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Turkish Federation of Breast Diseases Societies

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

SIS ISS SENOLOGIC INTERNATIONAL SOCIETY INTERNATIONAL SCHOOL OF SENOLOGY

NCBC National Consortium of Breast Centers

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European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

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

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

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

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

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

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

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

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

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European Journal of Breast Health

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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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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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Contents

European Journal of Breast Health

Contents

CASE REPORTS

EDITORIAL SUMMARY

Systematic Review

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Adverse Effects of Intraparenchymal and Peritumoral Application of Isosulfan Blue Dye in Sentinel Lymph Node Mapping in Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

We investigate the evidence for adverse effects of intraparenchymal and peritumoral application of isosulfan blue dye in sentinel lymph node (SLN) mapping in breast cancer patients. A meta-analysis on the adverse effects of intraparenchymal and peritumoral application of isosulfan application in SLN mapping was conducted using Medline and Embase databases up to 2023. Procedure-based adverse reactions were divided into three grades: Grade I (allergic skin reactions), Grade II (hypotension) and Grade III (requiring vasopressor support). Heterogeneity was expressed with I-squared and tau statistics. Subgroup analysis was conducted for administrative route. Univariable meta-regression was performed to assess dose-response effect on adverse reactions. Sensitivity analysis was conducted using fixed effect modelling. A total of 19,183 patients were identified from eight studies. The pooled total adverse event rate after isosulfan administration was 11.65 events per 1,000 patients [95% confidence interval (CI) 7.44–18.19]. The rate of Grade I reactions was 7.96 per 1,000 (95% CI 4.08-15.46); Grade II 0.08 per 1,000 (95% CI 0.00–1.31), Grade III 1.86 per 1,000 (95% CI 0.94–3.66), with no reported mortalities. Intraparenchymal administration was associated with 15.16 events per 1,000 (95% 8.64–26.45), versus 7.04 events per 1,000 (95% CI 5.24–9.45) in peritumoral administration (p=0.02). Univariable meta-regression did not show a significant association between volume of dye infused and total adverse events (-0.164 events per mL, 95% CI -0.864 to 0.534, p=0.645). Isosulfan has low adverse event rates regardless of injection technique or volume administered. Clinicians should have a high level of confidence in its use as an agent for SLN mapping, especially when administering it peritumorally.

Keywords: Breast neoplasms; isosulfan; sentinel lymph node mapping; systematic review; adverse events

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Key Points

- Isosulfan blue has an acceptable safety profile for sentinel lymph node mapping in breast cancer surgery.
- Intraparenchymal, intraparenchymal administration of isosulfan blue has a significantly higher adverse event rate than peritumoral administration.
- There was no dose-response relationship between isosulfan administration and the incidence of adverse events.

Introduction

Breast cancer is the second most common cause of female cancer mortality in the UK, after lung cancer (1). The sentinel lymph node (SLN) is the first node receiving lymphatic drainage from the breast tumour bed, and SLN status is an important determining factor in breast cancer prognosis, patient survival and treatment outcomes (2, 3). The introduction of SLN biopsy is one of the greatest advances in the surgical treatment of breast cancer. Following the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (the ALMAC) trial by Mansel et al. (4), SLN mapping is widely accepted as the gold standard technique in axillary lymph node mapping, and has an equivalent oncological outcome, with reported lower complication rates, compared to axillary node dissection (AND). AND involves the dissection of the entire axillary lymph node chain and results in greater morbidity relating to lymphoedema and injury to key stractures such as the axilliary vein, and in a considerable percentage of cases, the

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histopathological results following AND are negative, which means it could have been avoided. With the increasing use of SLN mapping, and its diagnostic accuracy therefore, AND is reserved for patients with axillary lymph node disease after SLN mapping.

Current SLN mapping agents include a variety of blue dyes and radioisotopes (5, 6). The principal problems involved with the latter, are their technological complexity and high costs. Different blue dyes have been used in SLN mapping and include methylene blue, patent blue and isosulfan blue, with similar reported rates of diagnostic accuracies in the setting of SLN mapping in breast cancer (7, 8).

Methylene blue is readily available and considered less expensive than the other two dyes. Although, it has a lower allergic and dermatological and allergic side-effect profile side effect profile compared to patent blue and isosulfan dyes, it is associated with skin necrosis and multi-systemic effects, especially the cardiovascular system and GI tract at higher concentrations (9). Isosulfan blue, an aniline dye (2.5-disulfan isomer of patent blue), was first introduced as an agent in SLN mapping by Giuliano et al. (10). It operates by binding to albumin in the lymphatic system in the axilla, allowing the sentinel node to be delineated. Its adverse effect profile, including allergic skin reactions, soft tissue necrosis and oxygen desaturation causing significant morbidity to patients, have been described in previous studies (11-14).

The aim of this meta-analysis was to synthesize evidence about the adverse effects of isosulfan blue dye in SLN mapping to raise awareness amongst clinicians. To the best of our knowledge, this is the first Level 1 study evaluating the adverse effects of intraparenchymal and peritumoral application of isosulfan dye in SLN mapping in breast cancer.

Materials and Methods

Search Strategy

The meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (15). Medline and Embase databases were searched from 1999 to 2023, inclusive. Search terms included "adverse", "reaction", "isosulfan", "blue", "dye", "sentinel", "lymph", "node", "biopsy", "breast", "cancer" together with the Boolean Operators "AND" and "OR".

