain significance	rs41293519	Not reported
26	S1031	36	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,953,960	c.9027delT p.H3010fs*18	23	Frameshift	Pathogenic	rs80359742	Disease causing mutation

Table 4. continued

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotide/amino acid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class/evidence
27	**S48**	**37**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,972,626**	**c.9976A>T p.K3326***	**27**	**Stop gain**	**Variant of uncertain significance**	rs11571833	Disease-associated polymorphism with additional supporting functional evidence
28	**S56**	**33**		**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,972,626**	**c.9976A>T p.K3326***	**27**	**Stop gain**	**Variant of uncertain significance**	rs11571833	Disease-associated polymorphism with additional supporting functional evidence
29	**S60**	**48**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,972,626**	**c.9976A>T p.K3326***	**27**	**Stop gain**	**Variant of uncertain significance**	rs11571833	Disease-associated polymorphism with additional supporting functional evidence
30	**S2003**	**44**	**+**	**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,972,626**	**c.9976A>T p.K3326***	**27**	**Stop gain**	**Variant of uncertain significance**	rs11571833	Disease-associated polymorphism with additional supporting functional evidence
31	**S2054**	**29**		**Female**	**BRCA2 NM_000059.4/ CHR 13: 32,972,626**	**c.9976A>T p.K3326***	**27**	**Stop gain**	**Variant of uncertain significance**	rs11571833	Disease-associated polymorphism with additional supporting functional evidence

Table 5. Detailed information about the patients and detected variants in the TP53 gene. In total, three patients had three different TP53 mutations, one of which was previously unreported

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotide/ aminoacid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class/evidence
1	**S904**	**27**		**Female**	**TP53 NM_000546.6/ CHR 17: 7,579,428**	**c.259C>T p.P87S**	**4**	**Missense**	**Variant of uncertain significance**	No dbSNP ID found	Not reported
2	**S154**	**39**	**+**	**Female**	**TP53 NM_000546.6/ CHR 17: 7,578,457**	**c.473G>A p.R158H**	**5**	**Missense**	Pathogenic	rs587782144	Disease causing mutation
3	**S1196**	**47**	**+**	**Female**	**TP53 NM_000546.6/ 17: 7,577,093**	**c.845G>T p.R282L**	**8**	**Missense**	Pathogenic	rs730882008	Disease causing mutation

Table 6. Detailed information about the patients and detected variants in the *CDH1* gene. In total five patient had five different *CDH1* mutations; one had a *BRCA1* mutation and one other had two *BRCA2* mutations. Four of the *CDH1* mutations were previously unreported

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotit/ aminoacid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class
1	**S133**	**38**	**+**	**Female**	BRCA1 NM_007294.4/ CHR 17: 41,276,047	c.66dupA p.E23fs*18	2	Frameshift	Pathogenic	rs80357783	Disease causing mutation
					CDH1 NM_004360.5/ CHR 16: 68,847,232	**c.1154C>G p.P385R**	**9**	**Missense**	**Variant of uncertain significance**	**No dbSNP ID found**	**Not reported**
2	**S1488**	**37**	**+**	**Female**	**CDH1 NM_004360.5/ CHR 16: 68,849,520**	**c.1423G>A p.V475M**	**10**	**Missense**	**Variant of uncertain significance**	**rs587782113**	**Disease causing mutation**
3	**S1602**	**59**	**+**	**Female**	**CDH1 NM_004360.5/ CHR 16: 68,855,982**	**c.1790C>G p.P597R**	**12**	**Missense**	**Variant of uncertain significance**	**No dbSNP ID found**	**Not reported**
4	**S2106**	**44**		**Male**	**CDH1 NM_004360.5/ CHR 16: 68,867,313**	**c.2560G>A p.D854N**	**16**	**Missense**	**Variant of uncertain significance**	**No dbSNP ID found**	**Not reported**
5	**S1579**	**39**	**+**	**Female**	BRCA2 NM_000059.4/ CHR 13: 32,911,995	c.3503T>A p.M1168K	11	Missense	Variant of uncertain significance	rs80358598	Not mentioned as a disease causing mutation
					BRCA2 NM_000059.4/ CHR 13: 32,911,802	c.3310A>C p.T1104P	11	Missense	Variant of uncertain significance	rs80358577	Disease causing mutation?
					CDH1 NM_004360.5/ CHR 16: 68,867,348	**c.2595G>C p.W865C**	**16**	**Missense**	**Variant of uncertain significance**	**rs778019174**	**Not reported**

Table 7. Detailed information about the patients and detected variants in the *PALB2* gene. In total eight patients had seven different *PALB2* mutations; two had the same mutation and one also had a *BRCA2* variant. Three of the mutations were previously unreported

	Analysis ID	Age of diagnosis	Family history	Gender	Gene/location	Nucleotide/ amino acid change	Exon	Impact	Mutation classification	dbSNP number	HGMD variant class
1	S206	35	+	Female	PALB2 NM_024675.4/CHR 16: 23,649,188	c.194C>T p.P65L	3	Missense	Variant of uncertain significance	rs62625272	Not mentioned as a disease causing mutation
2	S1914	49	+	Female	PALB2 NM_024675.4/ CHR 16: 23,647,033	c.833_834delTAinsAT p.L278H	4	Missense	Likely pathogenic	rs587778582	Disease causing mutation?
3	S1202	39		Female	PALB2 NM_024675.4/ CHR 16: 23,641,218	c.2257C>T p.R753*	5	Stop gain	Pathogenic	rs180177110	Disease causing mutation
4	S807	53		Female	PALB2 NM_024675.4/ CHR 16: 23,641,218	c.2257C>T p.R753*	5	Stop gain	Pathogenic	rs180177110	Disease causing mutation
5	S434	55	+	Female	PALB2 NM_024675.4/ CHR 16: 23,619,249	c.3285dupT p.N1096*	12	Frameshift	Likely pathogenic	No dbSNP ID found	Not reported
6	S252	67	+	Female	PALB2 NM_024675.4 CHR 16: 23,614,953	c.3388G>C p.A1130P	13	Missense	Variant of uncertain significance	No dbSNP ID found	Not reported
7	S959	58	+	Female	BRCA2 NM_000059.4/ CHR 13: 32,944,558	c.8351G>A p.R2784Q	19	Missense	Pathogenic	rs80359076	Disease causing mutation
					PALB2 NM_024675.4/ CHR 16: 23,614,913	c.3428T>A p.L1143H	13	Missense	Variant of uncertain significance	No dbSNP ID found	Disease causing mutation
8	S1690	39		Female	PALB2 NM_024675.4/ CHR 16: 23,614,894	c.3447C>A p.A1149A	13	Synonymous	Variant of uncertain significance	No dbSNP ID found	Not reported

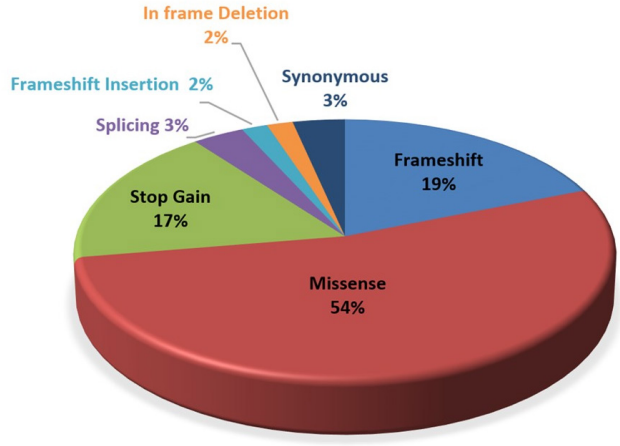

Figure 1. Detected variants' impacts

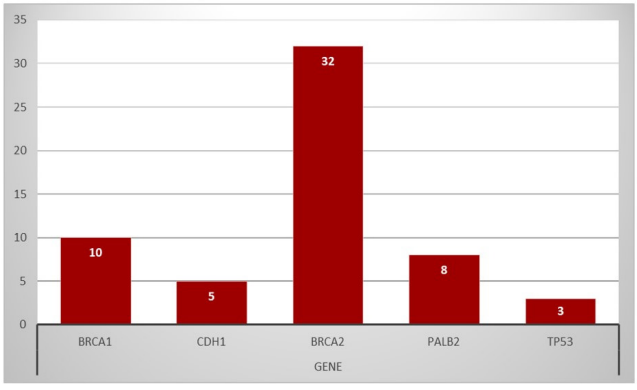

Figure 2. Distribution of variants by genes

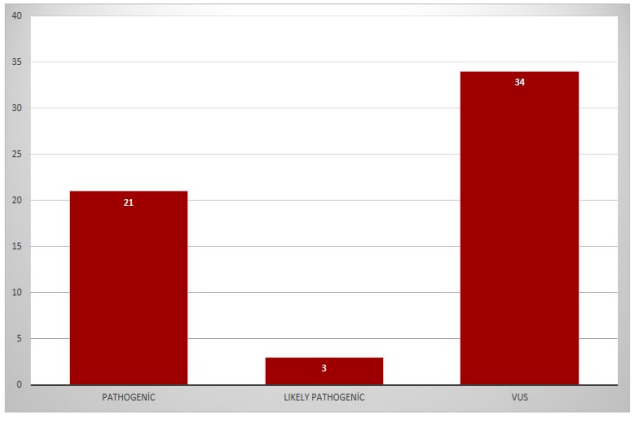

Figure 3. Distribution of variants by pathogenicity

Discussion and Conclusion

BRCA1 is predominantly a breast cancer gene and for carriers the estimated lifetime for breast cancer ranges between 50–85% (10). In the present study, eight different *BRCA1* variants were detected in nine patients, and four were considered pathogenic and four were VUS. Pathogenic variants were c.5266dupC (p.Q1756fs*74) and c.66dupA (p.E23fs*18) that are both frameshift mutations and c.1059G>A (p.W353*) and c.2800C>T (p.Q934*) that are both stop codon mutations. Frameshift mutations are particularly severe and cause changes in many bases downstream and can affect many of the amino acids in the protein. c.5266dupC (p.Q1756fs*74), which is one of the most common pathogenic variants in *BRCA1* gene, was found in three patients (1.54%) in this study. According to the previous studies the estimated prevalence of the mutation is between 2.5% and 7.1% in breast cancer patients (11). c.66dupA (p.E23fs*18), c.1059G>A (p.W353*) and c.2800C>T (p.Q934*) mutations have been reported previously, while the c.2800C>T (p.Q934*) mutation was previously recognized as a Japanese founder mutation (12). c.3833A>C (p.K1278T) and c.3082C>T (p.R1028C) mutations, which were both VUS and missense mutations, were found in the same patient. The c.3833A>C p.K1278T mutation has not been reported previously. In this case compound heterozygosity may be responsible for the disease. The c.1884T>G variant found in one patient, was not considered a disease-causing mutation in HGMD and was classified as VUS, and in ClinVar this variant was observed with hereditary breast and ovarian cancer syndrome (13). c.4358-3A>G, found in one patient in the present study, was a splicing mutation. The variant has no dbSNP ID yet and was previously identified in only two reports. One mentioned the susceptibility to breast and ovarian cancer and the other reported that it was observed associated with a cancer predisposition syndrome (14, 15). When we looked at the exons, exon 10 was remarkable. Out of the eight different mutations, five were in exon 10. In previous studies, similar data was given. Exon 10 was the most common location for *BRCA1* mutations and mutations were predominantly distributed around exon 10 (16).

Germline mutations in the *BRCA2* gene are highly penetrant for increased risks of breast and ovarian cancers, and male breast cancer, prostate cancer, pancreatic cancer, and melanoma (17). In this study 26 different *BRCA2* variants were detected in 32 patients with operated breast cancer and 10 were considered pathogenic, one likely pathogenic and 15 were considered VUS. Pathogenic variants were c.8585dupT (p.E2863fs*6), c.1763_1766delATAA (p.N588fs*25), c.9027delT (p.H3010fs*18), c.5576_5579delTTAA (p.I1859fs*3), c.4471_4474delCTGA (p.L1491fs*12), c.4631dupA (p.N1544fs*4), c.8351G>A (p.R2784Q), c.5791C>T (p.Q1931*), c.7007G>A (p.R2336H) and c.1055dupA (p.Y352*). Most of the pathogenic variants were frameshift mutations (6/10) while frameshift insertion, stop codon, missense and a splicing mutation were identified. In the present study five patients had c.9976A>T p.K3326* variant which was considered VUS. The variant was a stop codon mutation and in HGMD it was reproted that the variant was a disease-associated polymorphism with additional supporting functional evidence. For these patients further studies are needed to identify the additional findings. Two patients had c.6427_6428delTCinsAT (p.S2143I) variant, which was considered a VUS. The variant had no dbSNP ID at the time of writing and was previously reported in only two studies. Both studies mentioned that the variant was observed with hereditary risk breast/ovarian cancer (18, 19). Besides this variant, there were 11 more variants in exon 11 found in our study. Exon 11 is very important for the *BRCA2* gene, which comprises over 50% of the gene and encompasses half of the coding region. In our study, 12 mutations were found in exon 11 and four were pathogenic, one was likely pathogenic and seven were VUS. Out of four pathogenic variants, three were frameshift mutations and one was a stop codon mutation. We found c.4471_4474delCTGA (p.L1491fs*12) mutation in a male patient. This variant deletes four nucleotides in exon 11 of the gene and as a result, creates a frameshift and premature translation stop signal. Functional studies have not been reported for this variant but

is expected to result in an absent or non-functional protein product (20). The c.4033G>T (p.D1345Y) variant, considered a VUS, has no dbSNP ID and has not been mentioned as a disease-causing mutation. In the literature one report was found that related this variant with rectal adenocarcinoma (21). The c.2608A>G (p.I870V) variant found was considered a VUS, was not been previously reported and had no dbSNP ID, like the other c.5206_5208delCAA (p.Q1736del) variant that was considered likely pathogenic. The novel *BRCA2* mutation, c.5206_5208delCAA (p.Q1736del) was an in-frame 3 bp deletion that is predicted to result in the loss of one amino acid. A deletion is in-frame and if the reading frame of the gene is preserved and not disrupted, so a protein can be made and it may still be partially functional. These kinds of mutations are much rarer than the other types, such as stop, frameshift, and missense or splicing. In-frame deletions typically result in milder conditions but the functional impact and prognostic value of this novel in-frame deletion variant in *BRCA2* remains to be elucidated. The c.6626T>C (p.I2209T) variant, considered a VUS, was not mentioned as a disease-causing mutation in HGMD but in ClinVar, it was associated with hereditary breast and ovarian cancer syndrome (22). The c.2926_2927delTCinsAT (p.S976I) variant has no dbSNP ID at present and was previously reported in only two reports. Both mentioned that the variant was observed in association with breast cancer (23, 24). Two missense variants in the *BRCA2* gene, c.3503T>A (p.M1168K) and c.3310A>C (p.T1104P) and one variant in *CDH1* c.2595G>C (p.W865C), were found in one patient, and all of them are considered as VUS. c.3503T>A variant was not mentioned as a disease-causing mutation. The c.8671A>G (p.T2891A) variant that we identified, is considered a VUS, but was not mentioned as a disease-causing mutation. However, one report was found and mentioned that it was observed with breast cancer (25). In another case we identified the c.353G>A (p.R118H) variant, previously reported once, and the case was suffering from different types of cancer, including not only breast, but also endometrial and ovarian cancer (26). The c.1055dupA, p.Y352* was another variant that was not reported previously. This duplication of one nucleotide creates a nonsense variant, which changes a tyrosine to a premature stop codon. It was predicted to cause loss of normal protein function and was considered pathogenic because of the protein truncation or nonsense-mediated mRNA decay (27). In another case, we identified the c.7481G>A (p.R2494Q) variant and according to the literature there are some conflicting findings related to pathogenicity (28).

Germline mutations in the *TP53* gene cause a familial cancer predisposition, and carriers have a very high lifetime risk of malignancies, especially soft tissue sarcomas and breast cancer in women. The penetrance of breast cancer is very high and according to the National Cancer Institute Li-Fraumeni syndrome cohort cumulative incidence is 85% by age 60 years (29, 30). In the present study, three different variants were detected in three patients. All were missense mutation, one of which was a novel mutation, c.259C>T (p.P87S). The others had been reported previously and both were considered pathogenic.

Most recently, it was reported that 7% of all *CDH1* mutations are present in non-gastric tumors, especially being identified in cases with breast cancer. In our study, five *CDH1* gene variants were found, all of which were missense mutations and considered VUS. Four of them, c.1154C>G (p.P385R), c.2595G>C (p.W865C), c.1790C>G (p.P597R) and c.2560G>A (p.D854N) were all novel mutations and not previously reported. The patient with c.1154C>G variant also carried a pathogenic *BRCA1* variant, c.66dupA (p.E23fs*18). Another case who had the c.2595G>C (p.W865C) variant also had two *BRCA2* mutations, c.3503T>A (p.M1168K) and c.3310A>C (p.T1104P). The p.V475M variant (also known as c.1423G>A), results in a conservative amino acid change in the encoded protein sequence. This amino acid position is highly conserved. Although *in silico* tools predict a damaging effect on protein function, the data on variant occurrences in the general population are insufficient to allow any conclusion and the clinical significance of this alteration remains unclear (31, 32).

PALB2 mutations are found in 0.6 to 3.9% of families with a history of breast cancer. In previous studies, the estimated mean risk of breast cancer for female *PALB2* mutation carriers by 70 years of age is 35% (33). In the present study, seven *PALB2* gene variants were identified in eight cases, three of which were novel mutations and not reported before. The c.3285dupT (p.N1096*) mutation was considered likely pathogenic but has not been reported previously. The c.3388G>C (p.A1130P) and c.3447C>A (p.A1149A) variants were also previously unreported, were classified as VUS, and have no dbSNP ID. Another missense mutation, c.3428T>A p.L1143H, was identified in a patient who also had the *BRCA2* pathogenic c.8351G>A (p.R2784Q) mutation. This variant in the *PALB2* gene had no dbSNP ID, and was mentioned in only a few reports in the literature. In a study based in the Turkish population, this was observed with breast cancer (34). The c.194C>T (p.P65L) variant, considered a VUS, was not mentioned as a disease-causing mutation, but in the ClinVar database it was reported that this amino acid position was poorly conserved and thus the predicted effect will be tolerated by *in silico* analysis. Since supporting evidence is limited, the clinical significance of this alteration remains unclear (35). The c.833_834delTAinsAT p.L278H variant, classified as a VUS, and as functional studies have not been performed for this variant, the available evidence is insufficient to determine the role in the protein. *BRCA1, BRCA2, TP53, CDH1, PALB2* and *PTEN* genes and lifetime risks for breast cancer are summarized in Table 6 (10).

Besides medical geneticists, breast surgeons and oncologists are well placed as a resource for patients who could benefit from genetic testing. The patients must be evaluated in the multidisciplinary councils and informed about the risks and benefits, and also discuss risk management strategies. The American Society of Clinical Oncology and the NCCN recommend considering genetic testing for breast cancer in patients, especially diagnosed at early age, with bilateral breast cancer, ER-/PR-/HER2- disease status, strong family history of breast and/or ovarian cancer, or a combination of these characteristics (9). The identification of an inherited pathogenic mutation predisposing to breast cancer in genetic testing does not mean that risk-reducing mastectomy is indicated. While risk-reducing mastectomy can be considered in *BRCA1, BRCA2, PTEN* and *TP53*, the situation can differ in other gene mutations. However, when combined with a significant family history of breast cancer, prophylactic surgery may be appropriate for patients with mutations in other genes (36) but the risks of the surgery should be discussed with the patient. In a multicenter study investigating the prevention of breast cancer with nipple-sparing mastectomy, prophylactic nipple-sparing mastectomy was performed in 346 patients who were carriers of *BRCA1* and *BRCA2*. None of them developed breast cancer at the 56-month follow-up. In the risk analysis conducted in the same study, it was reported that if mastectomy was not performed, breast cancer was predicted to have developed in 22 of the patients (37). In another study, follow-up and prophylactic mastectomy were compared in order to reduce the risk of breast cancer in *BRCA*-positive patients. It was shown that mastectomy significantly

reduced the risk of developing breast cancer, but had complications and risks (38). Prophylactic oophorectomy in premenopausal women with pathogenic variants in *BRCA2* has also been shown to reduce the risk of breast cancer by approximately 50%. This rate is lower in *BRCA1* patients who underwent risk-reducing oophorectomy (39). Advanced screening is recommended for patients with *ATM, CDH1, CHEK2, NBN, NF1, PALB2,* and *STK11* mutations, but currently the data are insufficient to support risk-reducing mastectomy in the absence of other factors such as a strong family history. Risk is modulated by age, family history, and in some cases, a specific mutation in a particular gene. The guidelines broadly support the consideration of contrast and non-contrast breast magnetic resonance imaging and tomosynthesis mammography for annual screening, due to the increased risk of breast cancer in individuals with this group of mutations (36). As also seen in our study, studies assessing mutations, which are commonly identified in the young patient population, as treatment targets have been underway for a long time. Besides evaluating mutations in terms of recurrence, secondary malignancy development or familial risk, they have an important role in both treatment and prognosis, again emphasizing the importance of genetic analysis.

Analysis of the relationship between mutations and the histopathological characteristics of tumors show that *BRCA1* mutations are associated with breast cancers that have a basal-like gene expression profile, high histological grade, negative estrogen receptor status, and HER2-negative (triple negative) status. *BRCA2*-associated breast cancers are usually high-grade, estrogen receptor-positive, and HER2-negative (40). The 5-year survival rate for patients with metastatic breast cancer is reported to be 27%, whereas for patients with metastatic triple-negative breast cancer associated with a *BRCA1* mutation, this rate is only 11%. Therefore, new treatments that provide lasting benefits are needed in patients with advanced breast cancer associated with a germline *BRCA* mutation. Breast cancers with *BRCA1* and *BRCA2* mutations, are deficient in homologous recombination and disrupt the ability of cancer cells to repair DNA damage, and also known to be sensitive to both poly (ADP-ribose) polymerase (PARP) inhibitors and platinum agents (41). PARP is an enzyme family responsible for the cellular activities involved in DNA repair, such as the base excision repair pathway and genetic stability. PARP plays a key role in the repair of single-strand DNA breaks, which is important for the survival of the cell. The inhibition of PARP leads to continued single-strand DNA breaks, which causes replication forks to stop, and double-strand breaks to occur. In cells with normal homologous recombination, double-strand DNA breaks can be repaired by the homologous recombination repair pathway. However, in cells with homologous recombination deficiency, treatment with a PARP inhibitor results in cell cycle arrest, a concept called synthetic lethality, and apoptosis (42).