Inclusion criteria were: 1) Breast cancer; 2) SLN mapping or biopsy; and 3) Use of isosulfan blue dye. Exclusion criteria were: 1) Sentinel node mapping in other cancers, such as cutaneous melanoma; 2) Single patient case reports; and 3) Non-English language papers. These criteria were applied throughout the titles, abstract screening stages and the full-text article reviewing process.

Data Extraction

Quantitative data were extracted for demographics, volume of isosulfan blue dye and grade of adverse reaction.

We used the 3-level classification of adverse reaction previously described by Montgomery et al. (16): Grade I included skin changes such as urticaria, pruritis, and rash; Grade II reaction included hypotension (systolic blood pressure <70 mmHg) following administration; and Grade III reaction was defined as hypotension, and other cardiovascular and respiratory complications requiring vasopressor support.

Statistical Analysis

Meta-analysis of proportions was conducted on included papers as described by Barker et al. (17) to generate a pooled event rate for all events and grouped by grade. A generalised linear mixed model was used with random effects and a logit transformation to generate the pooled event rate. A Clopper-Pearson interval was used to calculate 95% confidence intervals (CIs). A p-value <0.05 was regarded as statistically significant. Funnel plots and Egger's test were used to assess publication bias.

Meta-analyses are presented as forest plots with events per 1000 patients as the outcome measure. Heterogeneity is expressed using the I-squared and tau statistics. Subgroup analysis by route of administration of isosulfan was conducted for all events. The chi-squared test was used to assess statistically significant differences between groups. Univariable meta-regression was performed on studies reporting volume of administration to assess for a dose-response effect of isosulfan administration on adverse reactions. A sensitivity analysis was also conducted using fixed effect modelling and is presented as a Supplementary Figure 1. All analyses were conducted with R version 4.3.0 (R Foundation, Vienna, Austria) with meta version 6.5 (18) and metafor version 4.2 (19) packages.

Results

Search Results

The initial electronic database search yielded 105 articles, with three additional studies being included following screening of references. From these, 10 articles were duplicates and 75 were non-full text articles (Figure 1).

Twenty-three full-text articles were subsequently reviewed and a further 15 articles were excluded for various reasons (non-breast cancers such as cutaneous melanomas, other blue dyes used in combination with isosulfan blue dye and results not fully available). A further 10

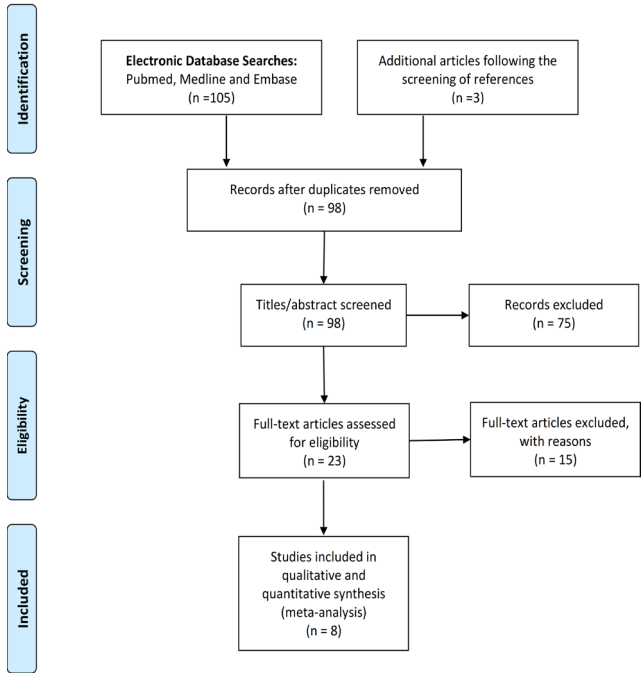

Figure 1. PRISMA flowchart of inclusion and exclusion of studies

articles were excluded as they were case reports. A further five articles were excluded because they only investigated the changes in pulse oximetry following isosulfan blue administration with no clear cut-off desaturation level established for definition of hypoxaemia.

Finally, eight articles were included for qualitative and quantitative analysis.

Summary of Results

The selected studies included 19,183 patients. The route of administration was reported in 14,205 cases (intraparenchymal injection=7,955 patients; peritumoral injection = 6,250 patients.) The mean volume of isosulfan blue dye injected from 12,110 cases was 4.3 mL (SD ± 0.98).

There were 231 adverse events reported across all studies after isosulfan administration: Grade I reactions were seen in 184 patients (79.7%); Grade II in 4 patients (1.7%) and Grade III reactions in 43 patients (18.6%) (Table 1). Thirty-eight patients required vasopressin support and 19 patients required admission to the intensive care unit for post-procedure monitoring. However, none of the patients required emergency intubation. There was no mortality associated with isosulfan blue dve use.

Meta-Analysis

The pooled total adverse event rate after isosulfan administration was 11.65 events per 1,000 patients (95% CI 7.44-18.19, Figure 2). The rate of grade I reactions was 7.96 per 1,000 (95% CI 4.08–15.46, Figure 3); grade II 0.08 per 1,000 (95% CI 0.00–1.31, Figure 4) and grade III 1.86 per 1,000 (95% CI 0.94–3.66, Figure 5).