Tumors with changes that inactivate *BRCA1/2*, can respond to PARP inhibitors, such as olaparib, talazoparib, rucaparib or niraparib, and chemotherapeutics that cause DNA damage, such as cisplatin and carboplatin (43, 44). In the "triple negative trial", a randomized phase III trial comparing carboplatin with docetaxel in patients with locally advanced metastatic or recurrent TNBC, patients with germline *BRCA1/2* mutations showed significantly better response to carboplatin compared to docetaxel (41). Two randomized phase III trials reported PARP inhibitor efficacy compared to physician's choice of chemotherapy in patients with metastatic breast cancer and one germline *BRCA* pathogenic variant. In the OlympiAD study (ClinicalTrials.gov descriptor: NCT02000622), olaparib was shown to improve progression-free survival with a hazard ratio of 0.58 [95% confidence interval (CI), 0.43–0.80] compared to standard chemotherapy. In the EMBRACA study (ClinicalTrials.gov descriptor: NCT01945775), talazoparib showed a progression-free survival contribution with a hazard ratio of 0.54 (95% CI, 0.42–0.71) (45). That these inhibitors offer oral treatments, and perhaps even more importantly, improve the quality of life of patients, makes them more attractive. In the NCCN Guidelines version 3.2022, both treatments are indicated as category 1 recommendation in the presence of a *BRCA1/2* mutation. In addition to metastatic diseases, there are studies that also report the positive results of PARP inhibitors in neoadjuvant and adjuvant therapies (46).

CDH1 may also play a potential strategic role in the clinical management of breast cancer patients as a predictor of prognosis and survival. To date, *CDH1* has not been defined as a molecular target for treatment, but *in vitro* studies have shown that the germ line function could be suitable for targeted therapy. Important new crosstalk mechanisms have been described. Growth factor signals are hyperactivated upon loss of *CDH1,* regardless of the somatic activating mutations in downstream effectors. In particular, the PI3K/Akt pathway is activated upon loss of *CDH1* in the absence of specific oncogens. *ROS1* gene rearrangements are a defined and approved therapeutic target in relation to different cancers. Bajrami et al. (47) have described a synthetic lethal interaction between *CDH1* and *ROS1*. The authors showed that ROS1 inhibition in *CDH1* defective breast tumor cell sequences and breast tumor xenografts derived from patients resulted in tumor cell death.

In contrast to the biomarker role of *TP53*, until recently very few studies were performed that target therapeutically mutant *TP53*. With the recent identification of several compounds capable of reactivating the mutant protein, however, PRIMA-1MET (p53 reactivation and induction of massive apoptosis, methylated derivative) also called APR-246 has been reported (48). In addition to inhibiting cell proliferation, APR-246 was seen to induce apoptosis and reduce migration in the investigated mutant p53 breast cancer cell sequences. Another anti-p53 compound, which has been investigated for anticancer activity in breast cancer cells is the 2-sulfo-pyrimidine molecule known as PK11007. Like APR-246, PK11007 stabilizes and reactivates mutant p53 (49). There are no FDA-approved therapeutic targets yet, either for *CDH1* or *T53*, but ongoing studies are promising. Studies are ongoing to identify the other mutations identified in the present study, both to determine suitability as treatment targets and to define their characteristics predicting prognoses.

This study identified a total of 58 mutations in a cohort of 195 women who had been operated for breast cancer, of which 35 were VUS and 14 were novel variants that have not been previously reported. We have highlighted the VUS in this report because the clinical significance of VUS is changing over time and variant classification is important for clinical molecular genetic testing and clinical guidance. In a previous study, the researchers reclassified specific VUS identified over a 13-year period, and the results showed that 5.6% were reclassified as pathogenic or likely pathogenic variants. Further investigation into the pathogenicity of VUS is required. With continued monitoring of patients with VUS mutations, reclassification must be suggested when sufficient evidence is collected (50). Besides clinical follow-up, genetic follow-up should occur. Knowledge and identification of mutations have important implications for predictive, preventive, personalized medicine, besides genetic counseling and development of specific treatment protocols.

This study has also provided risk assessment data, which may be useful for clinical management for *TP53, CDH1, PALB2* and *PTEN,* together with *BRCA1* and *BRCA2* genes in breast cancer patients and may also be important for surveillance of other family members. Further studies are needed to identify common variants in the Turkish population and to evaluate the pathogenity of VUS.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by İzmir Katip Çelebi Non-Interventional Clinical Studies Institutional Review Board (0028/20.01.2022).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Fear of Breast Cancer and Assessment of the Efficiency of Mammography Scanning in Working Women

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ABSTRACT

Objective: To determine the fear of breast cancer and assess the efficiency of mammography scanning among a female population working in a university.

Materials and Methods: This descriptive study was performed in a university in the city center of Samsun between March 2019 and October 2019. Instead of choosing samples, all volunteers were included. The data were collected by a study-specific form prepared by the researchers, the breast cancer fear scale and mammography efficacy scale. Descriptive statistical analyses were performed and data were analyzed using the Statistical Package for the Social Sciences, version 20.0.

Results: The mean age of women participating in this study was 38.07±8.58 (range 20–62) years and the mean health perception score was 7.46±1.51 (range 3–10). Most (70.3%) women were academic staff and 17.9% reported income less than expenses. Of the participants, 16.1% had breast-related health problem and 18.4% had breast cancer in the family. Most (85.0%) believed that they should have mammography scanning to be protected from breast cancer. The mean score on the breast cancer fear scale was 25.60±7.29, indicating a high score and the mean score on the mammography efficacy scale was 41.18±6.47, indicating a high score of mammography efficacy. The score of breast cancer fear scale was higher for; married women (26.19±7.21) than single women (24.33±7.39) and women with history of having health problem related with breast (28.94±7.30) while those without a history of health problem (24.96±7.13) and postmenopausal women (27.64±6.19) while non-menopausal women (25.30±7.40).

Conclusion: The score of breast cancer fear scale was higher for; married women, history of having health problem related with breast and postmenopausal women.

Keywords: Breast cancer; fear; mammography

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Key Points

- The majority of working women participating in the study know the importance of early diagnosis in breast cancer, believe that mammography is necessary for early diagnosis and consider it necessary.
- The high mammography self-efficacy scores of working women participating in the study is an indication of high breast cancer awareness.
- In order for the positive results seen in the above two items to be seen in women from all parts of society, awareness of this viewpoint and scientific studies on the subject should be increased.

Introduction

According to the Globocan (2020) data published by the World Health Organization, cancer is a global health problem that is the most common and the largest cause of mortality among non-communicable diseases. Among the top ten cancer types seen globally, breast cancer ranks second after lung cancer and has a rate of 11.7% among all cancer types. Worldwide, there were 2,261,419 new registered breast cancer cases in 2020. With 24,175 new breast cancer cases in Turkey, it has a rate of 10.3% among all cancer types (1, 2). It has been stated that 12.9 out of every hundred thousand registered breast cancer cases in the world in 2021 resulted in mortality. In addition, the International Agency for Research on Cancer argues that the reason for the increase in cancer cases in the world, 2–3 times higher incidence in cancer cases in developed countries compared to other countries may be due to limited access to diagnosis and treatment (2). In Turkey, according to the data of Head of Cancer Department, breast cancer in women is the most common and also the most common cause of death. Breast cancer is an important public

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health problem and in Turkey the lifetime risk of developing breast cancer for a woman is 7.8% and the risk of the mortality is 2.3%. Early detection has an important role in decreasing the mortality rate due to breast cancer. Although various methods have been proposed for early diagnosis, only the effectiveness of mammography has been proved. Breast cancer scans performed by screening mammography have been shown to decrease breast cancer mortality rate (3).

The Turkish Society of Gynecological Oncology (TJOD) has defined fear of breast cancer as the negative, psychological and physiological warnings that occur against the perceived threat of breast cancer and the response that individuals exhibit against this threat. TJOD has also reported that fear that prevents performing breast cancer early detection behavior occurs because of thoughts such as being diagnosed with breast cancer, losing the breast, death, and feeling of pain (4). Self-efficacy, on the other hand, is the individual's own will, determination and belief in performing the action in order to achieve the expected results, and fear is thought to be both a preventive and a facilitating factor in performing breast cancer early diagnosis behavior (5, 6). Studies have shown that women with a family history of breast cancer and risk factors experience fear of developing breast cancer (7). However, it has been claimed that the fear of having breast cancer does not always negatively affect early diagnosis behavior, but sometimes positively affects this behavior and facilitates early diagnosis promoting behavior (8). The frequency of mammography in Turkey is lower than in many other countries. Women's age, family history of breast cancer, mammography barriers, genetic risk in women, and the presence of individuals with breast cancer in their environment make women more sensitive to breast cancer, not knowing about mammography, not being able to spare time, not thinking that they will have breast cancer. Conditions such as not needing to have a mammogram, not giving importance to health, and concern about seeing a male doctor are factors that prevent mammography (9, 10).

Fear may have both a positive or negative effect on attendance for mammography, and situations such as mammography self-efficacy levels, knowledge about breast cancer and the presence of a family history of breast cancer will also be factors. This study was conducted to determine the fear of having breast cancer and assess the self-efficacy of having mammography in working women.

Research Questions Were:

1. What is the rate of women using cancer screening methods, specifically mammography?

2. Does the fear of breast cancer affect the effectiveness of mammography screening?

Materials and Methods

Type of Study: This research was planned as a descriptive and relational study in order to determine the fear of breast cancer and self-efficacy of mammography in women working at a university.

Study Place and Time: The study was conducted at a university in Samsun Province of Turkey in March-October 2019.

The Universe and Sample of the Research: The population of the research consisted of women working at a university in Samsun. No sample selection was made for the study because when the mean breast cancer score was found to be 23.81±9.71 in the power analysis, the sample size was calculated as 231 with a 5% margin of error. In total 347 women volunteered to participate in the study. While the research data were collected, oral consents were obtained from the women. In Post-hoc power analysis, the sample size conveyed a power of 93%. While the level of fear of having breast cancer and mammography self-efficacy status of the sample group were independent variables and women's socio-demographic characteristics, breast cancer history and mammography screening history were dependent variables.

Data Collection (Data Collection Tools): In the data collection, the question form prepared by the researchers, the breast cancer fear scale and the mammography self-efficacy scale were used (see below).

Questionnaire form consisted of 19 questions including the socio-demographic characteristics of individuals, their characteristics related to breast cancer and mammography, and their own health perceptions (11). The health perception measure was a general assessment measure to subjectively evaluate participants' overall health perceptions. This criterion was scored from 0 to 10 with "0" indicating very bad health and "10" indicating very good health. High scores indicate that participants perceive their own health as good. Expert opinions were received.

Breast Cancer Fear Scale (BCFS) was developed in 2004 by Champion, Skinner, Menon, Rawl, Giesler, Monahan and Daggy. Cronbach's alpha coefficient was 0.91 for the whole scale. A validity and reliability study of the Turkish version of the BCFS was performed by Secginli (12) in 2012. The Cronbach alpha coefficient of the Turkish version was 0.90. The scale, which was adapted to Turkish, consisted of eight items and the scale score has a minimum of 8 and a maximum of 40. The scale score ranges from "strongly disagree" 1 to "strongly agree" 5 points. A high score indicates that the level of breast cancer fear is high.

Mammography Self-Efficacy Scale (MSS); The Breast Cancer Fear Scale was developed in 2005 by Champion, Skinner, Menon, Rawl, Giesler, Monahan and Daggy. Cronbach's alpha coefficient was 0.87 for the whole scale. A validity and reliability study of the Turkish version of the MSS was performed by Secginli (12) in 2012. The Turkish version consisted of 10 items and the scale score was a minimum of 10 and a maximum of 50. The scale score ranges from "strongly disagree" 1 to "strongly agree" 5 points. A high score indicates that the level of mammography self-efficacy is high (12).

Statistical Analysis

Statistical analysis of the data was performed using Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Inc., Armonk, NY, USA). Significance level was accepted as $p<0.05$. The descriptive statistics (number, percentage and mean, standard deviation and range) were used for the questions in the questionnaire form prepared by the researchers. The t-test, Spearman correlation and ANOVA analysis were performed to investigate breast cancer fear scores, mammography self-efficacy scores and other variables.

Ethical principles: Permission for the research was obtained from the clinical research ethics committee of Ondokuz Mayıs University. Ethics committee decision no: 2019/244. Permission was obtained from the university for the research.

Results

The socio-demographic characteristics of participants is given in Table 1. Table 2 shows some characteristics of the women and breast

cancer early diagnosis (n = 347). The mean health perception score was 7.46±1.51. While 75.8% did not use oral contraceptives and 13.0% were menopausal. It was found that 63.7% participating in the study received information about breast cancer, 16.1% had breast health problems and 18.4% had a family history of breast cancer. Furthermore, 85.0% thought that mammography should be undertaken in order to prevent cancer and 82.5% of them believed in the necessity of mammography to prevent breast cancer and also knew of the importance of early diagnosis in cancer prevention (Table 2).

Table 3 shows data concerning the women's breast cancer fear scale scores and mammography self-efficacy scale scores. The mean BCFS score was 25.60±7.29 (given a minimum and maximum score of 8 and 40, respectively, and Cronbach's alpha was 0.92. The MSS mean score was 41.18±6.47, given a minimum and maximum of 10 and 50, respectively and Cronbach's alpha was 0.92. Table 4 shows the correlation analysis between the mean BCFS and MSS scores stratified by differences in a range of variables. There was no correlation between the educational status of women and BCFS scores or MSS scores according to income perceptions. BCFS scores were significant higher in married women compared to single women. In terms of MSS scores, no significant difference was found when comparing married women and single women. Menopausal women had higher BCFS scores than pre-menopausal women, and women with a family history of breast cancer had higher BCFS scores than women without such a family history. BCFS and MSS scores were higher among women who had breast health problems and who believed that mammography should be taken to prevent breast cancer. A significant weak positive correlation was found between increasing BCFS score and MSS score (r = 0.180, p<0.001).

Table 1. Distribution of women according to socio-demographic characteristics (n = 347)

Socio-demographic characteristics		
Age	**Mean ± SD 38.07±8.58**	**Range 20-62**
	n	%
Education status		
Primary school	10	2.9
High school	33	9.5
University and higher education	304	87.6
Perception of income satisfaction		
Income is less than expense	62	17.9
Income is equal to expense	179	51.6
Income is more than expense	106	30.5
Job description		
Academicals personal	244	70.3
Administrative staff	103	29.7
Marital status		
Married	237	68.3
Single	110	31.7
Having children		
Yes	217	62.5
No	130	37.5
Total	**347**	**100**

SD: standard deviation

Discussion and Conclusion

The women participating in this study were asked to judge how they perceived their own health on a scale of 0 to 10, and the subjective health perception mean score of women was 7.46±1.51, suggesting a relatively positive self-perception of health among participants In the

Table 2. Distribution of women according to some descriptive characteristics and breast cancer early diagnosis information (n = 347)

Descriptive characteristics and variables		
	Mean ± SD	**Range**
Health perception score average	7.46±1.51	3–10
	n	**%**
Using oral contraceptive		
Yes	84	24.2
No	263	75.8
In menopause period		
Yes	45	13.0
No	302	87.0
Getting information about breast cancer		
Yes	221	63.7
No	126	36.3
Having breast health problem		
Yes	56	16.1
No	291	83.9
Having breast cancer history in family		
Yes	64	18.4
No	283	81.6
Thinking that mammography is necessary to prevent breast cancer		
Necessary	295	85.0
Unnecessary	52	15.0
Believe in the need for mammography screening		
Believer	287	82.5
Unbeliever	60	17.5
Mammography screening		
Yes	284	81.8
No	63	18.2
Total	**347**	**100**

SD: standard deviation

study of Dinçel et al. (13), who made a similar assessment, 32.0% of women perceived their health as good, the majority (59.3%) as medium and 8.7% as bad.

Breast cancer is a common public health problem, and in order to combat this problem, it is necessary to know the factors prevent or increase early screening behavior. These factors are suggested to include having any breast health problem, having a family history of breast cancer, fear of having breast cancer, and not having enough information about breast cancer (14, 15). In the cohort of the present study 16.1% had breast health problems, 18.4% had a family history of breast cancer, and 63.7% had received information about breast cancer before. In a previous study, it was determined that 18.3% of women had a family history of breast cancer (16). In the study of Sönmez et al. (17) 28.7% of women had knowledge about breast and cervical cancer. In another study, 89.1% of women had no previous breast health problems, and 9.6% had a family history of breast cancer (18). Similarly, in the study of Dinçel et al. (13), 12.3% of women

Table 3. Distribution of breast cancer fear scale and Mammography self-efficacy scale scores

Scale	n	Items Numb.	Mean ± SD	Min	Max	Cronbach alpha	Cronbach Alpha
Breast cancer fear score	347	8	**25.60±7.29**	8	40	**0.92**	**0.90***
Mammography self-efficacy scale	347	10	**41.18±6.47**	10	50	**0.92**	**0.90***

[Cronbach Alfa: 0.90*, Seçginli (12)], SD: standard deviation; Min: minimum; Max: maximum

Table 4. Correlation analysis of mean breast cancer fear scale and mammography self-efficacy scale scores with variables

Characteristics and variables	Breast cancer fear scale score		Mammography self-efficacy scale score	
	Mean ± SD		Mean ± SD	
Education Status				
Primary school	27.40±6.27	F = 0.67	34.20±9.36	**F = 10.04**
High school	24.51±8.61	*p* = 0.50	38.54±7.69	***p*<0.01**
University and higher education	25.66±7.17		41.70±6.02	
Perception of Income Satisfaction				
Income is less than expense	25.19±8.11	F = 2.25	40.40±7.91	F = 0.95
Income is equal to expense	26.37±6.99	*p* = 0.10	41.09±6.38	*p* = 0.38
Income is more than expense	24.53±7.21		41.80±5.64	
Job description				
Academic personal	25.75±7.25	t = 0.58	41.85±5.69	**t = 2.99**
Administrative staff	25.25±7.41	*p* = 0.70	39.60±7.81	***p*<0.01**
Marital status				
Married	26.19±7.21	**t = 2.21**	41.59±6.92	t = 1.70
Single	24.33±7.39	***p* = 0.02**	40.31±5.30	*p* = 0.08
In menopause period				
Yes	27.64±6.19	**t = 2.01**	41.95±7.01	t = 0.85
No	25.30±7.40	***p* = 0.04**	41.07±6.39	*p* = 0.39
Having breast health problem				
Yes	28.94±7.30	**t = 3.81**	43.73±5.77	**t = 3.25**
No	24.96±7.13	***p*<0.01**	40.69±6.49	***p* = 0.01**
Having breast cancer history in family				
Yes	27.12±6.84	t = 1.85	41.34±6.21	t = 0.21
No	25.26±7.36	*p* = 0.06	41.15±6.53	*p* = 0.83
Believe in the need for mammography screening				
Believer	25.77±7.23	t = 1.30	41.41±6.50	**t = 2.00**
Unbeliever	24.08±7.81	*p* = 0.19	39.31±5.88	***p* = 0.04**

had a family history of breast cancer, while 52.0% of them had no knowledge of breast cancer. In the study conducted by Açıkgöz et al. (19), it was reported that 46.7% of the women had a family member diagnosed with cancer. In the study of Aslan and Gürkan (20), it was stated that 8.3% of the women had a family history of breast cancer. The results of the present study are similar to other studies in terms of women's knowledge about breast cancer. It can be said that this similarity is due to the increase in early diagnosis studies and the ease of access to information. In addition, while the rates of family history of breast cancer in our study were similar to most studies, it was observed that they differed from some studies. It can be said that these differences are due to the fact that the studies were carried out in different regions.

Although breast cancer is common, it is a cancer that develops slowly and, with early diagnosis, very successful treatment results can be obtained and the mortality rate can be reduced. In Turkey, the 5-year survival rate is 90.0% in women diagnosed at an before the cancer spreads in the bodyearly stage. Clinical breast examination and mammography are the main methods recommended for early diagnosis of breast cancer. Breast self-examination is recommended in conjunction with mammography as an effective tool in guiding women to seek appropriate medical diagnosis and treatment. It is estimated that mammography reduces the mortality rate in breast cancer by 20–70% (21). Fear of breast cancer is one of the factors associated with breast cancer screening behavior. In their study with African, American women, Champion and Scott (5). reported that women with moderate breast cancer fear were more likely to have a mammogram than women with low breast cancer fear. In the same study, it was determined that there was a positive relationship between women's moderate and high fears and the perception of mammography benefit. In the present study, the mean BCFS score was 25.60±7.29 and the mean MSS score was 41.18±6.47 and a weak positive correlation was identified between these scores. In the study conducted by Sağdıç (22) the mean BCFS score was similar at 26.35±6.61. In the study conducted by Polat (10) in Adıyaman and Şanlıurfa provinces, the mean MSS score was 37.37±13.35, and the mean BCFS score was 25.40±12.69, respectively. The weak positive correlation between IBCFS and MSS scores, also seen in the present study, has been reported previously (23). In a study conducted by Secginli (12), the mean BCFS score was 26.36±7.29, and the mean MSS score was 38.15±7.29, and in the same study, there was no significant difference between the BCFS scores of the groups that had and did not have mammography. Similarly, in another study, the mean BCFS score was 23.81±9.71 and in the same study, the mean BCFS score of women who had mammography was higher than those who did not have mammography (27.27±9.01 *versus* 21.89±9.62, respectively) (p = 0.00) which was reported to be significant (14). In the study of Miller et al. (23), a significant relationship was found between women's fear of breast cancer and undergoing mammography. Erdoğan (24) found that the fear of breast cancer was higher in women between the ages of 30–50 years, and the fear of being diagnosed with breast cancer was among the reasons why women do not go to the doctor. Although the results of the present study are similar to the previous results, we speculate that the level of breast cancer fear was effective in reporting approval of having mammography. Thus, fear of having breast cancer appears to be lead women to adopt early diagnosis behavior.