On subgroup analysis by route of administration, intraparenchymal administration of isosulfan was associated with a total adverse event rate of 15.16 events per 1,000 (95% 8.64–26.45), whilst peritumoral administration had an adverse event rate of 7.04 events per 1,000 (95% CI 5.24–9.45). This difference in adverse event rates was significant at $p = 0.02$ (Figure 6).

Univariable meta-regression of studies reporting the volume of isosulfan did not show a significant association of volume infused with total adverse events (-0.164 events per mL, 95% CI–0.864 to 0.534, $p = 0.645$). Funnel plotting of the included studies was symmetrical (Figure 7) and Egger's test gave $p = 0.239$, implying publication bias.

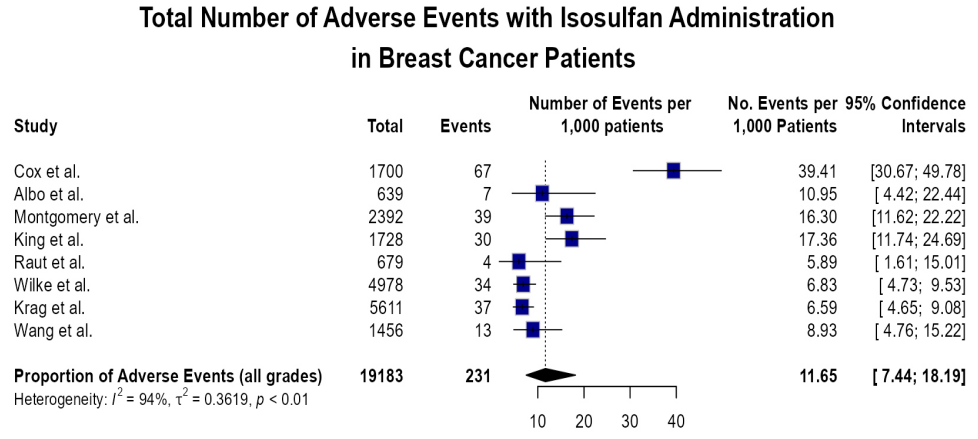

Figure 2. Forest plot of random effects meta-analysis of all adverse events after isosulfan administration

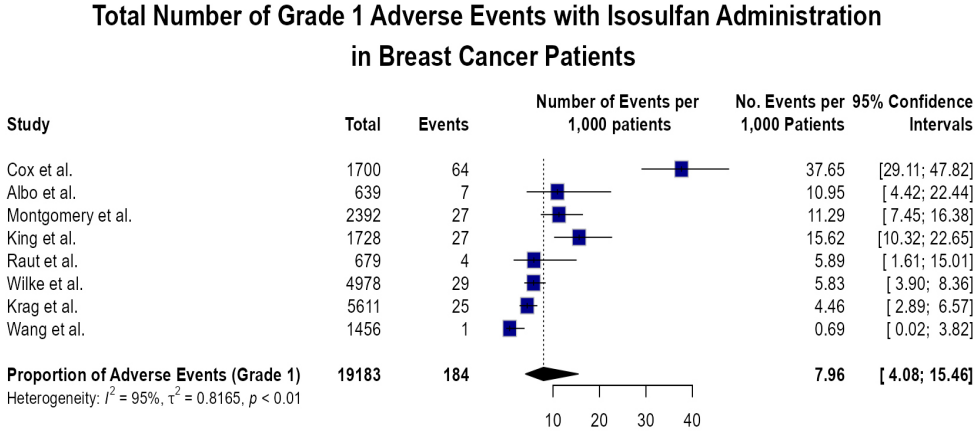

Figure 3. Forest plot of random effects meta-analysis of grade i reactions after isosulfan administration

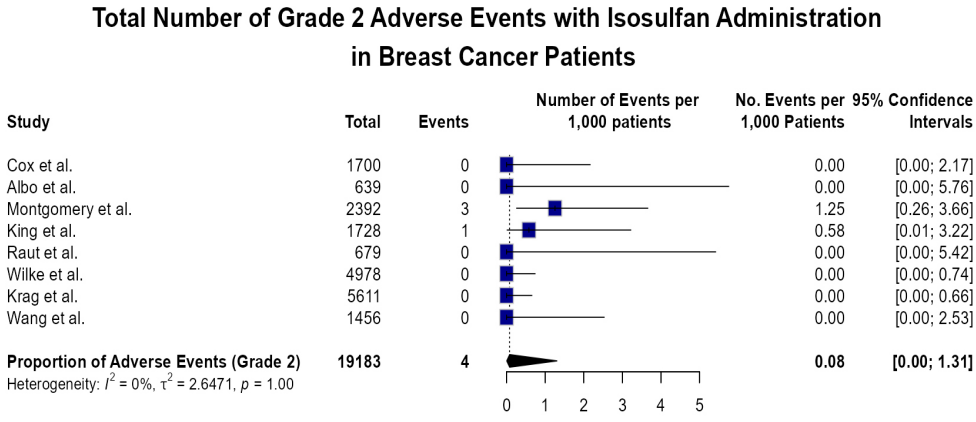

Figure 4. Forest plot of random effects meta-analysis of grade ii reactions following isosulfan administration

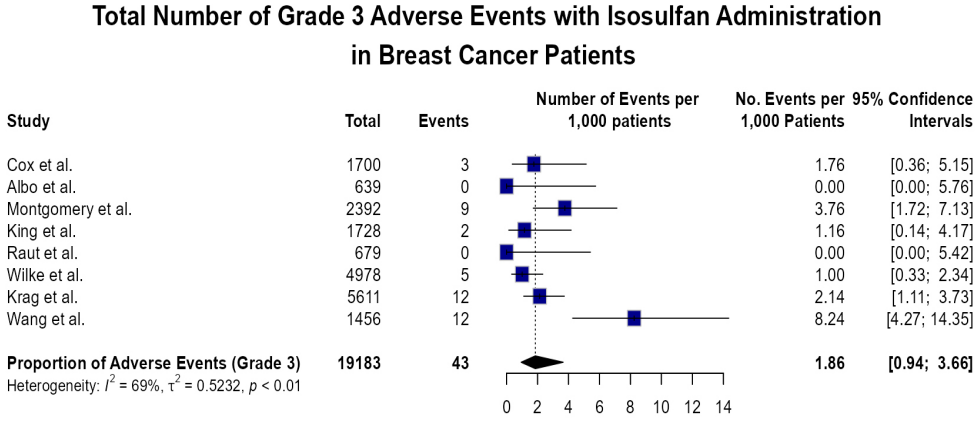

Figure 5. Forest plot of random effects meta-analysis of grade iii reactions after isosulfan administration

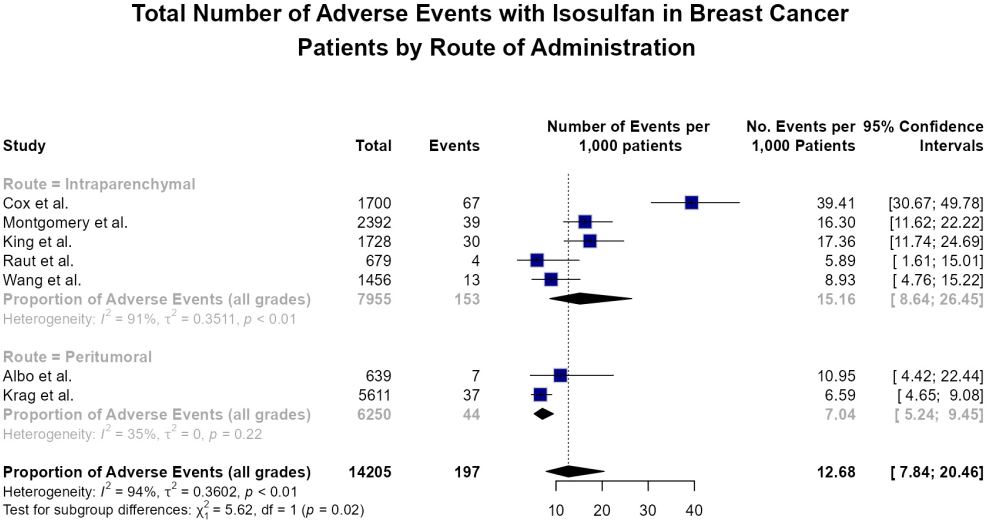

Figure 6. Subgroup analysis of all adverse events after isosulfan administration by route of administration

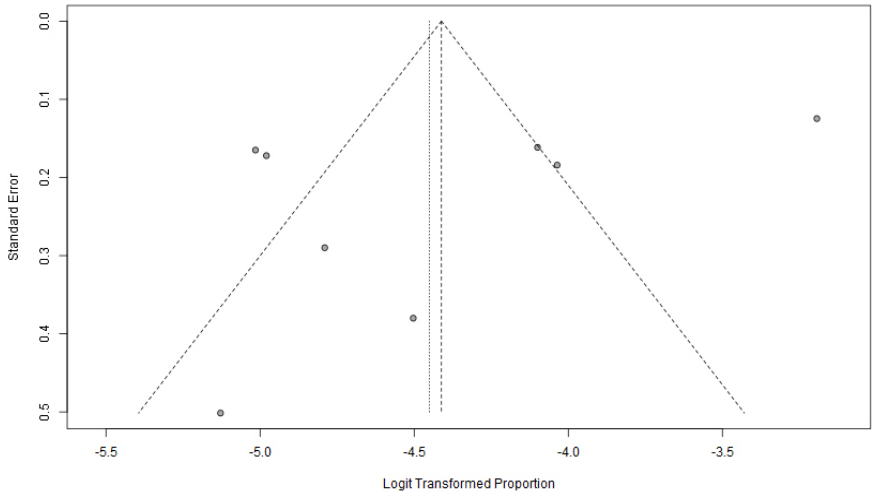

Figure 7. Funnel plot of included studies by total adverse even

Discussion and Conclusion

This is the first meta-analysis investigating the safety profile of intraparenchymal and peritumoral application of isosulfan blue as a sentinel node mapping agent in breast cancer. We show low adverse event rates, of which the majority are minor and non-life threatening, associated with its use. We further show that peritumoral infiltration of the dye is associated with significantly lower rates of adverse events than intraparenchymal infiltration. Our findings have broad implications for the use of isosulfan more widely in breast cancer surgery and in the technique for administration.

The paradigm of early breast cancer management has shifted from AND towards conservative diagnostic techniques, such SLN mapping in axillary staging, with comparative diagnostic outcomes with both techniques, while the latter is associated with a lower rate of lymphoedema as well as nerve and vascular injuries (3, 20).