There are many factors that affect early diagnosis behavior in breast cancer. These factors include structural and behavioral factors, such as education level, health insurance, doctor's advice, knowledge and health beliefs, and social support (21). In our study, the BCFS score of married women was significantly higher than single women. This appears to be age-related as married participants were older than single women and that the risk of breast cancer is known to increase with age which seems to increase the BCFS score. While a significant difference was found in BCFS score between women with and without a family history of breast cancer, no statistically significant difference was found between these groups and the MSS score. Moreover, the BCFS and MSS scores were higher in women who reported breast health problems. Studies have shown that women with a family history of breast cancer tend to undergo more mammography screening than those who do not (25, 26). In the study of Erdoğan (24), the rate of regular mammography in women with a family history of breast cancer was 38.0%, and 15.3% in those without a family history of breast cancer. It was also reported that women with a family history had higher mammography self-efficacy perception and breast cancer fear mean score than those without. It is thought that women's risk perception due to family history, fear of getting breast cancer, getting breast cancer information, and awareness of the importance of early diagnosis increased and this situation positively affected their participation in screening.

The study performed at a university so this was limitation of the study. Research results can be generalized only to these groups.

The BCFS and MSS scores increased in women with a family history of breast cancer. Furthermore, there was a positive weak relationship between BCFS and MSS, as previously reported. Higher BCFS scores were associated with the tendency to use early diagnosis methods. When the effect of fear of breast cancer on women's mammography self-efficacy was considered, there appears to be a need for further qualitative studies to investigate the causes in detail and these should include interventional nursing. In addition, it is suggested that new studies should be conducted with a greater variety of region, age, and socio-cultural characteristics of women and control groups. Finally there should be more social studies into the availability and effectiveness of early detection methods for breast cancer.

Ethics Committee Approval: Permission for the research was obtained from the clinical research ethics committee of Ondokuz Mayıs University. Ethics committee decision no: 2019/244. Permission was obtained from the university for the research.

Informed Consent: While the research data were collected, oral consents were obtained from the women.

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Authorship Contributions

Concept: N.K.B., D.K., İ.A.A.; Design: N.K.B., D.K., İ.A.A.; Data Collection and/or Processing: N.K.B., İ.A.A.; Analysis and/ or Interpretation: N.K.B., D.K., İ.A.A.; Literature Searching: N.K.B., D.K.; Writing: N.K.B., D.K.

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Original Article

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Radial Scars Without Atypia Diagnosed at Percutaneous Core Needle Breast Biopsy: Support for Imaging Surveillance

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ABSTRACT

Objective: Radial scar (RS) is a low-risk breast lesion that can be associated with or mimic malignancy. Management guidelines remain controversial for patients with RS without atypia on core needle biopsy (CNB). The aim was to evaluate the upgrade rate of these lesions and factors associated with malignancy risk and excision rate to more definitively guide management.

Materials and Methods: In this retrospective study, 123 patients with RS without atypia, diagnosed with CNB between January 2008 to December 2014 who were either referred for surgical excision or followed-up with imaging, were reviewed. The differences in clinical presentation, imaging features, and biopsy technique among the benign RS patients and those upgraded, as well as the excised versus the observed patients were compared.

Results: Of 123 RS reviewed, 93 cases of RS without atypia as the highest-grade lesion in the ipsilateral breast and with either 24-month imaging follow-up or surgical correlation were included. Seventy-four (79.6%) lesions were surgically excised and 19 (20.4%) were followed-up for at least 24 months. A single upgrade to malignancy (1%) and 15 upgrades to high-risk lesions (16%) were found. There was no association of any upgraded lesion with presenting symptoms or imaging features. The use of vacuum-assistance and larger biopsy needles, along with obtaining a higher number of samples, was associated with fewer upgrades and lower surgical excision rates.

Conclusion: The upgrade rate of RS without atypia in our population was low, regardless of the imaging features and biopsy technique utilized. Close imaging surveillance is an acceptable alternative to surgical excision in these patients.

Keywords: Radial scar; breast cancer; biopsy; ultrasound; mammography; upgrade

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Key Points

- Upgrade rate to malignancy was low in patients with radial scar lesions without atypia (1%).
- Close imaging surveillance rather than surgical excision is an acceptable management option for radial scar lesions without atypia.
- Vacuum-assisted biopsy and a larger number of samples allow better evaluation of the lesion and facilitate the follow-up decision for radial scars without atypia.

Introduction

A radial scar (RS), also known as a radial sclerosing lesion or complex sclerosing lesion when larger than 1 cm, is a proliferative, low-risk breast lesion characterized histologically by a central fibroelastic core with ducts and lobules radiating outward, giving the lesion its characteristic stellate appearance (1, 2). This appearance often translates mammographically to architectural distortion or a spiculated mass, commonly prompting core needle biopsy (CNB). Atypia or other high-risk breast lesions, when found in conjunction with a RS, are strong risk factors for malignancy with upgrade rates, defined as rate of transformation into malignant or other high-risk breast lesions, reportedly varying widely (0–20%) (3-5). It is therefore standard practice to surgically excise all RS with atypia found with percutaneous CNB, although most of these procedures will yield benign disease. The management of benign RS without atypia diagnosed with image-guided CNB remains controversial. Historically at our institution, we have referred patients with benign RS without atypia for surgical excision if vacuum assisted biopsy (VAB) was not

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performed or if fewer than 12 core samples were obtained, regardless of the biopsy technique used. More recently, however, after institutional review of all RS diagnosed at CNB, we now return patients without atypia to screening and only review cases of RS with atypia at our Multidisciplinary Breast Conference to determine whether these patients will be referred for surgical excision or mammographic follow-up. Although benign RS without atypia lesions carry a low cancer upgrade risk, treatment decisions remain non-uniform, often based on surgeon, radiologist, and patient preferences, patient clinical history and correlation of radiological and pathological characteristics (2-5).

Multiple small series have shown that, in the appropriate setting, RS diagnosed as benign at CNB can be safely followed-up (4, 6-9). Biopsy and pathologic criteria, such as the absence of atypical hyperplasia in biopsy samples, retrieval of at least 12 specimens, and extensive sampling with vacuum-assisted large-core biopsy devices have been identified as factors that may spare RS lesions from surgical excision (6, 9-11). National Health Service, Arbeitsgemeinschaft Gynäkologische Onkologie guidelines and the Swiss Consensus recommend excision of RS lesions with or without atypia with VAB, followed by routine screening (12-14). Alternatively, some studies have recommended that all RS be surgically excised because of possible underestimation of malignancy due to sampling limitations (15-17). Additionally, it can be challenging for pathologists to histologically identify a RS, as the presence of glands trapped at the center of this lesion can be confused with entities such as tubular carcinoma (18).

Studies looking at RS without atypia range in size from 50–400 cases, with most of them focusing on the pathologic features of the lesion (3-5, 7-9, 19-22). The primary aim of the present relatively large cohort study was to evaluate the surgical upgrade rate to malignancy of RS without atypia diagnosed with image-guided percutaneous CNB from a radiologic standpoint. Secondarily, we aimed to understand if any clinical or imaging factors correlate with the decision to excise the lesion and/or the rate of upgrade to malignancy to better understand the current variable practice patterns and consequently develop more standardized management algorithms.

Materials and Methods

This study is approved by the University of Texas Southwestern Institutional Review Board (IRB) with IRB number "STU 122013-053". In this study, we retrospectively reviewed all cases of RS without atypia detected by mammography, ultrasound (US) or magnetic resonance imaging (MRI) and confirmed with CNB or VAB, between January 1, 2008 to December 31, 2014 at our comprehensive hospital-based imaging centers: A safety-net community hospital, in which patients from a wide range of socioeconomic backgrounds are cared for, regardless of their insurance status or financial ability to pay for the care they received, and a tertiary-care university hospital.

Patient Selection and Data Collection

Patients with a pathologic diagnosis of RS without atypia as the highest-grade lesion in the ipsilateral breast and with either 24-month imaging follow-up or surgical correlation were included in this study. Patients with other ipsilateral high-risk breast lesions, including atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), flat epithelial atypia (FEA), and/or lobular carcinoma in situ (LCIS), ductal carcinoma *in situ* (DCIS) or invasive breast cancer were excluded from the study, while patients with contralateral high-risk lesions or breast cancer were not excluded. If a lesion was unchanged with 24 months or longer imaging follow-up, it was considered benign and the patient returned to routine screening. Patients who were not compliant with a 24-month follow-up were excluded, if surgery was not performed instead. Surgical pathologic correlation included both focal lesion excision and mastectomy specimens.

The imaging and pathology report was reviewed for each case by a radiologist specializing in breast imaging. For cases deemed concordant, pathology was not re-reviewed. If the RS was thought to be an incidental finding (for instance, RS diagnosed with several other associated benign pathologies), pathology was re-reviewed to confirm that the targeted lesion seen with imaging represented the dominant RS without atypia diagnosed pathologically.

Medical records were reviewed for patient demographics, patient symptoms (asymptomatic, palpable mass, pain bloody or non-bloody nipple discharge), history of ipsilateral or contralateral breast cancer, imaging modality of lesion detection, imaging guidance method for biopsy, radiologic lesion size, type of biopsy device (spring-loaded versus vacuum), needle size, and number of specimens obtained. Our cohort includes patients referred from screening and patients presenting with symptoms. Imaging and pathology reports were reviewed for all lesions. Histologic lesion size (mm), presence or absence of atypia, radiological lesion type (architectural distortion, focal asymmetry or mass, calcifications, MRI mass, MRI non-mass enhancement), and histologic classification of cancers (invasive cancer or *in situ* lesion) or high-risk lesions (ADH, ALH, FEA, LCIS) found upon surgical excision were recorded for each lesion.

Imaging and Biopsy Techniques

Digital mammographic examinations performed included at least standard mediolateral oblique and craniocaudal images (Hologic Selenia and Hologic Selenia Dimensions). Targeted sonography was performed using a broadband, 5–12 MHz linear array transducer (HDI 5000, GE E9, Philips iU22). Contrast enhanced breast MRI was performed using a 1.5 T magnet (GE 450W Optima and Philips Achieva). Percutaneous biopsy was performed using MRI, US or stereotactic (Hologic, Marlborough, MA, USA) guidance and a clip was placed to mark the biopsy site. In patients with mammographically detected microcalcifications, a specimen radiograph was obtained to confirm the presence of calcifications in the obtained biopsy samples. The biopsies were performed either with vacuum-assisted or spring-loaded devices.

All examinations were performed and/or interpreted by fellowship-trained breast radiologists, with 4–38 years of practice experience.

Reference Standard

The surgical pathology report for each excised lesion was classified according to the highest-grade lesion in one of the following categories: malignant (DCIS or invasive carcinoma), high-risk (ADH, ALH, FEA, or LCIS), or benign (proliferative changes without atypia, other benign lesions). These final pathology results upon excision served as the reference standard. Also, imaging follow-up without radiologic upgrade for >24 months are accepted as reference standard.

Data Storage and Statistical Analysis

Data were stored using a computerized spreadsheet (Microsoft Excel; Microsoft Corporation, Redmond, WA, USA). Statistical analysis was performed according to the reference standard with commercial software (SPSS, IBM Inc., Armonk, NY, USA). Differences in

categorical variables, imaging features and biopsy techniques among the benign vs upgraded (to malignancy or high-risk lesions) and observed vs excised RS were compared using the chi-square test. The number of biopsy cores obtained and biopsy needle sizes were categorized as <12 vs ≥12 cores and <14-gauge vs ≥14-gauge, respectively. The means, standard deviations (SD), and ranges of continuous variables (lesion size, patient age) were compared across the groups using the t-test and Wilcoxon–Rank Sum test.

Results

Patient and Lesion Characteristics

Of the 123 RS without atypia reviewed, 93 lesions diagnosed at percutaneous biopsy in 92 women were included in the study. The other 30 (24.4%) lesions were excluded due to history of ipsilateral breast cancer (n = 5) or insufficient imaging or surgical follow-up (n = 25). The patient selection is illustrated in a flowchart in Figure 1.

Among the 93 lesions from 92 patients included in the study, 79 (85%) patients were asymptomatic and were referred from screening, while 14 (15%) patients presented with symptoms. Of these, 74 (79.6%) lesions were surgically excised and 19 (20.4%) were followed-up with imaging for at least 24 months. The median (range) length of follow-up was 41 (24–61) months. The mean ± SD radiologic lesion size was 13.7±8.6 mm (range: 3–50 mm) and mean ± SD patient age was 51.5±9.3 years (range: 29–71 years). Of the 82 lesions diagnosed either with mammography or breast US, 31 (33.3%) were identified as architectural distortion, 24 (25.8%) were calcification and 27 (29%) were focal asymmetry or mass. Of the 59 VABs performed, 44 (74.6%) were stereotactic, 8 (13.5%) were US-guided and 7 (11.8%) were MRI guided. The other 34 lesions were biopsied with spring-loaded devices (≥14 gauge). Lesion features and information about detection and biopsy modalities are summarized in Table 1.

Factors Associated with Surgical Upgrade

Only one lesion among 93 [1.1%, 95% confidence interval (CI), 0–5.8%] was upgraded to malignancy after surgery. This single case of malignancy (intermediate grade DCIS) presented in a 62-year-old, asymptomatic woman as a 1 cm area of architectural distortion detected independently with both screening mammography and automated whole breast screening sonography. Six 14-gauge biopsy samples were obtained using US-guidance (Figure 2).

There were 15 (15/93, 16.1%, 95% CI: 9–25%) cases of high-risk pathology identified after surgical excision. These cases included ADH, ALH, FEA, and LCIS. There was no significant association of these lesions with upgrade to either atypia or malignancy with respect to patient symptoms, imaging modality of detection, lesion size, imaging guidance method for biopsy, type of biopsy device, needle size, or number of specimens. A meaningful statistical analysis could not be performed due to the limited number of upgrades. The mean lesion size of benign lesions was 13.2±8.5 mm and that of high-risk lesions was 15.3±9.0 mm (p = 0.4). The mean patient age was 51.0±9.2 years in the benign group and 53.5±9.5 years in the high-risk group (p = 0.3). The features of the high-risk lesions and the one malignant lesion are summarized in Table 2.

None of the 19 lesions followed-up for 24 months or longer developed any suspicious interval change and all were therefore considered benign at the end of the follow-up period. A case successfully followed up for 24 months is demonstrated in Figure 3.

Factors associated with Excision

The surgical excision rate was significantly lower in the university hospital (30/45, 66.7%) patients as compared to the safety net hospital patients (44/48, 91.7%) [odds ratio (OR): 0.18, 95% CI: 0.05–0.6, p = 0.003]. MRI masses (6/6, 100%), architectural distortion (27/31,

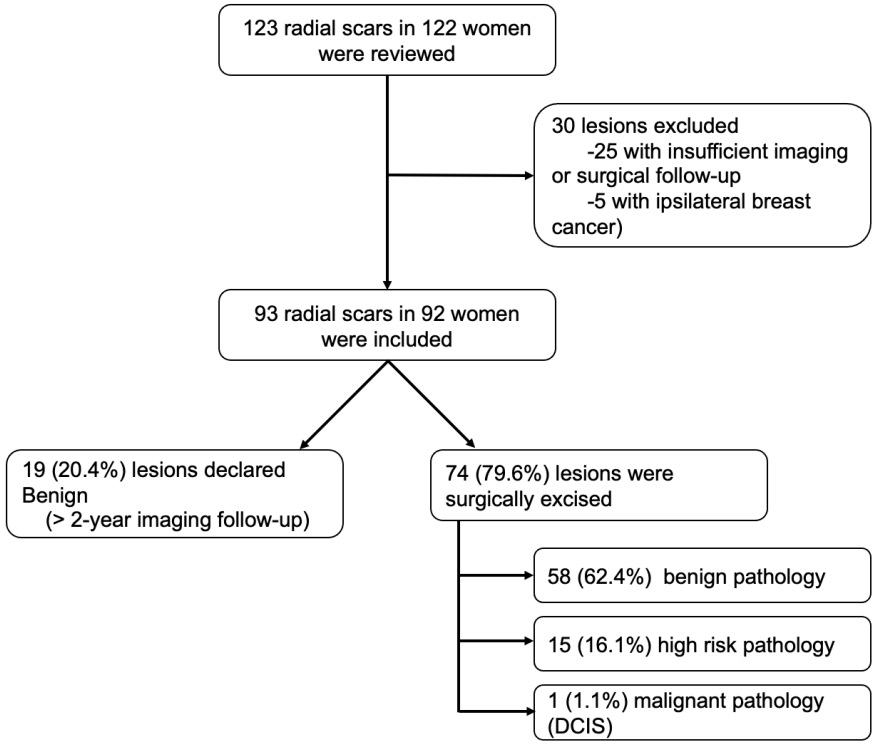

Figure 1. Flowchart describing patient selection

Table 1. Lesion and biopsy features

Features		Frequency (%)
Hospital	University Hospital	45 (48.4)
	Safety Net Hospital	48 (51.6)
Presenting symptom	Asymptomatic	79 (85)
	Mass	11 (11.8)
	Pain	1 (1.1)
	NBNDC	1 (1.1)
	BNDC	1 (1.1)
Lesion type	Architectural distortion	31 (33.3)
	Calcification	24 (25.8)
	Focal asymmetry or mass	27 (29)
	MRI mass	6 (6.5)
	MRI non-mass enhancement	5 (5.4)
Detection modality	US	9 (9.2)
	Mammography	73 (78.5)
	MRI	11 (11.8)
Biopsy modality	US	41 (44.1)
	Stereotactic	45 (48.4)
	MRI	7 (7.5)
VAB	Yes	59 (63.4)
	No	34 (36.6)
Needle gauge	9	53 (56.9)
	14	32 (34.4)
	Other	8 (8.6)
Number of biopsy samples[a]	<12	48 (51.6)
	≥12	41 (44)

NBNDC: non-bloody nipple discharge; BNDC: bloody nipple discharge; VAB: vacuum assisted biopsy; US: ultrasound; MRI: magnetic resonance imaging; [a]: This information is missing for 4 (4.3%) cases

87.1%) and palpable masses (23/27, 85.2%) were excised more frequently than calcifications without masses (15/24, 62.5%) and MRI non-mass enhancement (3/5, 60%) (p = 0.07). The surgery rate was significantly lower among VAB (43/59, 72.9%) compared to spring-loaded CNB (31/34, 91.2%) (OR: 0.26, 95% CI: 0.07–0.97, p = 0.035).

Although the biopsy modality was not significantly associated with the surgical excision rate (p = 0.08), lesions biopsied with smaller needles (≥14 gauge) were excised more frequently than those biopsied with larger needles (<14 gauge) [31/34 (91.2%), 43/59 (72.9%), OR: 3.8, 95% CI: 1.0–14.4, p = 0.03]. The number of core samples obtained during biopsy was also significantly associated with the excision rate, with lesions sampled with less than 12 cores being excised more frequently than lesions sampled with greater than or equal to 12 cores [44/48 (91.7%) vs 29/41 (70.7%), OR: 11.0, 95% CI: 0.7–2.4, p = 0.01].

The mean size of the observed lesions was 12±8.1 mm and that of the surgically excised lesions was 14.1±8.6 mm (p = 0.3). The mean patient age was 54.6±9.1 years in the follow-up group and 50.7±9.2 years in the surgery group (p = 0.1). The presenting symptoms and radiographic lesion types were not significantly associated with the decision to excise. The features of excised vs observed lesions are further summarized in Table 3.

Discussion and Conclusion

The rate of upgrade to malignancy was 1% (n = 1) among the 93 RS lesions without atypia in our series. The single case upgraded to malignancy was shown to be an intermediate grade DCIS upon surgical excision identified in an asymptomatic 62-year-old patient sampled with a 14-gaude needle using US guidance. There were no cases of invasive malignancy identified. Sixteen percent (15/93, 16.1%) of high-risk lesions were detected upon surgical excision including ADH, ALH, FEA, and LCIS. None of the 19 lesions followed-up

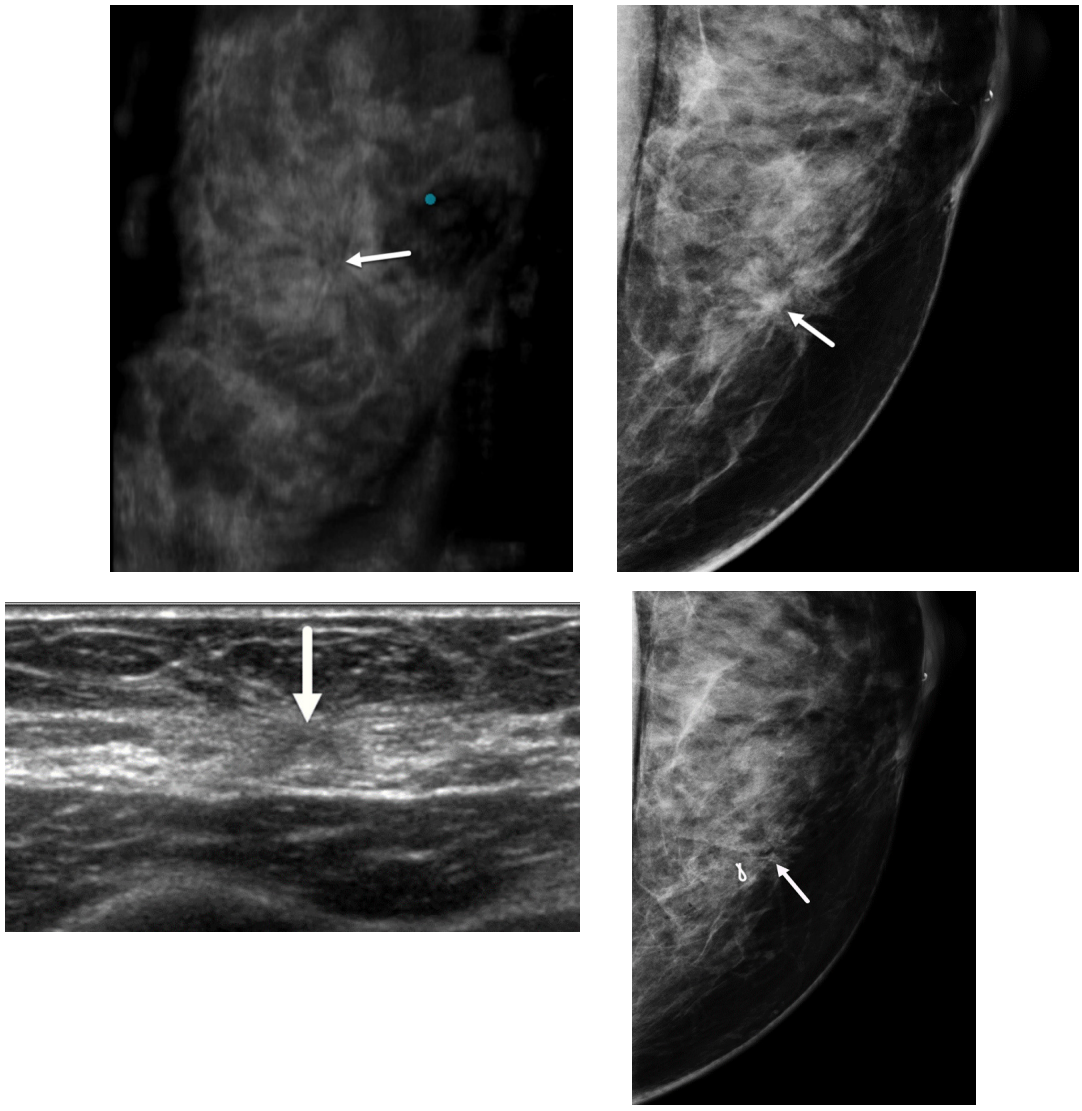

Figure 2. A benign radial scar case in a 62-year-old asymptomatic screening patient upgraded to DCIS upon surgical excision, **A.** Screening whole breast ultrasound revealed architectural distortion (arrow) in the lower inner quadrant of the left breast, **B.** Left craniocaudal (CC) image confirms distortion (arrow) medially within the left breast. **C.** Targeted ultrasound confirms an irregular hypoechoic mass with obscured margins (arrow) in the 9 o'clock left breast, located 4 cm from the nipple. An ultrasound-guided biopsy was performed with a 14-gauge core needle biopsy device, taking 6 cores. The pathology yielded benign radial scar with fibrocystic changes associated with microcalcifications. **D.** Left CC image following the biopsy confirms the placement of a ribbon-shaped clip (arrow) in close proximity to the distortion. Subsequent wire-guided localization (not shown) and excision also revealed intermediate grade ductal carcinoma *in situ* with positive margins requiring re-excision

DCIS: ductal carcinoma in situ

with imaging for at least 24 months developed malignancy. Our results agree with and further support those of other studies suggesting that concordant RS without atypia diagnosed with CNB have a low malignancy risk and can be safely followed-up rather than excised (9, 15, 20, 22-25).