Techniques for mapping and identification of the SLN can be broadly divided into radioisotopes and dyes (5, 6). Some investigators prefer the use of nuclear medicine techniques to identify the SLN due to the greater simplicity of those techniques compared to the use of dyes. Compared to dyes, however, they are associated with higher operative costs and some studies have highlighted their technological complexity (21). In this regard, the use of dyes is more economically viable, and this is important in healthcare resource allocation especially in developing countries. With these disadvantages of nuclear medicine, blue dyes have become popular SLN mapping agents. The commonly used blue dyes are methylene blue, isosulfan blue and patent blue. Identification rates of SLN are similar to that obtained with nuclear medicine techniques, reported to be as high as 98% in recent reports (23). Furthermore, once the SLN is identified, accuracy is the same, irrespective of the method used and the lymph node detection rate.

Isosulfan blue dye (2.5-disulfan isomer of patent blue) was one of the first dyes used in SLN mapping. It was adopted to breast cancer patients from Morton et al. (24) work in cutaneous melanoma (10). It is however not without adverse reactions which can compromise patient safety. Some of the frequently reported adverse reactions include changes to pulse oximetry reading, and soft tissue and body fluid discolouration, as well as allergic and anaphylactic (type 1 hypersensitivity) reactions (25-27).

Methylene blue, on the other hand, is a derivative of phenothiazine, and offers three main advantages over patent blue and isosulfan dyes: it is more readily available, cost less and appears to be a lower risk of anaphylaxis compared to the other dyes (9, 28). It does however have some disadvantages in comparison to isosulfan blue dyes. Firstly, it diffuses more rapidly in peripheral tissues, staining a larger portion of the breast with the blue dye and, to a certain extent, hampering the procedure. There are also reported cases of skin necrosis, cardiovascular and gastro-intestinal symptoms associated with high doses of methylene blue use (29, 30).

In our meta-analysis, we employed the 3-level systematic classification (Grades I-III) used by Montgomery et al. (16). Comparatively, we found our pooled total rate of adverse reaction to be 1.2%, similar to 1.6% in the review by Montgomery et al. (16) at the Memorial Sloan-Kettering Cancer Centre. Our study revealed that Grade I reactions were the most common following administration of isosulfan blue dye.

Proposed mechanisms for adverse reactions to isosulfan blue dye can be categorised into antibody-mediated, or anaphylactic, and antibody-independent, or anaphylactoid, pathways (31). Antibody-mediated, immediate-type hypersensitivity reactions have been suspected as the cause of reactions to patent blue dye, mediated by immunoglobulin E antibodies. Anaphylactic reactions usually occur after previous sensitisation to isosulfan blue and related patent blue agents, and are associated with Grade II and III reactions, but can result in Grade I reactions too.

Another study by Kalimo et al. (32) reported skin reactions on skin prick test two weeks following blue dye injection. They recommended a role for pre-lymphography skin prick testing to reduce Grade I reactions.

It is interesting that although isosulfan blue contains sulfa (SO_2NH_2) moieties, patients with a sulfa allergy are not more likely to experience

an allergic reaction to isosulfan blue dye, as reported in the study by Montgomery et al. (16), where only 2.6% of patients with a sulfa allergy manifested an allergic reaction to isosulfan blue.

Grade II and III reactions (anaphylactic shock with or without vasopressor support) was first reported in 1985 by Longnecker and colleagues following the administration of 0.5ml of 1% isosulfan blue subcutaneously (33).

Albo et al. (13) also report a Grade III reaction rate of 1.1% in their study of 1456 patients where 12 patients experienced severe cardiovascular compromise within 15 to 30 minutes following administration of isosulfan blue. In their study, all affected patients required aggressive resuscitation and subsequently admission to intensive care for post-operative monitoring. Our study reports a rate of 0.08 per 1,000 of Grade II reactions and 1.86 per 1000 patients of Grade III reactions. Our rates of Grade III events are lower than those reported by Albo et al. (13) and another study by Cox et al. (34). Despite our low rates of Grade II and III reactions in the meta-analysis, close monitoring is important in Grade II and II reactions as biphasic anaphylactic reaction with patent blue dye and its monomers, such as isosulfan, have been reported by Liang and Carson (25) when hypotensive episodes occurred 15 minutes and two hours following blue dye exposure.

In the study conducted by Raut et al. (27) the authors evaluated the role of glucocorticoids in reducing the adverse effects of isosulfan blue dye. In their study, patients who were given isosulfan blue dye were also administered a glucocorticoid, diphenhydramine, and famotidine intravenously just before or at induction of anaesthesia. Preoperative prophylaxis was found to reduce the severity, but not the overall incidence, of adverse reactions of isosulfan blue dye. Crucially, there were no life-threatening reactions noted in patients treated with preoperative prophylaxis. Based on these results, there is potentially a role for routine administration of prophylaxis to patients receiving isosulfan blue for lymphatic mapping and SLN mapping.

Subgroup analysis by route of administration of isosulfan was conducted for all events. We showed a much lower rate of adverse reactions associated with peritumoral administration of the dye compared to intraparenchymal administration. It is widely agreed that the accuracy of SLN detection is irrespective of route of dye administration but our study suggest the lower rate of adverse reactions with peritumoral injection makes it superior. It is also worth stating that another technique which has increasingly come into practice is subareolar injection. This approach is however associated with nipple complications which may be a problem for immediate breast reconstruction. Our study did not focus on this technique.

Studies reporting volume of administration to assess for dose-response effect of isosulfan administration showed no effect on the rate of adverse reactions, further reinforcing the safety of the dye.