Studies addressing the malignant upgrade of percutaneously diagnosed RS without atypia have reported variable upgrade rates, ranging from 0 to 20% (3-5, 8, 9, 19, 20, 26, 27). Such variability is attributable primarily to limited study cohort sizes, differences in inclusion criteria, and possible biases when making excision decisions. In addition to differences in sample size, variability in pathologists' interpretations of core biopsy specimens may also account for the differing results, as it can be challenging to distinguish RS from low grade carcinoma, especially those of tubular subtype (28). Despite numerous published studies, management of RS remains controversial. Radiologists and surgeons still routinely recommend excision of RS. Moreover, with tomosynthesis becoming commonplace in both the screening and diagnostic setting, there is increasing detection of architectural distortion that frequently yield RS. Thus, this study is more relevant than ever and has increasing ramifications on health care costs and overall patient care.

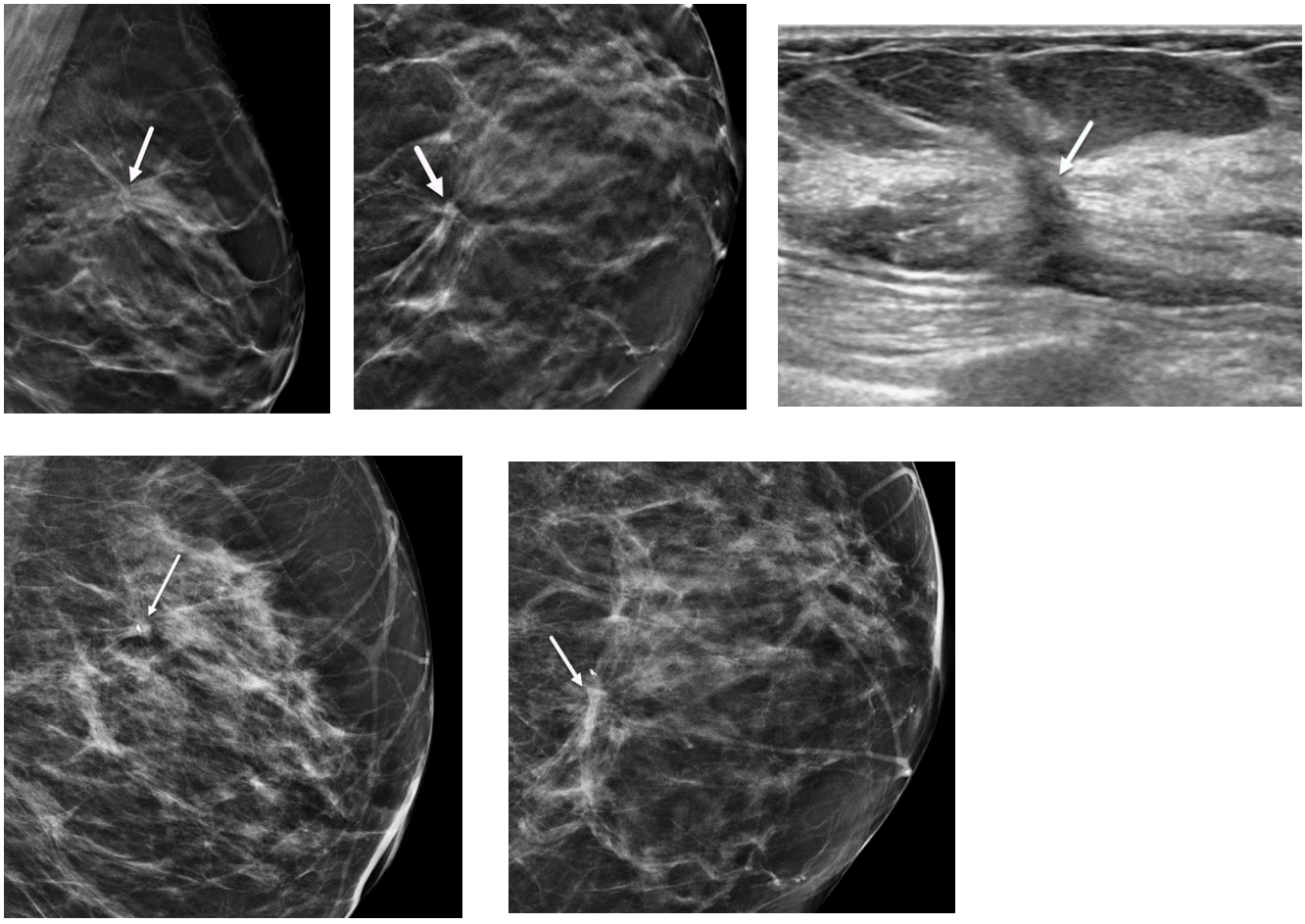

Figure 3. Radial scar case successfully managed with 24-month imaging follow-up in a 53-year-old woman who presented for screening mammography prior to planned lung transplantation, **A and B.** Left MLO and CC tomosynthesis slices depict architectural distortion (arrows) in the upper inner quadrant of the left breast. **C.** A targeted ultrasound of the distortion reveals an irregular hypoechoic mass with spiculated margins (arrow) in the 11 o'clock left breast, located 2 cm from the nipple. An ultrasound-guided biopsy was performed with a 14-gauge core needle biopsy device, taking three cores. The pathology yielded benign radial scar without proliferative changes. **D and E.** Left MLO and CC digital mammogram images 3 years after the initial biopsy show stable architectural distortion (arrows) and a nearby biopsy clip in the upper inner quadrant of the left breast

MLO: mediolateral oblique; CC: craniocaudal

Our study further supports imaging follow-up of RS as reasonable management, in that these lesions have a low probability of causing clinically overt disease (29-32). In our series, there was no significant difference in upgrade to atypia or malignancy with respect to patient symptoms, imaging modality of detection, lesion size, imaging guidance method for biopsy, type of biopsy device, needle size, or number of specimens. In contrast, some smaller studies have shown patient age, lesion size and calcifications within the lesion to be associated with an increased malignancy risk of these RS lesions (4, 5, 19).

The use of percutaneous CNB for the initial evaluation of clinically occult breast lesions is now widespread and is a practical alternative to open surgical biopsy for most patients. In previous studies, investigators have reported high rates of concordance between the histologic findings of percutaneous biopsy and surgical biopsy (9, 33-35). Compared with spring-loaded biopsy needles, VAB usually provides pathologists with larger individual samples, thereby inherently improving visualization of the architecture of RS (8). It has been suggested that the highest diagnostic yield with stereotactically-guided VAB can be achieved with 12 specimens per lesion and that this yield is not improved with more than 12 specimens (36). Although we did not observe any significant association between upgrade rate and the use of vacuum-assistance, biopsy modality guidance, needle size or number of cores obtained; the surgery rate was significantly lower when vacuum-assistance or a larger needle (<14 gauge) was used or when more cores were obtained (≥12 cores). Although there were no firmly adopted policies at either facility regarding excision or imaging follow-up of RS, these identifiable procedural parameters seen to be associated with excision of these lesions are important to highlight in order to better understand the current variable practice patterns and consequently develop more standardized management algorithms. This trend in and of itself introduces a bias regarding excision decisions.

Limitations of our study include apparent bias, as above, in regard to the decision to surgically excise lesions. Also, we did not perform pathologic re-evaluation to confirm the diagnoses of RS without atypia, except for pathologically discordant lesions and suspected incidental lesions. Additionally, if a patient in our cohort was not an established patient of a breast surgeon and the radiologist recommended follow-up

Table 2. Features of lesions upgraded to malignancy or atypia after surgical excision

	Site	Modality diagnosed	Lesion type	Modality biopsied	Age	Needle gauge	No of samples	Size (mm)	Vacuum biopsy?	Symptoms
M1	UH	Mammo	AD	US	62	14	6	10	No	Asymptomatic
HR1	SNH	Mammo	AD	US	52	14	4	15	No	Asymptomatic
HR2	SNH	Mammo	AD	Stereo	63	9	7	5	Yes	Asymptomatic
HR3	SNH	Mammo	AD	Stereo	55	9	12	13	Yes	Asymptomatic
HR4	SNH	Mammo	Calc	Stereo	40	9	12	35	Yes	Asymptomatic
HR5	SNH	Mammo	AD	US	61	14	3	8	No	Asymptomatic
HR6	SNH	Mammo	AD	Stereo	42	9	12	23	Yes	Asymptomatic
HR7	SNH	Mammo	AD	Stereo	39	9	12	12	Yes	Pain
HR8	UH	Mammo	Calc	Stereo	53	9	12	4	Yes	Asymptomatic
HR9	UH	Mammo	Calc	Stereo	67	9	12	10	Yes	Asymptomatic
HR10	UH	Mammo	AD	Stereo	72	9	12	25	Yes	Asymptomatic
HR11	UH	US	Mass	US	60	14	N	5	No	Asymptomatic
HR12	UH	Mammo	AD	US	48	14	7	25	No	Asymptomatic
HR13	UH	Mammo	Calc	Stereo	53	9	12	20	Yes	Asymptomatic
HR14	UH	MRI	NME	MRI	46	9	12	10	Yes	Mass
HR15	UH	US	Mass	US	49	14	4	20	No	BNDC

M1: malignant lesion 1; HR1-15: high-risk lesions 1 to 15; SNH: safety Net Hospital, UH: university hospital, Stereo: stereotactic; AD: architectural distortion; Calc: calcification; BNDC: bloody nipple discharge; N: this information is missing for this case

after CNB based on concordance and confidence in adequate sampling of the RS, that patient was not referred to a surgeon and excision was not performed. If, however, a patient was already established with a breast surgeon, the radiologist recommendation of excision versus imaging follow-up was noted, but the ultimate decision to excise was based on the surgeon and patient preference.

Notably, the excision rate was higher in the safety net hospital population compared to the university hospital (91.7% vs 66.6% p = 0.003). These variable excision rates are largely the result of the varying management of these lesions by the surgeons at our institution. One explanation for this difference in management is that the follow-up of safety net patients has proven to be difficult due to observed compliance issues within that population stemming from lack of transportation and language barriers. Additionally, the management of asymptomatic lesions, not otherwise managed by a surgeon, is driven by the radiologist and the radiologists' recommendations after biopsy of a benign RS without atypia was not consistent or formally standardized for concordant lesions. If the imaging appearance was discordant with the biopsy results, or if clinical symptoms warranted excision, these patients were referred for surgical consultation. With the present study, it was hoped to determine if any imaging features and/or the biopsy technique correlated with the decision to excise the lesion in order to better understand these discrepancies and hopefully develop more uniform management algorithms.

Another possible limitation of this study was the use of a 24-month imaging follow-up period as a surrogate for benign status. Although it is possible that a RS can develop associated high-risk lesions or malignancy beyond two years, it is highly unlikely (37). Furthermore, the median follow-up period in our study was 41 months (n = 19). In addition, practice guidelines regarding management of RS lesions without atypia was changed within the timeframe of our study, which could have caused variations in the management. Another potential limitation is that lesions without surgical correlation or 24-month imaging follow-up were excluded from the study (n = 27), decreasing our cohort size and statistical power. Given that our academic site is a tertiary care center, a subset of these patients may have returned to their referring institutions after the diagnosis and may not be truly lost to follow-up. The possibility of subsequent breast cancer among these patients could not be ruled out, as this information was not provided to us. Lastly, although this study included seven years of data and 93 RS, the relatively low rate of upgrade to malignancy among RS resulted in a lack of statistical power for finding predictors of upgrades. Future studies using an enriched population of RS cases with upgrade to malignancy may reveal factors associated with the malignancy risk of RS.

This study represents one of the largest multi-institution studies of RS without atypia diagnosed with CNB. RS without atypia has a sufficiently low upgrade rate to malignancy (1%) and high-risk lesions (16%) that imaging surveillance seems to be an acceptable alternative to surgical excision in the absence of another high-risk lesion that could change management. At our institution patients upgraded to high-risk lesions are individually presented at our Multidisciplinary Breast Conference to discuss the need for risk reduction chemoprophylaxis and/or enhanced imaging surveillance. Larger prospective studies or a meta-analysis of multiple studies may be helpful to determine if the patient's presenting symptoms, imaging features of the lesions or biopsy techniques are associated with the decision to excise and/or the upgrade rates.

Table 3. Features of excised vs observed lesions

Features		Surgery		
		Yes (%)	No (%)	*p*
Hospital	University Hospital (n = 45)	30 (66.6)	15 (33.3)	0.003
	Safety Net Hospital (n = 48)	44 (91.7)	4 (8.3)	
Presenting symptom	Asymptomatic (n = 79)	60 (75.9)	19 (24)	0.5
	Mass (n = 11)	11 (100)	0 (0)	
	Pain (n = 1)	1 (100)	0 (0)	
	NBND (n = 1)	1 (100)	0 (0)	
	BND (n = 1)	1 (100)	0 (0)	
Lesion type	Architectural distortion (n = 31)	27 (87.1)	4 (12.9)	0.07
	Calcification (n = 24)	15 (62.5)	9 (37.5)	
	Focal asymmetry or mass (n = 27)	23 (85.2)	4 (14.8)	
	MRI mass (n = 6)	6 (100)	0 (0)	
	MRI non-mass enhancement (n = 5)	3 (60)	2 (40)	
Detection modality	US (n = 9)	8 (88.9)	1 (11.1)	0.6
	Mammography (n = 73)	57 (78.1)	16 (21.9)	
	MRI (n = 11)	9 (81.8)	2 (18.2)	
Biopsy modality	US (n = 41)	32 (71.1)	13 (28.9)	0.08
	Stereotactic (n = 45)	37 (90.2)	4 (9.8)	
	MRI (n = 7)	5 (71.4)	2 (28.6)	
VAB	Yes (n = 59)	43 (72.9)	16 (27.2)	0.035
	No (n = 34)	31 (91.2)	3 (8.8)	
Needle gauge	<14 (n = 59)	43 (72.9)	16 (27.1)	0.03
	≥14 (n = 34)	31 (91.2)	3 (8.8)	
Number of biopsy samples[a]	<12 (n = 48)	44 (91.7)	4 (8.3)	0.001
	≥12 (n = 41)	29 (70.7)	12 (29.3)	

NBNDC: non-bloody nipple discharge; BNDC: bloody nipple discharge; [a]: This information is missing for 4 cases; VAB: vacuum assisted biopsy; US: ultrasound; MRI: magnetic resonance imaging

Ethics Committee Approval: The study was approved by the Southwestern Medical Center, Institutional Review Board (IRB-8843) (approval dare: February 10, 2014, number: STU 122013-053).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Comparing the Efficiency of Imaging Modalities in Detection of Recurrent Breast Cancer

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ABSTRACT

Objective: To investigate the effectiveness of the different imaging modalities in detecting recurrence in breast cancer follow-up.

Materials and Methods: Sixty-four women with recurrent breast cancer were examined between January 2020 and July 2022. Recurrency was divided into four categories: local; regional; second primary; and distant metastasis. The detectability of recurrent lesions with mammography (MG), ultrasound (US) and magnetic resonance imaging (MRI), was evaluated. In addition, recurrences that firstly appeared by positron emission tomography (PET) scan were recorded.

Results: Twenty-seven (42.2%) recurrences were local, 10 (15.6%) were regional and 27 (42.2%) were second primary. Forty-six (71.9%) of them were determined to have invasive carcinoma, 8 (12.5%) were ductal carcinoma *in situ*, and 10 (15.6%) were axillary metastases. Eight (12.5%) of them were first diagnosed by PET-computed tomography/MRI. Among the available images performed, 78.7% could be detected pathologically by MG, 95.2% by US, and 100% by MRI. Distant metastasis associated with other types of recurrence was detected in 6 (9.4%) cases.

Conclusion: MRI is the most powerful imaging modality in detecting recurrent breast cancer. With the addition of US to routine MG follow-up, a higher rate and early detection of recurrent cancers can be achieved.

Keywords: Breast cancer; magnetic resonance imaging; mammography; recurrence; ultrasound

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Key Points

- Mammography and ultrasound (US) are complementary modalities in breast cancer follow-up.
- US and magnetic resonance imaging (MRI) are the most potent imaging modalities in detecting breast cancer recurrence.
- Axillary US increases the accuracy of radiological imaging for regional recurrence in experienced hands.
- MRI and positron emission tomography imaging added to the algorithm in selected cases can significantly contribute to the detection of recurrence.

Introduction

The incidence of breast cancer is increasing with the effective use of screening programs and technological developments. According to Globocan 2020 data, breast cancer is the most frequently detected cancer in the female population in Turkey, with more than 24 thousand new cases reported annually (1). Thus, management and outcome have gained increasing importance in patients with breast cancer. Cancer screening and post-treatment follow-up aim to reduce morbidity and mortality rates with early diagnosis. Personal breast cancer history is a significant risk factor for being diagnosed with cancer for the second time (2-4). It has been reported that local recurrence is an independent factor predicting survival, and patients with recurrence have a higher risk for distant metastasis or death compared to non-recurrence patients (5). Each subtype of breast cancer or different gene expression shows different behavioural patterns (6). Particularly, luminal subtypes are expected to show recurrence at a lower rate over many years, while non-luminal subtypes show in the first years after initial treatment (7, 8). Therefore, it is crucial to understand the natural history of different tumors to detect the presence of residual or recurrence early for intervention.

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There is variability between guidelines for post-surgical follow-up in different disciplines. While some of the considerations in these guidelines are evidence-based, some are at the recommendation level. While some guidelines recommend starting imaging in the sixth month after radiotherapy, many recommend not starting until one year (9). Imaging frequency is recommended to be annual in most of the guidelines (9). However, according to the guidelines, mammography (MG) is the only evidence-based imaging method for detecting recurrence at follow-up (2, 3, 10, 11). However, in many centres, ultrasound (US), magnetic resonance imaging (MRI) and even positron emission tomography (PET) are used in addition to MG. In this process, there is a need for a multidisciplinary approach that includes physicians from different specialities, such as surgeons, radiologists and oncologists.

The aim of this study was to investigate the effectiveness of different imaging modalities in detecting recurrence in post-treatment follow-up in breast cancer to inform physicians.

Materials and Methods

The ethics committee of the University approved this retrospective study (approval number 449166, date: 05.08.2022). Among the cases treated for breast cancer, those who attended for screening or diagnostic purposes between September 2019 and September 2022 were incuded and retrospectively assessed. Cases categorized as Breast Imaging and Reporting Data System (BI-RADS) 4 or 5 according to the imaging findings were included in the study. The exclusion criteria of the study were: i) cases without any suspicious radiological findings for recurrency in follow-up; ii) radiologically suspicious but histopathologically benign lesions; iii) category BI-RADS 4 or 5 lesions with unavailable histopathological diagnosis; and iv) cases with histopathologically proven recurrence but missing imaging findings.

MG, US, and MRI images obtained radiologically were evaluated. The presence of mass, microcalcification, asymmetry, or distortion in MG and a vascularized mass or non-mass area on US and abnormal contrast enhancement on MRI was considered pathological. In addition, lesions that arose with abnormal fluorodeoxyglucose uptake with PET-CT/MRI for the first time were recorded.

Detection of tumoral tissue on follow-up images within three months after surgical treatment was considered residual disease. A new tumoral focus developing after this period was considered a recurrence. Recurrent lesions were divided into four groups (Figure 1):

1. Local recurrence - the new tumoral focus at the same site as the first primary after breast-conserving surgery (BCS) or in the chest wall after mastectomy;

2. Regional recurrence - ipsilateral axillary or supraclavicular lymphadenopathy;

3. Second primary - tumoral tissue of different localization or morphology from the primary lesion;

4. Distant metastasis.

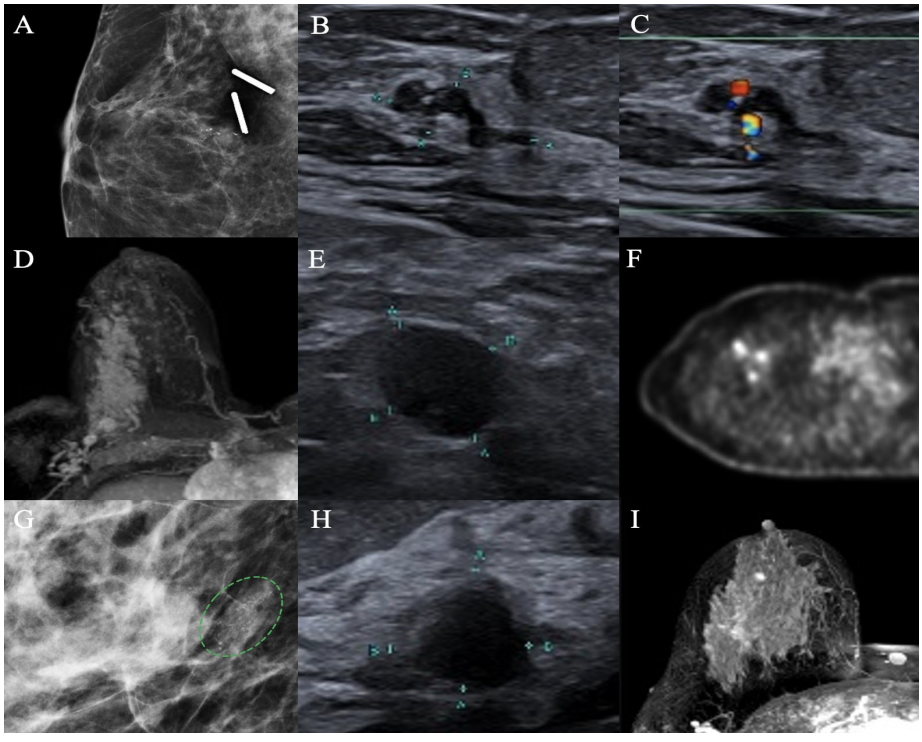

Figure 1. Types of recurrence **(A-C)** Local recurrence in a 55-year-old woman with a history of IDC. Indistinct density and accompanying microcalcifications in the operation site on the right MLO view and a non-mass hypoechoic area associated microcalcifications on US diagnosed as IDC **(D-F)** Regional recurrence in a 53-year-old woman with a history of grade 3 DCIS with microinvasive carcinoma. Preoperative MRI demonstrating extensive non-mass enhancement of DCIS, US shows ALN metastasis with the absence of hilar echogenicity **(G-I)** Secondary primary in a 50-year-old with a history of grade 2 IDC. MG shows a cluster of pleomorphic microcalcifications, while US and MRI demonstrate a mass appearance at the retro areolar area diagnosed as IDC

IDC: invasive ductal carcinoma; US: ultrasound; MRI: magnetic resonance imaging, MG: mammography; DCIS: ductal carcinoma in situ; MLO: mediolateral oblique

Age, family history, physical examination findings, side, BI-RADS categorization, histopathological diagnosis and timing of the primary and recurrent breast carcinoma, histologic grade, molecular subtype, and axillary status were recorded. Recurrence-free survival time for each case was calculated in months and recorded. In addition, the treatment method of the primary tumor and axillary approach and, if applicable, the treatment protocol of the current tumoral focus were documented.

Recurrent tumors were divided into two groups, with primary pathology being ductal carcinoma *in situ* (DCIS) or invasive carcinoma.

In the descriptive analysis, the frequency of all variables was recorded.

Results

A total of 64 recurrent lesions were identified in the data extraction process. Local recurrence was detected in 27 (42.2%) cases, regional recurrence in 10 (15.6%) and second primary in 27 (42.2%) (Figure 2). Initial and final histopathological results of the recurrences arising during follow-up are detailed in Figure 3. There was no recurrence presenting as distant metastasis, while it was accompanied by the other types of recurrence in six (9.4%) cases. The primary pathology of 11 (17.2%) cases was DCIS with a recurrence-free survival time of 12471.83 months, and 53 (82.8%) were invasive carcinoma with a recurrence-free survival time of 122.576.45 months. Of the invasive carcinomas, 71.9% (n = 46) were luminal, 6.3% (n = 4) were human epidermal growth factor receptor 2-enriched, and 4.7% (n = 3) were in the triple-negative breast cancer subgroup. Family history was positive in only 23.4% of the cases. Demographic data are summarized in Table 1.

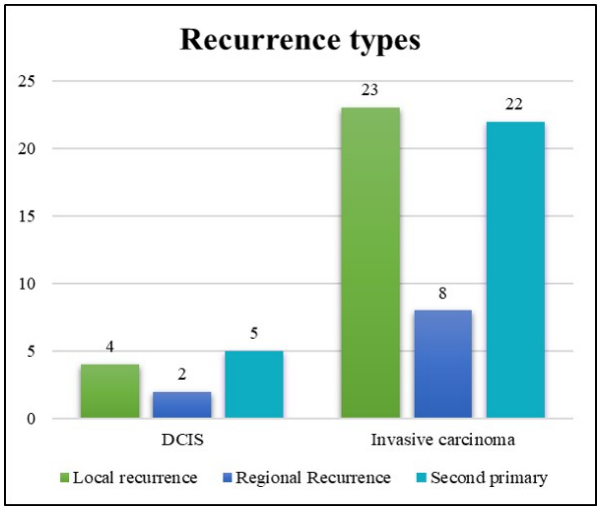

Figure 2. Distribution of the types of recurrence

Table 1. Demographic data

	n = 64
Age, mean ± SD (min–max)	57.96 11.25 (28–89)
Recurrence-free survival time, mean ± SD (min–max) (months)	122.81 75.1 (6–312)
Family history, n (%)	
Yes	15 (23.4)
No	49 (76.6)
Initial tumor side, n (%)	
Left	36 (56.3)
Right	28 (43.7)
Initial diagnosis, n (%)	
DCIS	11 (17.2)
Invasive carcinoma	
Luminal	46 (71.9)
HER2-enriched	4 (6.3)
TNBC	3 (4.7)
Initial axillary operation, n (%)	
None	10 (15.6)
SLNB	22 (34.4)
Dissection	32 (50)
Initial axillary involvement, n (%)	
No	32 (50)
Yes	32 (50)

DCIS: ductal carcinoma *in situ*; HER2: human epidermal growth factor receptor 2; SD: standard deviation; SLNB: sentinal lymph node biopsy; TNBC: tripple negative breast cancer

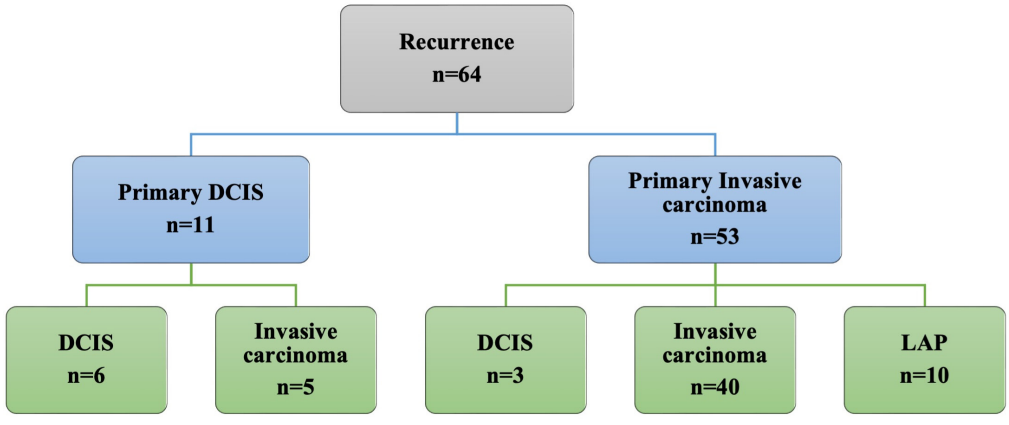

Figure. 3. Initial and final histopathologies of cases with recurrence

In 26.5% (n = 17), MG could not be obtained due to mastectomy or other reasons. Breast density was type A in 1.6% (n = 1), type B in 31.2% (n = 20), type C in 39.1% (n = 25) and type D in 1.6% (n = 1). In cases with type B, US could detect regional (axillary) recurrences that MG could not detect in three cases and local recurrence in one case, while MG was superior in detecting the second primary in one case. Among type C cases, US could detect regional (axillary) recurrence in two cases, local recurrence in one case and the second primary in one case, which MG could not detect. Both US and MG detected the pathology in cases with type A (n = 1) and type D (n = 1) density.

Among the available images examined, 78.7% of recurrences could be detected pathologically by MG, 95.2% by US, and 100% by MRI. Eight (12.5%) recurrences were first diagnosed by PET-CT/MRI. Of these, six were local, and two were regional recurrences (Figure 4). US was positive in all of these cases while 2 of 3 cases with MG were positive. Physical examination was positive in only two cases. These cases were not scanned by MRI.

Forty-six (71.9%) of recurrent lesions were reported to have invasive carcinoma, 8 (12.5%) were DCIS, and 10 (15.6%) were axillary lymph node metastases. The histologic grades of primary pathology and the type of recurrence are summarized in Table 2.

Initial surgical, local and/or systemic therapies and other relevant demographic data are summarized in Table 3, as the cases were divided into two groups according to the final pathology.

While locoregional recurrence was observed in 71.9% of the cases whose initial operation was BCS, this rate was 43.7% in cases with mastectomy.

The physical examination findings were negative in 80% (n = 8/10) of the cases recurrent with lymphadenopathy (LAP). Among all recurrences, sentinal lymph node biopsy (SLNB) was performed in 22 cases, dissection in 32 cases, and there was no intervention performed in the axilla in 10 cases at the time of initial diagnosis. In 60% of regional recurrences occurring with LAP, no surgical intervention was applied or SLNB was performed, while 40% underwent axillary dissection.

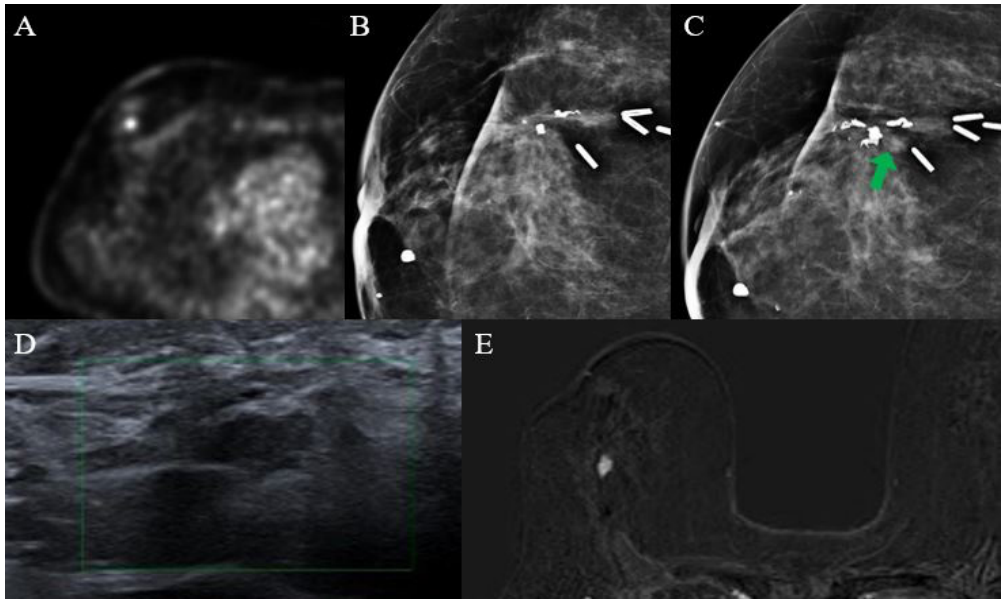

Figure 4. A local recurrence in a 58-year-old woman with a history of mucinous carcinoma **(A)** Abnormal FDG-uptake at the operation site on PET scan **(B)** Postoperative changes on the right CC view that examined in 2018 and followed by consecutive PET scans **(C-E)** But also visible on MG, US and MRI

PET: positron emission tomography; US: ultrasound; MRI: magnetic resonance imaging, MG: mammography; FDG: fludeoxyglucose; CC: craniocaudal

Table 2. The types of primary and recurrent tumors

Recurrent tumor		**Primary tumor**		
		DCIS	**Invasive carcinoma**	**ALN metastasis**
DCIS (n = 11)	n (%)	5 (45.4)	6 (55.6)	-
Invasive carcinoma (n = 53)				
Grade 1 (n = 2)	n (%)	-	1 (50)	1 (50)
Grade 2 (n = 38)	n (%)	3 (7.5)	28 (70)	7 (17.5)
Grade 3 (n = 13)	n (%)	-	11 (84.6)	2 (15.4)

ALN: axillary lymph node; DCIS: ductal carcinoma *in situ*

Table 3. Initial and final status of the disease

		DCIS	Invasive carcinoma
Initial surgery			
Mastectomy	n (%)	6 (54.5)	26 (49)
Breast-conserving surgery	n (%)	5 (45.5)	27 (51)
Hormonal/Chemotherapy			
Yes	n (%)	1 (9)	51 (96.2)
No	n (%)	10 (91)	2 (3.8)
Radiotherapy			
Yes	n (%)	3 (27.2)	30 (56.6)
No	n (%)	8 (72.3)	23 (43.4)
Axillary surgery			
None	n (%)	4 (36.4)	6 (11.3)
SLNB	n (%)	7 (63.6)	15 (28.3)
Dissection	n (%)	-	32 (60.4)
Recurrence-free survival time, mean SD (min–max), months		12471.83 (6-206)	12376.45 (8-312)
Recurrence type			
Local	n (%)	6 (54.5)	22 (41.5)
Regional	n (%)	-	10 (18.9)
Second primary	n (%)	5 (45.5)	21 (39.6)
Distant metastasis	n (%)	-	6 (11.3)
Final imaging purpose			
Screening	n (%)	7 (63.6)	31 (58.5)
Diagnostic	n (%)	4 (36.4)	22 (41.5)
Final physical examination			
Normal	n (%)	7 (63.6)	31 (58.5)
Pathologic	n (%)	4 (36.4)	22 (41.5)
Final BI-RADS			
IV	n (%)	7 (63.6)	25 (47.2)
V	n (%)	4 (36.4)	28 (52.8)

BI-RADS: Breast Imaging and Reporting Data System; DCIS: ductal carcinoma *in situ*; SD: standard deviation; SLNB: sentinal lymph node biopsy

In terms of treatment, 22 patients received systemic treatment, two received only radiotherapy, and 31 received chemoradiotherapy after surgery. Remarkably, there was no treatment given to nine cases.

Of the recurrences, 25 were treated with mastectomy, 15 with BSC, 4 with axillary dissection and 2 with excision. Twelve cases were referred to the medical oncology department for systemic treatment before surgery. While four cases were planned for surgery, the outcome of two cases could not be learned.

Discussion and Conclusion

In the present study, US and MRI were found to be the most effective imaging modalities for detecting the recurrence of breast cancer, with rates of 95.1% and 100%, respectively. Although this rate was recorded as 78.7% for MG, it was remarkable that clinicians' tendency to request MG was lower. Physical examination was positive in only 59.3% of the cases. Therefore, it appears that supporting the algorithm with US and, if necessary, MRI, in addition to physical examination and MG in the post-treatment follow-up will increase the diagnostic efficiency.

Postoperative follow-up in breast cancer aims to prevent treatment-related side effects or complications and to detect possible local/systemic recurrence or a second primary focus as early as possible, ideally while still asymptomatic. Thus, high mortality rates may be prevented because recurrent breast cancer can be successfully treated if detected earlier. In the study of Pawloski et al. (12), patients with mastectomy were found to be at higher risk for recurrence, as index tumors are more aggressive and diagnosed at a more advanced stage. However, it has been reported that the recurrence rate is higher in DCIS patients who underwent BCS compared to mastectomy (12). In the same study, a higher rate of invasive carcinoma was found in recurrences after mastectomy and an equal rate of invasive and *in situ* cancers after BCS (12). Therefore, the authors highlighted that, regardless of the primary surgery, an annual check-up should be performed in every case treated for DCIS (12). In our study population, most patients'

primary pathology was invasive carcinoma (82.8%) and the most frequent type of recurrence was invasive carcinoma (75%).

It has been reported that the frequency of recurrence after mastectomy varies between 2-15% according to the tumor type and stage. The recurrence most frequently occurs in the skin and subcutaneous soft tissue adjacent to the pectoral muscle (13). Physical examination is one of the most critical steps in follow-up. However, physical examination alone is not reliable. It has been stated that MRI can be advantageous in the presence of suspicious physical examination findings, and some clinicians primarily advocate MRI for follow-up for implant integrity (13). In the present study, there was no significant physical examination finding in any of the cases smaller than 1 cm and any of the regional recurrences with LAP. Physical examination was negative in 59.4% of the cases. Most of them were regional recurrence to the axilla or second primary. These results reinforce the importance of radiological imaging.

MG, on the other hand, is the primary imaging method for the breast, used for both screening and diagnostic purposes. It is also used in the follow-up of successfully treated breast cancer. Annual screening MG after BSC is recommended by many authors (9, 14). Henderson et al. (15) indicated that in the early postoperative period, imaging was performed more frequently than recommended in the guidelines with different modalities, while the tendency to use imaging over time decreased after surgery. It has also been stated that MG can detect lesions with a better prognosis in the early period compared to the other techniques, and the survival rate is higher in MG-detected lesions (16). However, the sensitivity and specificity of MG in women treated for breast cancer are lower than in women without cancer (17-19). Furthermore, on MG imaging findings suggestive of recurrence the similar to findings in malignancy (20).

US may complement MG and is also a highly effective imaging modality for chest wall and axillary evaluation where MG is insufficient (21). For this reason, US is used in follow-up to investigate locoregional recurrence in patients with mastectomy. In addition, US provides additional information in distinguishing between postoperative changes and local recurrence. US imaging is recommended at regular intervals in the postoperative period (22, 23). In the present study, US did not detect recurrence in only three cases; one was a subpectoral mass, one was DCIS, and the other was LAP.

Breast MRI is more sensitive for detecting cancer than MG and US (21). However, evidence about the post-treatment role of MRI in breast cancer is limited. Especially after the first year of surgery, MRI has been reported to have high sensitivity and specificity in differentiating postoperative changes and recurrent breast cancer (24, 25). However, Park et al. (26), after reviewing over one thousand MRI examinations, reported that MRI was more effective after the third year of surgery. In addition, some authors have highlighted that women with personal breast cancer, especially after BCS, benefited greatly from MRI scanning (26). Thus, this use of MRI for follow-up is still controversial due to the lack of conclusive evidence. In the present study, 48.4% of the cases were scanned with MRI, and all recurrences were successfully detected.

The sensitivity of PET imaging in detecting breast cancer recurrence has been reported to range from 89–100% (27). However, in addition to containing radiation exposure, the lack of anatomical and morphological details reduces its specificity (28). In our case series, all PET-detected recurrences were demonstrated by conventional imaging prior to undergoing PET. When evaluated with other imaging methods, all but one axillary LAP, which could not be detected on US, could be seen. This finding shows that US is a valuable method for the follow-up and has high accuracy in experienced hands.

There are some limitations of this study. First, this is not a cancer outcome study. We only included the cases detected for recurrence in a limited period of time. Second, most cases were still having NAC regimens or were on the treatment list. So, it is not possible to report the final outcome for all patients. Third, factors affecting recurrence were not investigated, which were beyond the scope and design of the study. Last, due to the limited number of cases, it was not possible to draw robust conclusions about the ability of the various modalities to detect recurrence in terms of breast density.

MG and US, the primary imaging methods for the breast, are complementary modalities in follow-up. Although not adequately supported in the guidelines, in experienced hands, US can be used effectively to assess regional lymph nodes in addition to the breast. Systematic reviews of clinical trials are needed to support the adoption of US in guidelines. In addition, MRI and PET imaging, added to the algorithm in selected cases, may significantly contribute to the detection of recurrence.

Ethics Committee Approval: This study was approved by Istanbul University-Cerrahpasa, Non-Interventional Clinical Research Ethics Committee on 05.08.2022 with the decision number 449166.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.K., P.K., Y.K., T.O.; Concept: S.A.K., A.B.; Design: S.A.K.; Data Collection and/or Processing: S.A.K., P.K., Y.K., T.O.; Analysis and/ or Interpretation: S.A.K., P.K.; Literature Searching: S.A.K., A.B.; Writing: S.A.K.

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

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Original Article

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A Dosimetric Comparison of Volumetric Modulated Arc Therapy and Intensity Modulated Radiotherapy in Patients Treated with Post-Mastectomy Radiotherapy

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ABSTRACT

Objective: Radiotherapy continues to play an important role in the management of breast cancer. This study compared the dosimetric differences between the techniques of intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) in breast cancer patients who had radiotherapy after mastectomy.

Materials and Methods: Forty post-mastectomy patients (19 right-sided breast and 21 left-sided breast) treated with the IMRT technique using 7-9 fields who were re-planned with VMAT using 2 coplanar arc on the Varian Vital beam linear accelerator between January, 2020 and August, 2021 were included in this study. The patients received 42 Gy in 15 fractions to the chest wall, lymph nodes and supraclavicular nodes. The dosimetric parameter for planning target volume (PTV), organs at risk (OAR) and the integral dose to the body were analysed. Student's t-test for two independent means was used to analyse the dosimetric differences between the plans.

Results: Clinical goals were achieved for both techniques. In terms of PTV coverage at 95% (IMRT: 712.17±233) vs (VMAT: 694.9±214) and the homogeneity index (IMRT: 0.075±0.04) vs (VMAT: 0.104±0.03), IMRT resulted in better dose coverage and homogeneity than VMAT. However, with the conformity index, no significant difference was seen. As regards the OARs, the mean doses, V_5, V_{10}, V_{20}, V_{30}, and V_{40} for the Ipsilateral-lung were lower in IMRT plans than in VMAT plans with a non-significant variation (p-values = 0.141, 0.416, 0.954, 0.443, and 1 respectively). Regarding the mean dose to the heart, low-dose volumes V_5, V_{10}, and high-dose volume V30 were significantly reduced in IMRT compared to VMAT. When comparing the dose to the contralateral breast, IMRT achieved a significantly lower mean dose than VMAT (2.9 vs 3.62, p = 0.0148). For MU, VMAT showed lower MU compared to IMRT with a non-significant difference.

Conclusion: With IMRT, better PTV coverage, homogeneity and OAR sparing were observed. Additionally, VMAT resulted in a lower delivery time than IMRT. Overall, both techniques offered dosimetric qualities that were clinically acceptable.