Current consensus guidelines in the UK (35), US (36) and Europe (37) recommend blue dye and radioisotope localisation of SLN, but do not specify the actual dye used as diagnostic accuracies in SLN mapping associated with all commonly used dyes are comparable. Indocynanine green (ICG) is a newer agent which fluoresces proportionally to its uptake by tissues. This fluorescence can be quantified with cameras used intra-operatively after injection with the brightest points corresponding to lymph nodes. ICG has been shown to have superior detection rates of positive SLNs compared to blue dye and radioisotope mapping (38). Adverse event rates are lower than isosulfan, while cost per application is similar (39). This method continues to be evaluated and has not found widespread adoption. The use of newer techniques may require a learning curve as well as investment in new equipment, such as detectors, which may be prohibitive.

Isosulfan blue continues to be used widely despite the known limitations, as an accurate mapping modality, with a wide evidence base and familiarity amongst surgeons. This study strengthens the case for isosulfan as a SLN mapping agent by quantifying its low overall adverse event profile and extremely low rate of serious adverse events.

Footnotes

Authorship Contributions: Surgical and Medical Practices: J.A., P.P., S.S.; Concept: J.A., A.Y.; Design: J.A., A.B., A.Y.; Data Collection or Processing: J.A., A.B., A.Y.; Analysis or Interpretation J.A., A.B., A.Y.; Literature Search: J.A., A.B., A.Y.; Writing: J.A., A.B., A.Y.

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

Financial Disclosure: The author declare that this study received no financial. disclosure.

Table 1. Summary of included studies

Author, year	Evidence level	No. of patients	Route used	Volume used (mL)	Total Reactions	Grade 1 reaction	Grade 2 reaction	Grade 3 reaction
Cox et al. (33)	IV	1700	Intraparenchymal	5	67	64	0	3
Albo et al. (13)	III	639	Peritumoral	-	7	7	0	0
Montgomery et al. (16)	III	2392	Intraparenchymal	3.9	39	27	3	9
King et al. (39)	III	1728	Intraparenchymal	2.8	30	27	1	2
Raut et al. (26)	III	679	Intraparenchymal	5	4	4	0	0
Wilke et al. (40)	III	4978	-	-	34	29	0	5
Krag et al. (41)	II	5611	Peritumoral	5	37	25	0	12
Wang et al. (25)	III	1456	Intraparenchymal	-	13	1	0	12

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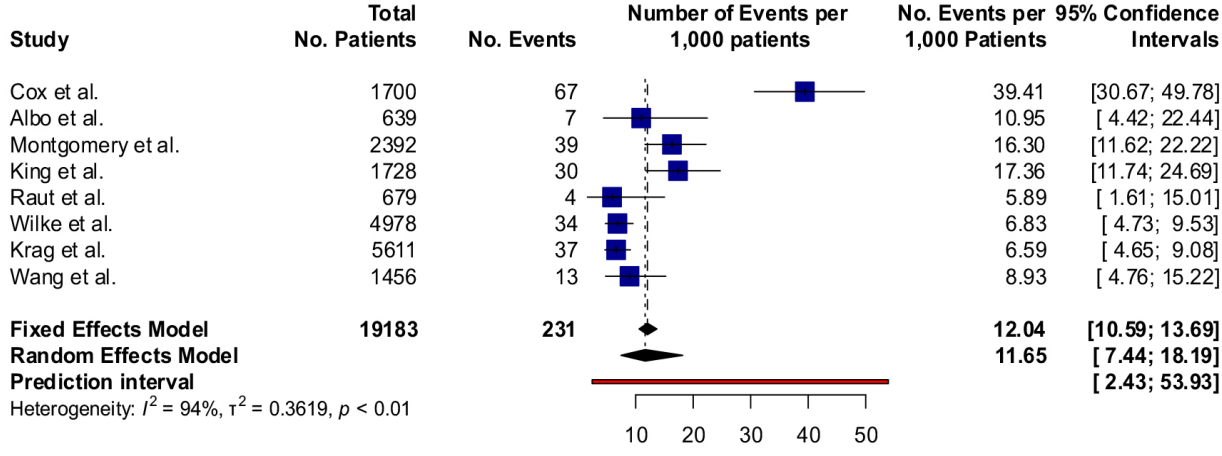

Supplementary Figure 1. Sensitivity analysis of meta-Analysis of total adverse events after isosulfan administration with fixed effects model

Review

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A Comprehensive Review on Current Knowledge and Future Potential of Topical Therapies in Breast Cancer Treatment

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ABSTRACT

Breast cancer remains one of the most prevalent malignancies among women globally. Despite advances in therapeutic options, the prognosis often remains challenging. Breast cancer typically originates in the epithelial lining of glandular tissue ducts (85%) or lobules (15%). Initially confined to these areas (*in situ*), it generally remains asymptomatic and poses little risk of metastasis. The primary treatments for breast cancer include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Although these interventions have advanced significantly and have improved patient survival rates, they are connected with numerous im mediate and long-term side effects. Effective breast cancer treatment aims to maximize efficacy while minimizing adverse effects. Given that many breast cancers are specific to the breast, developing safe and targeted therapeutic strategies will be of benefit. This review examined the current literature on the effectiveness of topical therapies for breast cancer. Studies and clinical trials were evaluated that have investigated these treatments, focusing on their safety, ease of application, and patient acceptance. Recently, topical drug delivery is transforming breast cancer therapy, offering precision and reduced systemic toxicity. Emu oil-enhanced tamoxifen showed superior transdermal effectiveness, while raloxifene gel achieved 2.77 times greater bioavailability than oral forms. Tamoxifen nanoemulgels and microneedle arrays with resveratrol further enhanced localized delivery, These therapies have gained patient acceptance due to their non-invasive nature, lack of gastrointestinal side effects, ease of application, and favourable safety and therapeutic profiles and setting a new benchmark for innovative and patient-friendly treatments. This review summarizes the findings from various studies, highlighting the benefits and limitations of topical therapies. Topical therapies offer a promising noninvasive option for breast cancer treatment with fewer side effects. These treatments have shown favorable therapeutic and safety profiles, making them an attractive option for patients.