Keywords: Cancer; conformity; homogeneity; mastectomy; radiotherapy

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Key Points

- The dosimetric properties of intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) for post-mastectomy patients were evaluated on 40 patients.
- Dosimetric paramaters of planning target volume and organs at risks were obtained and evaluated from the DVH.
- Quality of plan was analyzed including the integral dose to normal healthy tissue.
- Both techniques achieved clinical goals, VMAT reduce monitor unit than IMRT.

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Introduction

Three-dimensional conformal radiotherapy (3D-CRT) had been the standard technique for several years until the advent of more sophisticated machines which have resulted in advanced treatment techniques. These advancements in recent decades have improved radiotherapy treatments for breast cancer. The 3D-CRT poses some dosimetric challenges in delivering a uniform dose to the target due to the overlaying concave shape of the target, which can result in more dose to the adjacent structure, especially when treating the left-side chest wall (1). Further improvements in technology have enabled the intensity modulation of beams, permitting fluence across the radiotherapy fields, a technique known as intensity modulated radiotherapy (IMRT). Through beam modulation, regular and irregular shaped dose distribution can be attained, leading to an improvement in cosmetic results and minimizing toxicity to normal tissues (2). It also increases the therapeutic goals via improved target dose homogeneity and conformity for breast cancer treatment with the added sparing of the surrounding normal tissues (3).

An innovative modification of IMRT which allows optimum three-dimensional dose distribution to be delivered to the target in a single or multiple gantry rotation was introduced in 2007 (4). This novel technique, termed volumetric modulated arc therapy (VMAT), is an arc-based technique which leads to highly conformal dose distributions by employing beam fluence modulation, variable dose rate, and gantry speed. While VMAT results in similar or better planned target volume (PTV) coverage and better sparing of organs at risk (OARs) in comparison to IMRT, its major advantages are fewer deliveries of monitor units (MUs) and reduced total treatment time. Hence, it aids the fast delivery of treatment. Chest wall irradiation is complicated when compared to whole breast treatment due to its shape post-mastectomy. Hence, in this study, we aimed to dosimetrically evaluate the impacts of IMRT and VMAT on post-mastectomy patients.

Materials and Methods

Patient Enrolment

The computed tomography (CT) simulation cross-section data of 40 post-mastectomy patients (19 right-sided breast and 21 left-sided breast) referred for radiotherapy with invasive ductal carcinoma (T1–T3 N0–N2) to the ipsilateral chest wall, axillary nodes, and supraclave and who had been treated with the IMRT technique using the Varian Vital beam linear accelerator between January, 2020 and August, 2021 were used in this study. The ages of the patients were within the 25–64 years range. All of the patients were prescribed a total dose of 42 Gy in 15 fractions to the chest wall. A re-plan of the same set of patients treated with IMRT was carried out with the VMAT technique for the purpose of this research.

At the time of the CT simulation, the patients were positioned supine on an angled breast board with the sternum parallel to the couch and both arms raised above their heads. The simulation was carried out using a GE CT (Optima 580; GE Healthcare, Waukesha, WI, USA) of 16 slices and 2.5 mm thickness. The Eclipse treatment planning system (version 15.6.05) was used for contouring and treatment planning, while the anisotropic analytic Algorithm was used for dose calculation.

Target Delineation

The Clinical Target Volume (CTV) which included the chest wall (CW), axiliary nodes (AN), intermammary node (IM) and supraclave (SC), were delineated manually from the axial-CT images and outlined by a radiation oncologist following the radiation therapy oncology group (RTOG) recommendation. The PTV of the CW, AN, and SC was linked to the reference frame of the machine and was delineated by expanding from the CTV with a uniform 0.5 cm margin to account for physiological and daily set-up variations/uncertainty. The total PTV (PTV_{tot}) consisted of the PTV_{CW}, PTV_{AN}, and PTV_{SC}, all of which were limited to the skin surface. The heart, ipsilateral lungs, contralateral lungs, contralateral breast, spinal cord, and thyroid were contoured as critical organs and non-tumour tissue. Figure 1 describes the target and OAR delineation.

Planning

For each patient, one IMRT and one VMAT plan were created and optimization was achieved using the Photon Optimizer algorithm (version 15.6.05) with objectives specified accordingly to the planning goal. A typical IMRT plan consists of 7–9 photon fields spaced according to the planner's discretion at a single isocenter using 6 MV energy. The gantry angles were individually selected for each patient's CT dataset to achieve optimal dose target coverage and minimize entry and existing dose to the OARs. During the intensity optimization, dose constraints and priority were set for the PTV, NS ring control, and OARs following the quantitative analysis of normal tissue effects in the clinic (QUANTEC) analysis and RTOG report 62 guidelines as shown in Table 1 below. A 0.5 cm tissue equivalent bolus was placed over the PTV-CW to ensure sufficient target coverage near the CW surface.

Each plan was optimized so that 95% of the PTV would receive 95% of the prescribed dose (i.e., V95=95%). The doses were calculated using the anisotropic analyses algorithm (version 15.6.05) and efforts were taken to maintain the 3D dose max below 107%.

Additionally, VMAT plans were generated using the same isocenter and energy level as their corresponding IMRT plans, employing two partial coplanar arcs and 30-degree collimation with a starting angle of 179°

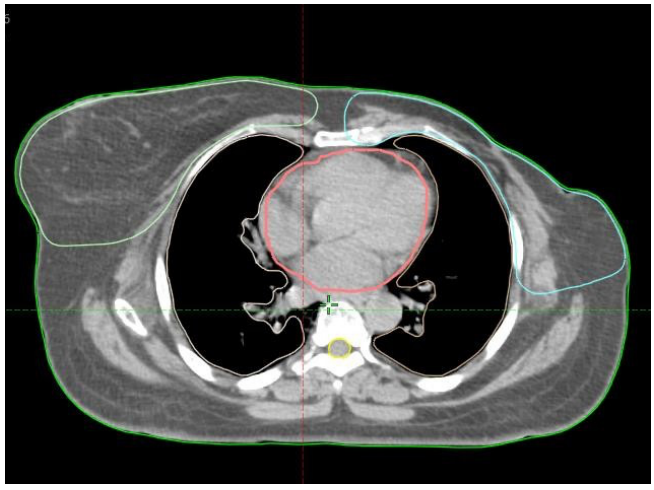

Figure 1. Target and OAR delineation

OAR: organs at risk

and an ending angle of 181°. These plans were optimized according to institutional practice, following the same dose objectives as used for the IMRT planning technique. The IMRT field arrangement and VMAT arc arrangement are shown in Figure 2 below. The planning goals for the plans are described in Table 1.

Plan Quality

For plan quality comparison, the dose homogeneity index (HI), conformity index (CI), integral dose (ID), MU and dose to OAR using the parameters obtained from the dose volume histogram are shown in Table 2. The CI was computed according to the definition proposed by RTOG (5) and estimated as:

$$CI = \frac{V95\%}{TV} \quad \text{----------} \quad (1)$$

Where V95% is the volume of the target receiving 95% of the prescribed dose and TV is the total volume of the target. The closer the value of CI is to 1, the more conformity there is to the plan. This study utilized two distinct HI formulas (HI_1 and HI_2). HI_1 was obtained based on the definition proposed by ICRU-83 (6) and is presented below.

$$HI_1 = \frac{D2\% - D98\%}{D95\%} \quad \text{----------} \quad (2)$$

Where $D_{2\%}$ and $D_{98\%}$ represent the minimum dose received by 2% and 98% of the target volume, indicating the maximal and minimal doses to the target, respectively, and $D_{95\%}$ represents the dose received by 95% of the target. The closer the value of HI is to 0, the more homogenous the plan. HI_2 is calculated as given below (7). In this mode, the closer the value is to 1, the better the homogeneity.

$$HI_2 = \frac{D5\%}{D95\%} \quad \text{----------} \quad (3)$$

ID is calculated as D_{mean} (Gy)*V(L), where D_{mean} (Gy) is the mean dose and V is the volume of the organ. Normal healthy tissue (NHT) was delineated by subtracting the target volumes from the body volume.

NHT= BODY - PTV. The percentage volume of the NHT receiving 5 Gy was obtained from the DVH.

Statistical Analysis

Student's t-test for two independent means was used to analyse the dosimetric differences between the plans. It was carried out on the social sciences window software version 18 (IBM Corp. Armonk, NY, USA), and *p*-values <0.05 were considered statistically significant.

Table 1. Planning goal for OAR

Organ	Objectives
Ip lung	V25 Gy ≤10%, V20 ≤20%, V30 ≤25%
Cont-lung	V5 ≤20%
Heart	V25 Gy ≤10%, V30 ≤5%
Contralateral breast	Mean 3 Gy
Thyroid	V26 ≤20%

OAR: organs at risk

Table 2. Dosimetric parameters

	Parameter
PTV	**D_{mean}, $D_{2\%}$, $D_{5\%}$, $D_{95\%}$, $D_{98\%}$, and D_{means}**
OAR	
Ipsilateral lung	V_{5Gy} (%), V_{10Gy} (%), V_{30Gy} (%), and V_{40Gy} (%)
Contralateral lungs	V_{5Gy} (%), V_{10Gy} (%), V_{15Gy} (%), and V_{20Gy} (%)
Heart	D_{mean}, V_{5Gy} (%), V_{10Gy} (%) and V_{30Gy} (%)
Contralateral breast	D_{mean}, V_{5Gy} (%), V_{10Gy} (%), and V_{20Gy} (%)
Thyroid	V_{20Gy} (%), V_{30Gy} (%), and V_{40Gy} (%)
NHT	D_{mean}, $V_{95\%}$ (cm)

D_{mean} is the mean dose received; D% (Gy) is the dose received by percentage of target volume; VGy (%) represents the percentage volume of the OAR receiving the particular dose. PTV: planning target volume; OAR: organs at risk; NHT: normal healthy tissue

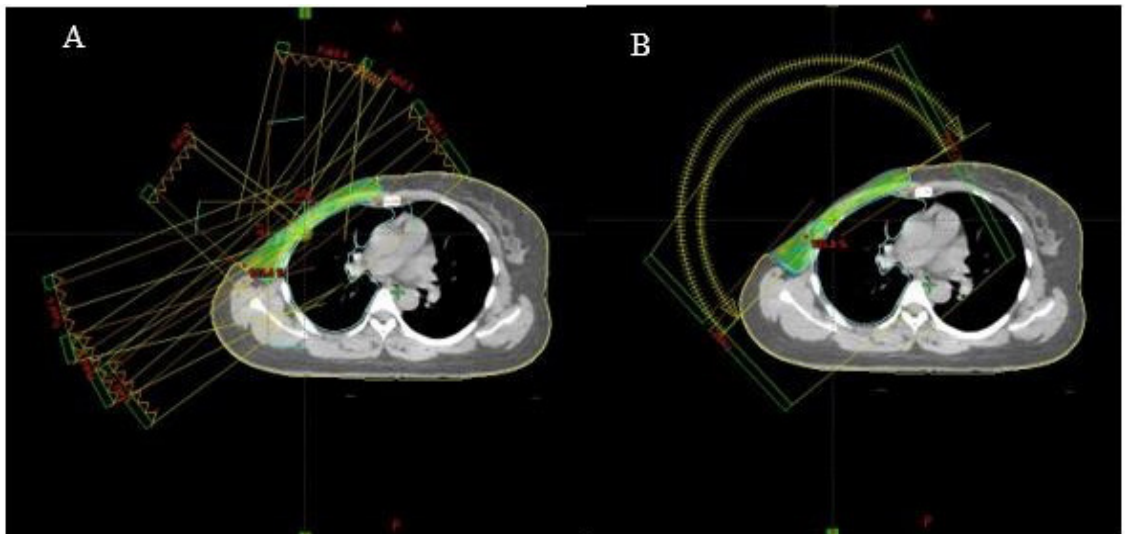

Figure 2. Field arrangement for (A) IMRT, (B) VMAT plans

VMAT: volumetric modulated arc therapy; IMRT: intensity modulated radiotherapy

Ethics Approval

This study protocol was reviewed and approved by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC) ADM/DSCST/HREC/APP/4664.

Informed Consent

All patients were informed and their consent was taken.

Results

The IMRT plan for each patient was reviewed and approved by the radiation oncologist before delivery of treatment. In total, 40 IMRT plans (21 left-sided and 19 right-sided) and 40 VMAT plans were created for this study and the dosimetric results of the two techniques are presented in the tables below.

PTV Dose Analysis

Both treatment techniques achieved 95% PTV coverage with a non-statistical difference. Table 3 summarizes the PTV result in terms of mean dose, min dose, max dose, D_5, D_{95}, CI, HI, and GI. The VMAT and IMRT techniques had no significant difference in CI (0.962 vs 0.981, p = 0.084). A similar result was obtained with the mean dose (42.226 Gy vs 42.39 Gy, p = 0.211). However, when compared to the VMAT plan, the IMRT technique showed more dose homogeneity as the difference between them is statistically significant (H1: 0.075 vs 0.104, p = 0.0003; H2: 1.056 vs 1.082, p = 0.0005). Statistically significant comparisons were also seen for the max dose D_2 (43.52 Gy vs 43.88 Gy, p = 0.0037) and min dose D_{98} Gy (39.77 Gy vs 39.52 Gy, p = 0.0007). The comparisons of dose volumes between the two techniques are shown in Figure 3.

Dose Analysis of OARs

In Table 4, the dosimetric parameters of the OAR observed in IMRT and VMAT plans are summarised. The mean doses, V_5, V_{10}, V_{20}, V_{30}, and V_{40} for the Ip-lung were lower in the IMRT plans than in the VMAT plans with an insignificant variation (p-values = 0.141, 0.416, 0.954, 0.443, and 1 respectively). However, in both techniques, the doses were within clinically acceptable limits. For the contralateral

Table 3. Comparison of dose coverage for PTV_{total} for both planning techniques

PTV	VMAT	IMRT	*p*-value
V_{95} (cm^3)	779.6±268.5	712.17±233.03	0.234
D_{mean} (mean dose) Gy	42.26±0.4	42.39±0.47	0.211
D_{98} (min dose) Gy	39.52±0.1	39.77±1.7	0.0007
D_2 (max dose) Gy	43.88±0.65	43.52±0.32	0.0037
$D_{5\%}$ (Gy)	43.56±0.47	43.31±0.31	0.008
$D_{95\%}$(Gy)	40.28±0.84	41.044±1.3	0.003
HI_1	0.104±0.03	0.075±0.04	0.0003
HI_2	1.082±0.03	1.056±0.04	0.0005
CI	0.962±0.04	0.981±0.06	0.084
GI	1.531±0.28	1.341±0.39	0.0134
MU	305.538±46.077	306.570±64.880	0.935

VMAT: volumetric modulated arc therapy; PTV: planning target volume; IMRT: intensity modulated radiotherapy; HI: homogeneity index; CI: conformity index; MU: monitor unit

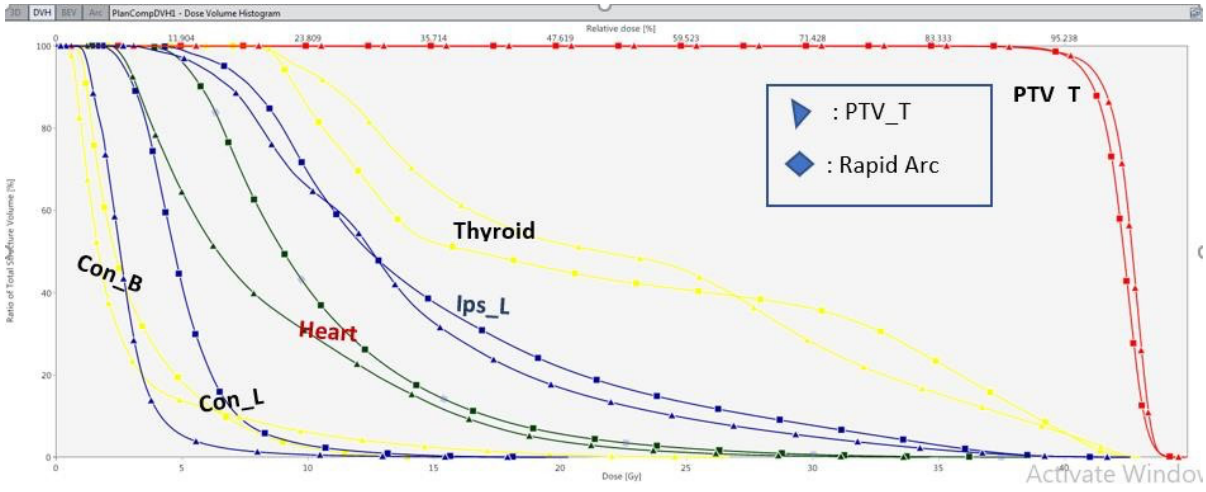

Figure 3. DVH comparison of IMRT and VMAT plan

VMAT: volumetric modulated arc therapy; IMRT: intensity modulated radiotherapy; PTV: planning target volume

Table 4. OAR dose comparison between both planning techniques

Organ	VMAT	IMRT	*p*-value
IP-lung			
Mean dose (Gy)	14.42±1.35	13.952±1.48	0.141
$V5_{Gy}$ (%)	96.28±1.35	93.61±6.388	0.416
$V10_{Gy}$ (%)	65.48±12.28	65.3±14.65	0.954
$V30_{Gy}$ (%)	6.26±1.91	5.96±1.57	0.443
$V40_{Gy}$ (%)	0.09±0.17	0.09±0.22	1
Cont-lung			
Mean dose (Gy)	5.6±0.81	4.6±1.52	0.001
$V5_{Gy}$ (%)	52.32±15.76	38.78±18.83	0.001
$V10_{Gy}$ (%)	5.4±4.43	6.7±6.85	0.328
$V15_{Gy}$ (%)	1.62±5.56	0.74±1.08	0.489
$V20_{Gy}$ (%)	0.71±3.52	0.18±0.37	0.248
Heart			
Mean dose (Gy)	11.17±2.41	8.88±2.83	0.0002
$V5_{Gy}$ (%)	92.66±18.18	69.7±23.72	0.00001
$V10_{Gy}$ (%)	47.95±4.06	35.045±19.83	0.0033
$V30_{Gy}$ (%)	2.6±4.06	1.12±1.54	0.0344
Cont-breast			
Mean dose (Gy)	3.62±0.93	2.9±12.19	0.002
$V5_{Gy}$ (%)	18±11.4	15.19±12.19	0.291
$V10_{Gy}$ (%)	2.38±4.32	1.84±2.6	0.503
$V20_{Gy}$ (%)	0.1±0.43	0.025±0.08	0.503
Thyroid			
Mean dose (Gy)	23±5.94	23.71±2.97	0.636
$V20_{Gy}$ (%)	51.36±15.03	52.5±10.23	0.781
$V30_{Gy}$ (%)	36.45±12.18	34.59±10.15	0.603
$V40_{Gy}$ (%)	13.79±10.65	15.16±11.11	0.693

VMAT: volumetric modulated arc therapy; IMRT: intensity modulated radiotherapy; OAR: organs at risk

lungs, both techniques yielded similar results for V_{10}, V_{15}, and V_{20}. However, the mean dose and V_5 of the cont-lungs were significantly spared in the IMRT plan in comparison to the VMAT plan (mean dose: 4.6 Gy vs 5.6 Gy, $p = 0.001$; V_5: 38.78% vs 52.32%, $p = 0.001$).

The mean dose to the heart, low-dose volume $V_{5,}$ V_{10}, and high-dose volume V_{30} were significantly reduced in IMRT in comparison to VMAT. In comparing the dose to the contralateral breast, IMRT achieved a significantly lower mean dose than VMAT (2.9 vs 3.62, $p = 0.0148$). However, there was no significant difference in terms of V_5, V_{10}, and V_{20}. VMAT, on the other hand, indicated a low mean dose and volume dose for thyroid, although there was no significant difference between the two plans.

The average MU for each fixed angle beam in the IMRT plan was 303.34, while that for each partial arc trajectory was 307.54 in the VMAT plan. There was no significant difference in MU for both plans.

The planning volumes for each patient were well inside the planning CT scans, so the irradiated normal tissues were included in the CT volumes. Table 5 shows the ID to the non-tumour tissue (ID_{NTT}) and no significant difference in normal tissue ID was observed ($p = 0.493$) in either technique.

Discussion and Conclusion

Conformal techniques have proven to be of great benefit in radiotherapy for mastectomy breast cancer. It is essential to evaluate the dosimetric properties of these techniques. In recent times, such studies (8) have evaluated the dosimetric properties of 3D-CRT and IMRT in post-mastectomy irradiated patients. Additionally, several trials have made comparisons of the VMAT technique, which uses an arc trajectory, against the fixed angle beam IMRT technique. However, this has led to a debate on which technique should be employed in radiotherapy. The current study compares the above-mentioned radiotherapy techniques often utilized in the treatment of post-mastectomy breast cancer and evaluates these plans using the dosimetric parameters obtained from the DVH. A plan with good target coverage has the benefit of maximizing the efficacy and improving the local control to ensure homogenous dose coverage by avoiding cold spots (PTV receiving less than 90% of the prescribed dose) and hot spots (outside PTV receiving a dose greater than PTV) as well as minimizing normal long-term tissue toxicity. The findings from our work showed that both plans met the target coverage with a non-significant difference in the conformity index, which indicates successful avoidance of hot spots (i.e., areas of relative overdose). However, VMAT showed significantly lower dose homogeneity in PTV_{total} than IMRT, indicating that the

Table 5. Comparison of dose coverage for body and non-tumour tissue for both planning techniques

	VMAT	IMRT	*p*-value
NTT_{volume} (liter)	23.43±6.77	23.43±6.77	1.000
Mean dose	5.57±1.16	6.45±8.07	0.497
$V_{5Gy}(cm^3)$	7,518.23±1,446.85	7,008.71±1,446.6	0.119
ID_{NTT}	125.103±24.08	142.937±161.84	0.493

VMAT: volumetric modulated arc therapy; IMRT: intensity modulated radiotherapy; ID_{NTT}: The non-tumour tissue

IMRT plan reduces the cold spot issue to a greater extent, which might decrease local reoccurrence.

Radiation doses to the ipsilateral lungs can result in induced pneumonitis, a deterministic effect of breast cancer treatment (9), hence, the need for proper optimization of the lung during planning. Conventionally, the dosimetry parameters influencing radiation-induced pneumonitis include V_5 Gy, V_{10} Gy, and V_{20} Gy. However, the main predictors among these parameters remain debatable. Yorke et al. (10) researched dosimetric factors of radiation-induced pneumonitis and reported that the V_5 Gy and V_{10} Gy of the lung may be effective predictors, whereas Caudell et al. (11) concluded that V_{20} Gy and radiation-induced pneumonitis are related. In this study, the volume dose of both plans was within the QUANTEC recommendations, and there was no significant difference between the VMAT and IMRT plans for all the dose parameters of the ipsilateral lung (mean dose, V_5 Gy, V_{10} Gy, V_{30} Gy, and V_{40} Gy), indicating that both techniques reduced the radiation dose while ensuring sufficient radiation to the target area, which may reduce the incidence of radiation-induced injury.

To prevent cardiac morbidity, it is essential to limit the heart dose as much as is reasonably achievable in patients, particularly those with left-sided breast cancer. However, the required level of sparing is unclear. In this study, the IMRT significantly outperformed the VMAT in sparing the heart in cases of the left-sided CW (based on mean dose, V_5 Gy and V_{10} Gy; $p<0.00001$), both offered similar heart sparing in cases of the right-sided CW.

The minimization of the irradiation of the contralateral breast needs to be highly prioritized. This is required to reduce the possibility of radiation-induced carcinogenesis (12). Although there are risk models which quantify the relationship between low-medium dose levels and the induction of secondary cancer (13, 14), clinical validation is inadequate. As a result, optimization is required (i.e., applying the ALARA principle). As shown in the results presented above, the mean dose to the contralateral breast differed significantly where the IMRT plan complied with the QUANTEC restriction of less than 3 Gy, although the dose-volume (V_5, V_{10}, and V_{20}) was similar.

The delivery of low-dose irradiation to healthy tissue has been estimated to double the risk of subsequent malignancy, and this risk increases with increasing dosages (15). According to the findings of this study, it was observed that VMAT resulted in a significant reduction in the mean dose to the healthy tissue compared to IMRT ($p = 0.00001$). Based on the report by D'Souza and Rosen (16), the non-tumour integral dosage is mostly determined by beam margin size and energy, with the fractionation scheme playing a minor role. Smaller margin size and higher energy result in a constant reduction in non-tumour tissue ID, regardless of the number of beams. This study observed a similar non-tumour ID ($p = 0.493$) as the same energy and fractionation scheme were utilized.

The results of this study are in line with the findings of Dumane et al. (17), who compared the plan quality of three techniques (IMRT, VMAT, and 3D-CRT) on the right CW. According to their study, HI and PTV coverage were found to be best with IMRT, while IMRT and VMAT improved conformity similar to the 3D-CRT plan (improved by as much as 25%). OAR are spared more with VMAT in comparison to IMRT (by as much as 17.1% decrease for the ipsilateral lung and 16.22% for the contralateral lung). The study by Ma et al. (18) on dosimetric comparison of three radiotherapy techniques (3D-CRT, IMRT, and VMAT) agrees with our results as their IMRT plan achieved better homogeneity than the other plans (IMRT: 0.114 vs VMAT: 0.143, $p = 0.002$; IMRT vs 3D, $p = 0.001$) while both IMRT and VMAT achieve similar CI ($p = 0.425$). Also, the mean dose to the contralateral breast was higher in VMAT (5.79 Gy) than in IMRT (2.81 Gy), with $p = 0.016$.

In contrast to our findings, Johansen et al. (19) reported that better dose homogeneity and PTV conformity were observed in VMAT (HI and CI; $p<0.05$). In addition, the mean dose to the contralateral breast was lower in VMAT than in the other techniques (IMRT and conventional plan), however, these differences were not significant. Past studies have reported lower MUs in VMAT than in IMRT. The higher the MU, the longer the beam-on time and vice versa. Our findings agree with the report published by Zhang et al. (2). From their findings, VMAT reduced the number of monitored units by 24% and treatment time by 53%. They also reported that VMAT achieved better normal tissue sparing than IMRT, although both techniques (VMAT and IMRT) showed similar PTV dose homogeneity ($p = 0.048$). The average MU for each fixed angle beam in the IMRT plan was 306.57±64.88, while that for each partial arc trajectory in the VMAT plan was 305.538±46.077. This implies that the overall delivery time for the VMAT plan is lower than that of IMRT, although the MU result showed no significant difference.

The deep inspiration breath-hold technique to reduce the heart dose in breast cancer management has been studied (20), however this was not the focus of our study. This study's design was not intended to evaluate the advantage of one modality over another in terms of toxicity. A lengthy follow-up would be necessary to address the effects of inverse planning techniques on survival.

From a dosimetric perspective, it is concluded that both plans investigated in this study offer quality patient treatments. However,

the IMRT plans achieved a better dosimetric advantage for the CW owing to enhanced PTV coverage, better dose homogeneity, and enhanced sparing of the OAR, such as the contralateral breast, heart, and lungs compared with VMAT. On the other hand, VMAT, while maintaining a good degree of conformity similar to IMRT, had the advantage of a lower MU than IMRT, thereby decreasing the overall treatment plan times.

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Informed Consent: All patients were informed and their consent was taken.

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Authorship Contributions

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

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Original Article

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The Evaluation of a Cost-Effective Method for Tumour Marking Prior to Neo-Adjuvant Chemotherapy Using Silver Rods

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ABSTRACT

Objective: The lack of objective documentation of pre-neoadjuvant chemotherapy (NAC) tumour margins is a major constraint in performing safe breast conserving surgery (BCS) in patients with breast cancer. Using a novel method of marking pre-NACT tumour margins with indigenous silver wire markers, this retrospective observational study attempted to assess the feasibility of safe BCS in breast cancer patients by performing excision wide of the marked pre-NACT margins.

Materials and Methods: This retrospective observational study was conducted on breast cancer patients who were attending our oncology centre between May, 2015 and April, 2022. All patients had received NAC followed by surgery as recommended by our multidisciplinary team. All the patients had a primary operable solitary breast cancer. We used radiopaque metallic rods made from silver to localize tumour margins prior to NAC.

Results: Sixty-four breast cancer patients were included; none had marker-related complications. Following NAC, BCS could be easily performed in 60 patients guided by the silver markers, which were used as temporary implants and removed during surgery. Only 2 patients were seen with positive margins and were converted to mastectomy.

Conclusion: Breast cancer localization using sterile silver markers before the initiation of NAC is safe, easy, inexpensive, and effective, causing no morbidity or significant pain to the patients.

Keywords: BCS; breast cancer; breast imaging; neoadjuvant chemotherapy; silver rod localization

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Key Points

- Tumor marking before neoadjuvant chemotherapy is importnant in cases with expected complete response.
- Silver wire markers are faesible , safe and inexpensive tumor marking method.
- It is effective method and wire could be dected in nearly all cases.

Introduction

Neoadjuvant chemotherapy (NAC) has become a cornerstone of the multidisciplinary treatment approach for breast cancer and has a long history which goes back almost forty years (1). Several values have been proven for NAC, such as downsizing the breast tumour to facilitate breast conserving surgery (BCS), down-staging the axilla to allow sentinel lymph node biopsy in node positive cases and permitting *in vivo* tests of treatment response (2). To date, surgery is essential even in those cases which achieved complete clinical response (3). The BCS after down-staging by NAC has proven to be safe in terms of local recurrence and survival. However, selection criteria should be fulfilled, and accurate localization of the tumour bed should be carried out before surgery. Usually, marking the tumour location is difficult if no pre-treatment localization method has been performed, and the surgeon experiences a dilemma when he is unable to localize the tumour bed and sometimes finds himself forced to perform a mastectomy (4). That is why pre-treatment tumour localization has become the standard in patients undergoing NAC and planned for BCS (5). Globally, several pre-treatment localization methods have been described and accepted. Tattoo inks, radioactive iodine seeds and

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metallic clips have been studied. However, no standard approach has been settled upon (6). This study aimed to evaluate the safety and accuracy of an inexpensive method for marking the margins of breast tumours before initiating NAC by using radiopaque metallic rods made from silver wire.

Materials and Methods

This retrospective observational study was conducted between May, 2015 and August, 2022. All cases received NAC and then underwent subsequent surgery according to our multidisciplinary team (MDT) decision. All patients gave informed consent before enrolment in this study. Our study was approved by the local institutional board (R.22.09.1869). Patients were included when presenting with unifocal operable breast cancer which required NAC and subsequent BCS after NAC. Those with metastatic disease, inflammatory types of breast cancer, those with unplanned excision, recurrent cancer, multicentric or multifocal lesions, those with WHO performance status >2 or those with echocardiography which showed an ejection fraction (EF) ≤45% were excluded from this study. Moreover, patients who progressed on NAC were transferred for surgery and were excluded from this study. The patient and tumour characteristics are listed in Table 1.

Initial Evaluation

All of the patients received anamnesis and clinical examination to assess their palpable breast tumour location, nipple and/or skin affection and enlarged locoregional lymph nodes. All cases had undergone an ultrasound guided core needle biopsy, with histopathological and immunohistochemical staining for ER, PR, HER2, and Ki67. Breast imaging included mammogram and breast magnetic resonance imaging (MRI) (if indicated as in cases of dense breast, doubtful multifocality or multicentricity, lobular cancer, or discrepancy between mammography and ultrasound). Routine metastatic work-up was carried out. Alkaline phosphatase was used for early-stage disease, and whole body computed tomography scan and bone scan for locally advanced disease. Pre-chemotherapy routine laboratory investigations (CBC, liver functions, renal functions etc.) and echocardiography were performed. According to our MDT decisions, the patients were designated for NAC followed by BCS based on their biological subtyping and the tumour/breast ratio.

Tumour Localization Prior to Neoadjuvant Therapy by Silver Wire Rods

The tumour margins were marked by 3–5 metallic rods made from silver wire which was bought from a supplier as a roll and designed to be 1-meter in length and 1-mm in diameter. This roll was cut into small rods which were 2–3 cm long and were sterilized by autoclave, then kept in a plastic sterile bag (Figure 1). One metallic rod was placed at each margin of the tumour (upper, lower, medial, lateral, and posterior if possible). One metallic rod was loaded into a 20-gauge spinal needle (Figure 2), which was introduced through the skin after a local anaesthetic injection. Our radiologist propelled the spinal needle tip to reach one margin of the tumour under ultrasonography (US) guidance. The metallic rod was pushed with the needle's stylet when the spinal needle tip touched the margin (Figure 2). This was repeated for each margin. To confirm the correct placement of the markers, a mammogram was carried out after the procedure (Figure 3, 4A).

Neoadjuvant Chemotherapy

Our patients received the standard regimens according to the molecular type and as recommended by our medical oncologists. CBC was performed before each cycle. The full course of the planned neoadjuvant therapy regimens was administered. The patients were examined after each cycle, and their response was recorded by clinical examination. The only indication for cessation of NAC and referral to surgery was disease progression.

Table 1. Patients and their tumour characteristics

Median age (year, range)	43.5 (26–74)
Mean BMI (range)	27 (23–31)
Mean initial tumour size (cm, range)	4.65 (2.8–6.58)
Mean pathological tumour size in cm (range)	1.8 (0–3.2) *
Pathological type (tru-cut biopsy)	
IDC	52
ILC	12
Biological type (by IHC)	
Luminal A	25
Luminal B	20
HER 2 enriched	8
Triple negative	11
Stage at diagnosis	
Stage II	40
Stage III	24

*0 value in range refers to the ten cases who achieved PCR. BMI: body mass index; IHC: immunohistochemical analysis

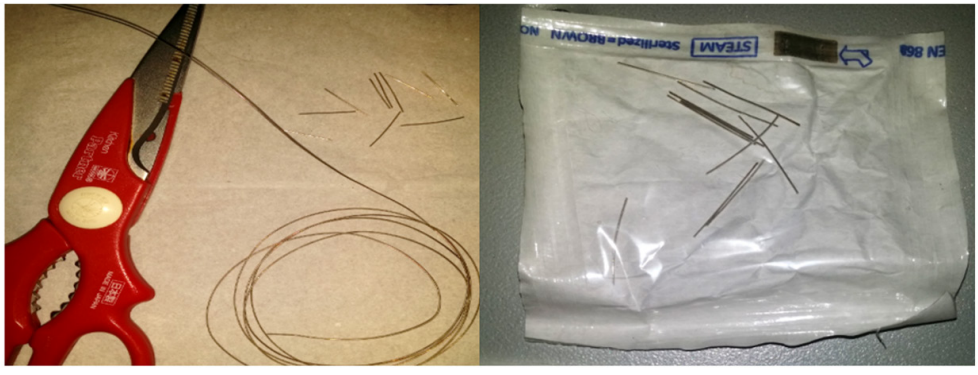

Figure 1. Silver wire roll cut into small rods and pocketed in a sterile plastic bag after autolaving

Clinical Response

The assessment of clinical response was based on imaging studies (Table 2). US was performed for all patients to assess clinical tumour size and LN status after finishing the planned treatment (Figure 4B). Breast MRI was performed on 28 patients as requested by our radiologists. Response to treatment was categorized as complete, partial, stationary, and progressive according to RECIST criteria.

Surgery

After the completion of preoperative therapy, the patients underwent surgery at least 14 days after the last cycle to attain normal CBC. Patients who fulfilled the criteria for breast preservation were offered BCS either by traditional lumpectomy or by oncoplasty.

Tumour Bed Identification

Pre-operatively, if the tumour became impalpable, a skin mark was placed by the radiologist in order to allow easy identification of the tumour bed (Figure 5). When the residual lesion became invisible on imaging, the radiologist relied on the metallic markers to localize the tumour bed and place his mark. Intraoperatively, we performed wide local excision (WLE) of the tumour bed by obtaining a distance of about 1 cm to the of the palpated markers. We were usually able to detect the markers in almost all cases and used them as a guide when addressing the WLE, taking care to remove all visible or palpable rods (although there are newer tools to detect the wire but they are more sophisticated and not yet available in our practice) (Figure 6).

Table 2. Clinical and pathological responses to NAC*

Clinical response (n = 64)	
Complete clinical response	12 (18.75%)
Partial clinical response	49 (76.5%)
Stationary response	3 (4.6%)
Pathological response (n = 64)	
PCR	10 (14%)
Partial pathological response	51 (79.7%)
Minimal or no response	3 (4.6%)

*Neoadjuvant chemotherapy

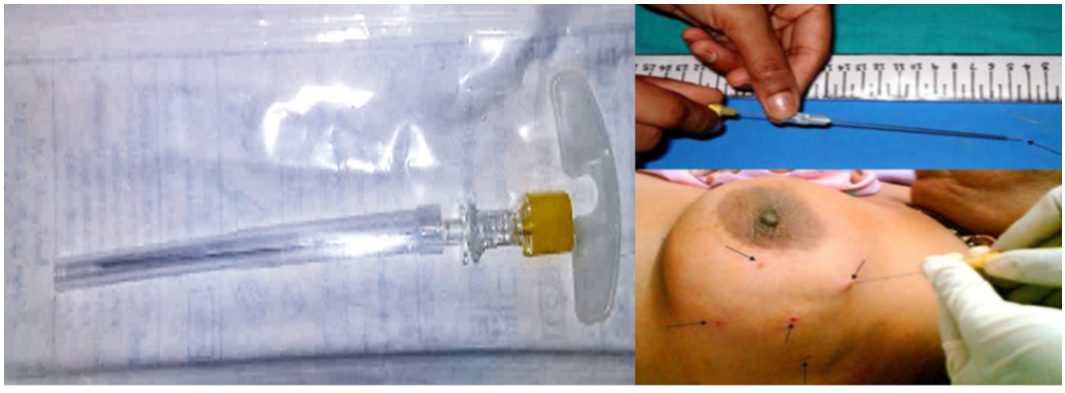

Figure 2. Twenty gouge spinal needle and technique of marker insertion

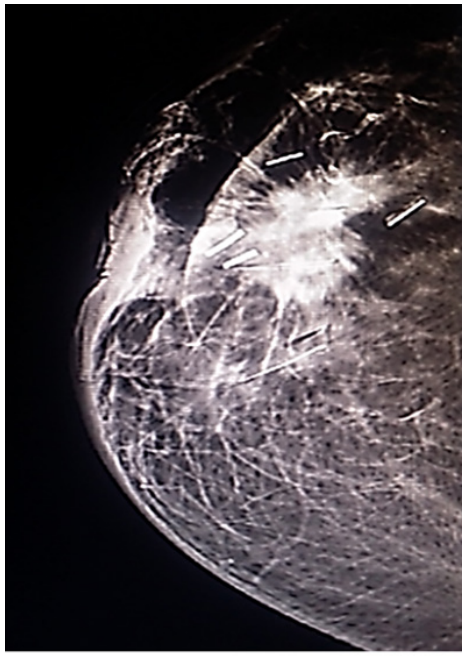

Figure 3. Post-procedural mammogram showing 4 silver markers at tumor margins

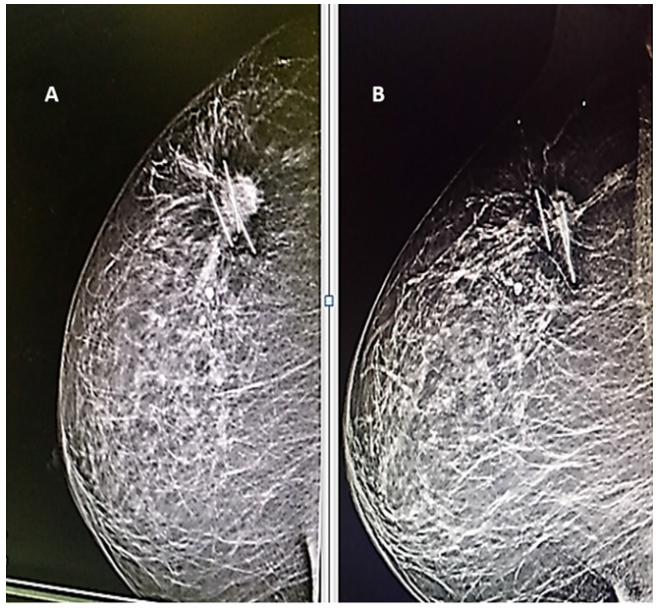

Figure 4. A. Pre-neoadjuvant therapy mammography showing the silver rods incorporated into the tumor margins, **B.** Post-treatment mammography showing marked tumor regression with the markers in place

Imaging of the specimen by mammogram was carried out in order to confirm the extraction of all markers. The pathologist could detect the rods during sectioning of the tumour (Figure 7). Confirmation of clear safety margins was performed by intraoperative frozen section examination.

Results

Sixty-four patients with operable breast cancer were enrolled in our study. The mean age of the cases was 43.5±10.5 years (range 26–74 years). At diagnosis, forty patients had stage II and 24 had stage III disease. Fifty-two patients had invasive duct carcinoma and 12 patients had invasive lobular carcinoma. The mean clinical tumour size was 4.65±1.6 cm. The mean pathological tumour size was 1.8±1.4 cm.

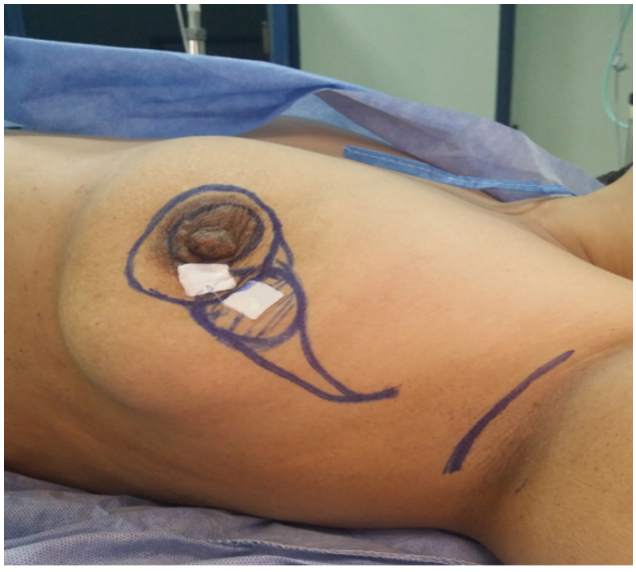

Figure 5. Preoperative skin marking at site of silver markers

At the end of the neoadjuvant course, 49 patients (76.5%) showed partial response, 3 patients (4.6%) showed stationary response and 12 patients (18.75%) showed complete response of whom, 10 (14%) had achieved pathological complete response (PCR) at their final pathological examination. The patient and tumour characteristics are provided in Table 1. Table 2 shows the clinical and pathologic response to the NAC. Metallic silver rods were placed in all cases with a median number of four (range 3–5) prior to NAC. No patient complained of pain after one day of marker insertion. Six patients complained of feeling the markers in their breast owing to its superficial placement, and their complaints were easily managed by assurance and mild analgesia. No patient had allergy, infection, or extrusion of the markers. After completion of NAC, the markers were easily detected by US in all cases without any reported migration with the radiologist fixing the new borders or clips in cases of complete response with an external marker on the patient's skin (Table 3). In the 28 cases who

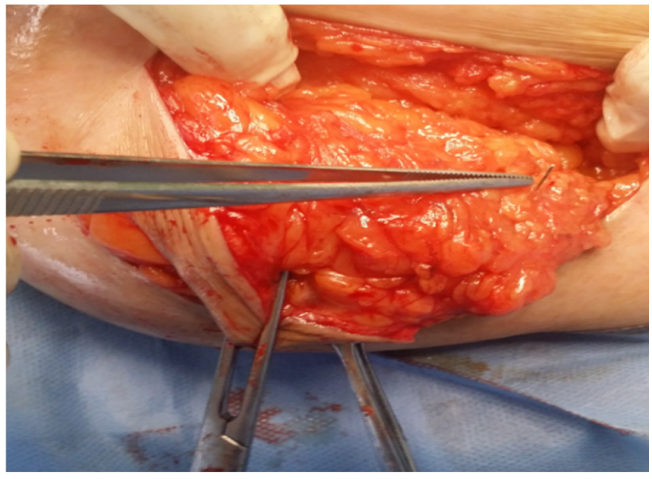

Figure 6. Intra-operative silver marker detection

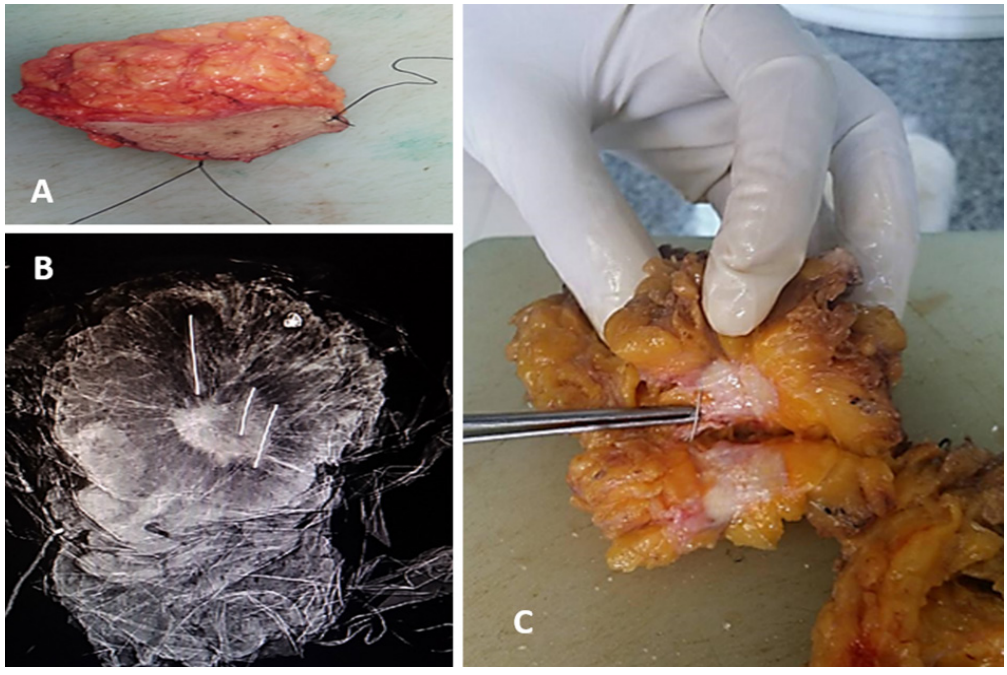

Figure 7. A. Lumpectomy specimen marked by threads, **B.** Specimen mammography showing the markers at tumor margins, **C.** Silver marker detected during gross pathology examination

Table 3. Complication rate (n = 64)

Migration	0
Allergy	0
Infection	0
Significant pain	0
Feeling discomfort	6 (9.3%)

had MRI, the residual lesions, if present, were clearly described despite marker artefacts, which did not substantially limit the interpretation of the radiologists. All patients underwent surgery. Sixty out of 64 patients underwent BCS and 4 patients underwent mastectomy (one patient was not amenable to BCS and mastectomy was preferred for the other 3). In all 60 patients who underwent BCS, we were able to perform WLE with 1 cm wide margins guided by the metallic markers placed at the tumour borders, which could be easily palpated in all cases. The specimen mammogram documented the primary removal of metallic markers in 56 patients at the first attempt. The other four cases required re-excision to ensure the removal of all of the markers. Fifty-eight cases had clear margins at final pathology with acceptable cosmetic results. Only two cases had positive margins and had to convert to mastectomy (conversion rate 3.3%). Table 3 shows complications related to this technique.