Keywords: Breast cancer; topical treatment; breast skin; local transdermal therapy; nanoformulation

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Key Points

- Topical therapies are localized treatments that target the breast tumour location specifically.
- By limiting the drug's exposure to the rest of the body, this strategy lowers the possibility of systemic adverse effects.
- The efficacy of the therapy may be increased by direct application to the tumour location.
- These therapies function by directly targeting cancer cells through skin penetration, which can help minimise tumour size and relieve symptoms.
- To increase the overall effectiveness of treatment, topical treatments are frequently used in conjunction with other therapies including radiation, surgery, or systemic chemotherapy.

Introduction

In 2022, Globally 670,000 individuals died of breast cancer. Around fifty percent of all breast cancers occur in women who have no recognised risk factors beyond their gender and age. In 2022, breast cancer was the most common cancer among women in 157 of 185 countries (1). It can affect women post-puberty, with incidence increasing notably later in life, equating to one new case every 14 seconds. Survival is more difficult in advanced stages of cancer development. More than fifty percent of Indian women have breast cancer at stages three and four at diagnosis.The post-cancer survival rate for women with breast cancer is reported at 60% in India, while in the United States, it stands at 80% (2). Breast cancer chemoprevention may be necessary for women who are at an increased risk of developing the disease. This entails using pharmacological medications to delay the early stages of carcinogenesis and development.

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Premalignant cells lead to invasive illness. Current standards imply that tamoxifen and raloxifene were administered orally for a period of five years. However, systemic exposure to these medicines is linked to a higher risk of endometrial cancer and thromboembolism (3). Advances in therapeutic interventions have been facilitated by the increasing incidence of breast cancer. As a result, the administration of local and systemic antitumor medications has improved patient survival rates, including survival without illness and overall survival (4). In clinical and survivorship studies for breast cancer, however, standard of living has surpassed survival as the most important outcome metric due to technological advances in disease detection and treatment over time (5).

Individuals who have received a breast cancer diagnosis undergo a variety of management strategies, such as hormonal therapy, radiation therapy, targeted therapy, chemotherapy, and conserving surgery (lumpectomy) (6). Less invasive alternatives to surgery include cryotherapy, microwave irradiation, radiofrequency ablation, laser irradiation, and high-intensity focused ultrasound ablation. The most suitable candidates for these interventions are patients who have small (2-3 cm) tumors that are at least 1 cm away from the chest wall or skin and have minimal to no *in situ* component (7). Despite this, the majority of these approaches have significant limitations; therefore, it is imperative to explore innovative therapeutic methods (8). The primary objectives of treatment for individuals with distant metastases are typically to increase survival rates and life expectancy. For the treatment of breast cancer, a number of modern medications are suggested (9). In individuals at increased risk of developing breast cancer, the administration of anti-estrogens (e.g., raloxifene or tamoxifen) as part of medical therapy may prevent the disease. In certain circumstances where a woman has an elevated risk of developing cancer, an additional preventive measure involves the surgical removal of both breasts (10).

The emphasis on early-stage breast cancer has grown, due to the awareness of the treatment's long-term impact on health, patient involvement in treatment selection, and the availability of less invasive alternatives offering comparable medical benefits (11). Consistently, over the course of several years, clinical research has demonstrated that the majority of therapeutic approaches reduce relative recurrence rates across the risk spectrum as determined by anatomical stage (12).

Recent research findings from countries that have robust early-stage breast cancer screening programs suggest that the prognosis for the majority of women diagnosed with this malignancy continues to improve (13). Advances in treatment and early detection for breast cancer have led to better outcomes for women diagnosed with small, early-stage tumours. These patients often receive a combination of treatments known as "multidisciplinary treatment". This approach has greatly improved their chances of recovery, lowering the risk of cancer recurrence and increasing survival rates (14). However, the treatments are not without their drawbacks, both immediate and prolonged, including cardiovascular complications, an increased risk of secondary cancers, peripheral neuropathy, anemia, myelosuppression, thrombosis, and psychological distress (15). Furthermore, it is possible that the decreased survival rate is attributable to the rapidity of cancer development and metastasis (16). For breast cancer treatment to guarantee patients a high quality of life, it must be as effective as feasible while causing the fewest adverse effects possible. A carefully selected combination of therapeutic interventions affords patients the opportunity to optimize their treatment outcomes while simultaneously mitigating or eradicating unfavourable consequences, recurrence and resistance (17).