Discussion and Conclusion

Neoadjuvant systemic therapy has become an integral part of the treatment panel for breast cancer. The response to neoadjuvant therapy is dramatic in some patients, and the rate of PCR has been recorded to be as high as 32.9% in some publications (6). However, an excellent response to NAC may make identification of the tumour bed extremely difficult on post treatment imaging studies, and, therefore, precise localization and safe BCS may be impossible (7). Edeiken et al. (8) found that 46.9% of tumours (23/49) were not detected on mammography after NAC. Moreover, Dash et al. (9) found that no residual tumours were visualized on 35.7% of mammograms (10/28). In such cases, preoperative marking and intraoperative identification of the tumour bed is nearly impossible if a breast tissue marker has not been placed previously. As localization is required in order to decide the extent of surgery and to guide pathologists to identify the main residual lesion, the insertion of breast tissue markers is crucial for breast cancer patients before starting NAC (10). The BCS after NAC has proven to be safe in terms of local recurrence and survival. However, to perform optimal disease eradication at WLE, the whole tumour bed situated within the pre-NAC margins should be resected (11) although there are a newer trends which recommend resection according to the new tumour borders after response to NAC (12). Typically, safe BCS after NAC is sometimes uncertain owing to the difficult identification of the tumour bed by examination and imaging studies once the tumour has regressed. Thus, marking the tumour bed before initiation or after the first few cycles of neoadjuvant therapy is crucial to perform safe BCS (13). To date, there is no standard method to mark the tumour bed prior to neoadjuvant therapy (14). Multiple tumour localization techniques have been studied. The devices used for marking the tumour site prior to chemotherapy in clinical practice include tattoo ink, radioactive iodine seeds, ultrasound detectable clips, and magnetic implants (15). Cutaneous tattoos are among the cheapest and most rapid techniques used to mark breast lesions, but they are less accurate than metallic clips (16). Another marking method is the intralesional injection of a charcoal suspension. During surgery, the target area is visually identified by the dark stain left on the patient's skin. Its major drawbacks are the risk of colour migration to nearby healthy tissue or the risk of confusing the charcoal suspension with the tumour architecture on histopathological examination (17). Radioactive markers can be used as well. This is an effective technique, but it requires complex safety regulations (18). In addation to these methods, magnetic implants such as the MagSeed® have been approved for long-term implantation in any soft tissue, thus allowing the direct insertion of the magnetic seed in the lesion before NACT (19). However, the most popular method used in practice is commercial titanium clips. Generally, to avoid an extra session for the placement of the clips, their placement is performed in the same session of the core needle biopsy. A commercial breast marker needle is inserted through the same small incision for the core biopsy needle. As the exact response to NAC cannot be anticipated, the placement of breast markers has become routine (20). There are several versions of titanium-based commercial breast markers on the market offered by several companies. In Egypt, the price of one commercial titanium clip ranges from 3000 LE to 4000 LE which is considered too expensive and so this technique has not become popular in our country (21). In our study, we used small rods made from silver which acts as radiopaque metallic markers and are placed at the tumour margins via the well-known spinal puncture needle. The placement of the silver markers was easy to perform, and the procedure was carried out in less than 10 minutes. Since the silver rods were autoclaved, and insertion was performed with US-guidance under aseptic condition, it was considered a relatively safe technique with low complication rates. Several trials have been made to replace the expensive commercial breast clips and they have shown that low-cost metallic markers are effective for tumour localisation and do not interfere with post-treatment radiologic assessments, including MRI (22). Youn et al. (23), in South Korea, inserted surgical clips with a semiautomatic gun using a guiding needle and concluded that surgical clips are easy, safe and low cost. The same results were reported by Uematsu et al. (24), but in their study, the surgical clip was introduced via an automated gun. In 2008, Aggarwal et al. (5) published a feasibility study on safe BCS in patients with locally advanced breast cancer using silver wire to mark tumour borders prior to NAC. They performed the same technique used in our study, but the insertion of silver markers was carried out by palpation without US guidance. They concluded that these wire markers were safe, effective, and low cost. One of the possible complications of silver marker insertion is migration. The low tissue resistance of breast parenchyma may allow the rods to move from their original location; however, the rods are generally lodged in the border of the tumour with half being inside it. Thus, the possibility of marker migration was low owing to higher tissue resistance (18). Although the mean duration between marker insertion and surgery was approximately four months, there were no cases of marker migration in our study as shown in post treatment imaging studies and specimen mammograms after surgery. Additionally, other possible complications such as allergic reactions, infections and intolerable pain were not reported. Many publications have proven that radiopaque markers are crucial for tumour localization without disturbing post treatment imaging assessments, including MRI (25-28). We could assess tumour response to therapy and make sure of the marker location by use of multimodal imaging studies; the markers were seen as a radiopaque metal density on mammogram, and as a hyperechoic linear structure with or without posterior shadowing on US. While breast MRI has proven better than mammography in evaluating tumour response after

NAC (28, 29), metallic markers may result in artefacts on MRI, based on clip quality, magnetic susceptibility, shape, size, position, orientation, and the MRI parameters used (29). In our study, the silver markers created a small signal void on MRI; however, the residual disease was easily evaluated on MRI. In this study, even when the tumour completely disappeared in response to NAC, we were still able to identify the tumour bed preoperatively by imaging as well as intraoperative by palpation. This can explain the low rate of positive margins as we had removed the whole pathologic tissue, including all tumour-bearing breast parenchyma guided by the metallic markers placed at the tumour margins. A reduction of 2.8 cm in tumour size, on average, as revealed by the centripetal displacement of the margin markers and a reduction in the palpable tumour size suggest that the tumour tissue had been replaced by fibrotic tissue in response to NAC, leading to a shrinkage of the margins. The use of radiopaque sterile silver rods for marking the borders of breast cancer is one of the few attempts of its kind, despite the fact that they have been routinely used for marking radiation portals with good safety in different body tissues by radiotherapists (30). We used silver wire, which is available on the market in the form of rolls of one meter in length and 1 mm in diameter, which can be cut into small pieces and sterilized by autoclaving. In comparison to commercial titanium clips, the silver markers are much less expensive, and their length can be adjusted to be easily palpated in the breast tissue during BCS. The use of silver markers and the spinal puncture needle for their insertion costs approximately 40 LE. The anticipated complications associated with leaving silver markers in the breast for a few months, migration from their original site, allergic reaction and infection were not reported in any of our cases. None of the patients complained of significant pain one day after the procedure. A few patients complained of discomfort owing to the superficially placed markers, and their complaints were easily addressed by counselling. Some limitations should be discussed in this study. Firstly, this was a retrospective study, and only those patients who had accepted to have silver marker insertion and had preoperative imaging for scheduled BCS after NAC were selected. Therefore, a selection bias may exist. Secondly, the number of cases was limited to only 64, which may not allow for a generalisation of our results to the total population. Further studies are required for the evaluation of this procedure. Thirdly, the insertion of the metallic marker using a spinal puncture needle is not a globally approved method.

Breast cancer localization using sterile silver markers before the initiation of NAC is safe, easy, inexpensive, and effective, causing no morbidity or significant pain to the patients.

Ethics Committee Approval: Our study was approved by the Mansoura University Ethics Committee Institutional Review Board (R.22.09.1869, date: 03.11.2022).

Informed Consent: All patients gave informed consent before enrolment in this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H., A.E.B., A.K., A.S., S.R., K.A., E.H.; Concept: A.H., A.E.B.; Design: A.H.; Data Collection and/or Processing: A.H., A.E.B., A.K., A.S., S.R., K.A., E.H.; Analysis and/ or Interpretation: A.H., A.K., A.S., S.R., K.A., E.H.; Literature Searching: A.H., A.K.; Writing: A.H., A.E.B., A.K., A.S., S.R., K.A., E.H.

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Letter to the Editor

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European Guidelines Concerning the Transplantation of Organs from Donors with a History of Breast Cancer

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Dear Editor,

The Council of Europe (CoE), based in Strasbourg (France), is an international organization that promotes cooperation among European countries in the areas of human rights, democracy, rule of law, culture and public health. Founded in 1949 by the Treaty of London, the CoE is composed of 46 member states. The CoE is a separate body from the European Union (EU), with 27 state countries, that have conferred some national legislative and executive powers to the EU, with the aim of achieving a high level of integration. In contrast, member states of the CoE maintain their sovereignty, but cooperate on the basis of common values and political decisions, and commit themselves through conventions. The CoE and the EU have a close collaboration in the field of transplantation of human organs*, tissues** and cells***, jointly promoting fundamental ethical principles, as the non-commercialization of substances of human origin, and common quality and safety standards. Within the CoE, work in the transplantation field is coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM), which recently published the 8th edition of the Guide to the quality and safety of organs for transplantation (1), providing professionals and authorities with guidance to ensure a high level of protection for organ donors and transplant recipients.

In Europe, organ transplantation activities have steadily increased during the last few decades, except during certain periods of the Coronavirus disease-2019 pandemic (2). This increase, however, has been insufficient to cope with the transplantation needs of the European population. In 2021, 36,548 solid organ transplants were performed in CoE member States, an activity that lagged behind the volume of the transplant waiting list, estimated to include more than 138,0000 patients per annum. Approximately 20 patients have died each day on the waiting list because no organ became available (3).

There are different reasons for organ shortage, as failure to identify and refer possible organ donors, opposition to postumous donation, or medical unsuitability. One reason why possible organ donors are deemed ineligible is a past or present history of cancer, due to the risk of transmitting cancerous cells, the development of which may be facilitated by the immunosuppressive treatments required by transplant recipients. Given the increase in the number of indications for transplants and the shortage of organs, along with a decline in the incidence of brain death and the increasing evidence about the safety limits in the utilization of organs from donors diagnosed with a variety of diseases, the current trend is to expand criteria for donor eligibility, particularly regarding donors with a history of cancer. In the 8th edition of the EDQM Guide on the quality and safety of human organs for transplantation (1), the chapter concerning the risk of transmission of cancer has been entirely reviewed to provide current evidence for assessing the risk of transplanting organs from donors with a past or present history of cancer, and from donors with a genetic predisposition to develop cancer. Though not legally binding, this document supports professional decision-making according to the best available evidence.

A history of breast cancer (BC) has a prominent place in the debate concerning the transplantation of human organs. BC is the commonest cancer type among women in Europe, and its incidence continues to rise (with 531,086 new cases, 141,765 deaths and 2,138,117 five-years prevalence in 2020). The cumulative risk of BC (0–74 years) for a European woman is 6.28% in Central and Eastern Europe, 8.45% in Southern Europe, 9.35% in Northern Europe and 9.69% in Western Europe. Western Europe is placed third in the world in terms of prevalence of

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BC, following Australasia (10.41%) and Northern America (9.71%) (4). In case of a donor with a history of BC, the risk of transmitting potentially fatal cancer cells to recipients of their organs is a major concern, notably depending on the type of BC. There is a wide variety of BC with the World Health Organization (5) describing 34 different histological BC subtypes. Some subtypes are associated with almost no risk of metastases, such as low-grade ductal carcinoma *in situ* (DCIS), while others are highly proliferative with a particularly unfavorable prognosis in the short term, such as triple negative BC, and others have a risk of late re-evolution, sometimes decades after the diagnosis, for example invasive lobular carcinoma. Therefore, before deciding on the clinical use of organs obtained from a woman with a past or current history of BC, it is essential to know the BC prognosis based on its histological subtype, molecular characteristics, including expression of hormone receptors, human epidermal growth factor-receptor 2 and proliferation index, together with stage, completeness of treatment, time since the diagnosis and regularity and normality of follow-up.

Tumor cell dormancy is a well-recognized phenomenon in BC. Tumor cells can spread to distant sites early during cancer progression. They can stay dormant and clinically undetectable after resection of the primary tumor for many years. Metastases in BC usually manifest asynchronously with the primary tumor and show variable time to become clinically detectable. For example, a large study (6) of 62,923 patients under 75 years of age treated for hormono-dependant invasive cancer [T0-2 N0-3 of the American Joint Committee on Cancer (AJCC) classification] showed the following risk of metastases at 20 years: T1N0: 13% (low grade 10%, intermediate grade 13%, high grade 17%), T1N1: 20%, T1N2: 34%, T2N0: 19%, T2N1: 26% and T2N3: 41%). Interestingly, the authors showed not only the importance of tumor size and lymph node involvement (stage), but also of tumor grade.

The EDQM has now reconsidered the criteria for acceptance of organs from donors with a history of BC, acknowledging the key role of medical teams in performing a risk-benefit assessment for each particular case. Since BC has high potential for late and aggressive recurrence and metastases, even after many years of complete remission, patients with BC should only be accepted as organ donors with the highest caution and for very selected recipients.

What Criteria Must be Checked Before Accepting an Organ Donation in Case of BC History?

First, an extended cancer-free period (generally more than 5 years) before accepting a donor with BC is recommended. Secondly, donor examination for BC recurrence and/or metastases, including careful clinical examination and imaging, is necessary even after a long disease-free survival. In patients with a history of BC, a whole-body computed tomography scan of thorax, abdomen, and pelvis, including cerebral scan in particular cases, should be carried out, if possible, to evaluate the current disease status and to ensure the highest possible safety for organ recipients. Any suspicious finding on imaging should be further evaluated for significance. If there are explicit features of active malignancy, organ donation should be discontinued. If there is doubt about a radiological diagnosis of malignancy, histopathological examination should be performed during organ recovery. In contrast, the routine screening of tumor markers (e.g., CA 15–3) is generally not recommended before donation, except for donors in whom tumor markers were previously used to monitor disease remission and with previous values available, to help assess the state of disease.

What are the Consensual Indications of Organ Procurement in Case of BC History?

Low and intermediate nuclear grade DCIS are considered as low risk for transmission. High nuclear grade DCIS (which can be associated with an occult invasive BC) and invasive BC stage 1A (T1N0, AJCC, 8th edition) with curative surgery and cancer-free period >5 years seems to be associated with low to intermediate risk of cancer transmission. All other invasive BC stages are considered as high-risk for transmission, independent of the presumed recurrence-free survival and treatment. Newly diagnosed invasive BC and past or present history of breast sarcoma are deemed to be of unacceptable risk for organ donation.

Different guidelines have been released in other regions outside the CoE. In the United States, the American Society of Transplant Surgeons estimates that, for lesions classified as pT1a or pT1b, organ donation would be possible after 10 years of remission, whereas it would no longer be indicated beyond pT1c, regardless of the time of remission (7). Conversely, the organ procurement and transplantation network/united network for organ sharing considers that the risk of transmission for invasive BC is high (>10%) due to the occurrence of late secondary lesions indicating that organs should not be used but only in exceptional situations (8). In the United Kingdom, the advisory committee on the safety of blood, tissues and organs (SaBTO) considers that donors diagnosed with a pT1a BC with a remission period of more than 10 years are associated with a low risk of disease transmission (0.1–2%) and pT1a BC with a remission period of 5–10 years with an intermediate risk (2–10%) (9). In France, the Agence de la Biomédecine (a state agency dealing with public health related issues regarding organ, tissue and cell transplantation) has established a list of breast specialists to perform a risk-benefit assessment for particular cases of donors diagnosed with a present or past history of BC.

In summary, in many countries, organs from donors with low risk of BC transmission are accepted for clinical use, while keeping in mind the theoretical risk of transmission due to possible late cell dormancy. Traceability (data to identify every organ from donor to recipient and *vice versa* must be kept for a minimum of 30 years) and biovigilance (reporting and management of serious adverse events and reactions) are legal requirements in the EU setting and in standards promoted by the CoE (10). For instance in France, to optimize transplantation security, the Agence de la Biomédecine has established a traceability system called "CRISTAL donor/recipient". Thus, if the recipient of a solid organ develops a cancer and there is suspicion of a donor-origin, the various medical teams in charge of patients who have received organs (and tissues) from the same donor must be alerted to activate a coordinated assessment, investigation and management of the case and take preventive and therapeutic measures on recipients affected and recipients at risk.

The number of organs accepted from donors with a previous or current history of cancer seems to be increasing, but the frequency of documented cancer transmission is low and estimated at 3–6 cases per 10,000 solid organ transplants (11). Under-reporting of transmission cases due to the previous lack of mandatory reporting cannot be ruled out. Within the EU legal framework, and with mandatory reporting to national health authorities (including suspected/confirmed cases of malignancy transmission), it should be possible in the future to more precisely assess the frequency of malignancy transmission through organ transplantation. Ideally, to better understand this risk, detailed donor cancer data should be included in national registries and efforts be made to define a basic data set to link international data.

Donors with a Genetic Predisposition to Cancer

Several genetic conditions (e.g., *BRCA1, BRCA2, PALB2, CDH1, PTEN*) predispose to BC. For EDQM, in a donor with a known genetic predisposition, two safety precautions must be considered. First, a careful examination of the organs known to be at risk of developing malignancy must be performed, to ensure no active cancer is present (e.g., breasts and ovaries for *BRCA1/2*, breasts and stomach for *CDH1*). Secondly, transplanting an organ with a genetic risk of malignancy is not advised (e.g., uterus for *PTEN*). When possible, a local expert in cancer genetics should be consulted. In France, the Agence de la Biomédecine has established a list of onco-geneticists to perform a risk-benefit assessment for particular cases of patients having a genetic predisposition of BC.

Specific Characteristics of Living Donors

Unlike the situation with a deceased donor, in the case of a living donor with a personal history of BC, it is possible to propose a complete workup to assess the individual risk of transmission. Indeed, there is more time to decide the eligibility compared to deceased donors, and there are no or minimal restrictions to perform a complete follow-up workup, including clinical examination of the breasts and complementary tests such as mammography, ultrasound or breast magnetic resonance imaging, CA 15–3 assay or positron emission tomography-computed tomography. However, the normality of a complete workup should not authorize organ donation in case of high-risk of transmission, and recommendations should also be applied in this context. Nonetheless, potential solutions in the case of living donors for reducing the risk of cancer transmission during transplantation are currently under investigation, such as circulating markers assays (tumor cells and tumor DNA), but to date they are not validated in clinical practice (12).

Treatment of Donor-transmitted Cancers and Future Perspectives

When diagnosed, donor-transmitted cancers are difficult to treat. Indeed, treatment may consist in cessation of immunosuppression, and/or explantation of the graft, and/or classical oncological treatments. This treatment is challenging and may cause several complications, including the need for re-transplantation in case of vital organs. Nonetheless, new possibilities are currently under investigation. For instance, mammalian target of rapamycin (mTOR) inhibitors, which have both immunosuppressive and antiproliferative properties, are increasingly being used after organ transplantation in clinical trials (13). Interestingly, they have potential advantages as anti-cancer agents for virus-induced malignancies but also for other types of cancers. Some authors have hypothesized that mTOR inhibitors could have a benefit for patients receiving an organ from a donor with a history of malignancy; however, at present further research is needed to evaluate the benefit (13). Moreover, some cases treated with immune checkpoint inhibitors to enhance immune response have been published, with positive outcomes (14, 15). In the treatment of donor-transmitted cancers, the link between immunity and cancer plays a central role. Within this rapidly growing field of research, scientific advances may provide new therapeutic leads in the future.

Footnotes

* Organs: Heart, lung, liver, kidney, pancreas, and small bowel

** Tissues: Cornea, bones, cartilages, heart valves, and skin

*** Cells: Hematopoietic stem cells

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