Despite the efficacy of these medications being established through successful breast cancer preventive studies, they have been poorly received by women at high risk for developing the disease (18). Reductions in quality of life, the likelihood of more severe side effects, as well as healthy women's unwillingness to use oral medicine for prevention, are among the factors. However, in order to manage breast cancer, the medication should only be applied to the breast; systemic exposure is unnecessary and potentially harmful (19).

Most breast malignancies are non-metastatic and breast-specific, including ductal carcinoma (over 75% of cases) and lobular carcinoma, both treatable with targeted therapy. Developing safe therapeutic strategies for breast cancer is important, therefore (20). Transdermal drug delivery (TDD) is an effective means of delivering drugs via the skin, reducing the risks and limits associated with oral medication administration. TDD is an effective alternative to oral treatment, avoiding gastrointestinal absorption, hepatic first-pass metabolism, and minimizing deleterious effects from peak plasma drug concentrations (21).

The investigation of topical administration of anticancer medications to the epidermis of the breast has also been undertaken as a targeted therapy strategy (22). The unique anatomical structure of the mammary papilla (nipple) presents a possible avenue for administering drugs directly to the underlying breast tissue. The nipple's surface duct apertures are directly connected to the numerous terminal duct lobular units of the breast (23). Moreover, the epidermis of the nipple-areola complex are thinner compared to the skin. The nipple-areola complex comprises various appendages, including sebaceous, apocrine, and eccrine perspiration glands, all of which have the potential to serve as transport routes to the underlying breast tissue (24, 25). This review offers a concise synopsis of the research conducted on topical treatments for breast cancer, encompassing *in vitro*, preclinical, and clinical investigations.

A Critical Analysis of Recent Research on Topical Breast Cancer Treatment

Endoxifen *In Vitro* Evaluation in Human Epidermis

To enhance endoxifen (ENX) uptake to match that of transdermal estradiol (EST), Lee et al. (26), studied the skin permeation of tamoxifen's metabolites, N-desmethyl-4-hydroxytamoxifen (ENX) and 4-hydroxytamoxifen (4-OHT) through human skin. Oral tamoxifen, despite its efficacy in breast cancer prevention, has low acceptance due to adverse effects. The study found that ENX's skin penetration was initially inferior to 4-OHT. However, adding 1% oleic acid (OA) significantly enhanced ENX absorption and tissue penetration over 24 hours. For effective transdermal delivery using a 60% ethanolic vehicle, the optimal OA concentration was 0.25–0.5%. Combining ENX with OA improved skin deposition and absorption to levels comparable to EST. While 4-OHT also showed increased penetration, ENX's improvement was more pronounced, indicating its promise for transdermal delivery (26).

Treatment of Breast Cancer via Iontophoretic Administration

Komuro et al. (27), applied iontophoresis to the nipple as an innovative drug delivery system (DDS) to enhance miproxifen phosphate (TAT-59) efficacy against ductal tumors compared to systemic delivery (IP

administration). Using rat epidermis, they found that iontophoresis facilitated TAT-59 transfer. Autoradiography confirmed direct delivery of TAT-59 to lactation ducts via IP administration. The plasma concentrations of TAT-59 and its active metabolite DP-TAT-59 were lower following IP treatment compared to DDS. In mammary tissue, DDS delivery provided drug availability approximately three times greater than IP treatment at a six-fold lower dosage. This approach minimizes systemic exposure and potential adverse effects because of low plasma concentrations. The study concluded that DDS effectively delivers DP-TAT-59 to ductal lesions, highlighting its suitability for targeted therapy (27).

Drug Delivery via Transpapillary Means to the Papilla and Breast

The objective of the research conducted by Dave et al. (24) investigated the topical administration of the hydrophobic compound EST and the hydrophilic substance 5-fluorouracil (5-FU) to the breast via the mammary papilla (nipple).

***In Vitro* Diffusion Study**

In vitro diffusion experiments using Franz diffusion cells showed that the penetration of 5-FU through human nipples was significantly reduced by keratin inserts compared to porcine nipples and breast skin. Removing the keratin plug from the human nipple significantly reduced latency time and increased flux and total 5-FU penetration compared to human breast epidermis. Similarly, for hydrophobic compound like EST, the keratin plug significantly impacted penetration through the human nipple, with EST concentration three times higher in the nipple than in the breast epidermis. Removing the keratin plug made EST absorption through pig nipples similar to human nipples, resembling 5-FU behaviour.

***In Vivo* Studies**

In addition to *in vitro* methods, the study includes *in vivo* tests where 5-FU was topically applied to rat nipples. The efficacy of localised administration was assessed by measuring the drug's concentration in the breast tissue following application and comparing it to systemic levels in plasma and other organs.

High Drug Concentration in Breast Tissue

The findings showed that, following six hours of topical application, the concentration of 5-FU in the breast tissue was two to three times more than that obtained by transdermal and intravenous (IV) administration. This implies that localized medication administration to the breast can be accomplished effectively through the nipple.

Minimal Drug Amounts in Plasma

Crucially, the study discovered that topical treatment of 5-FU resulted in substantially lower amounts of the drug in plasma compared to transdermal and IV delivery. This reduced systemic exposure indicated that the localized administration technique could decrease potential side effects often associated with higher plasma drug levels.

The *in vivo* results demonstrated the feasibility of localized topical delivery through the nipple, supporting the idea that this method can achieve targeted therapeutic effects in the breast while limiting drug distribution to other organs. These investigations highlight the potential of using the nipple as a direct route for drug delivery, particularly for treatments aimed at breast cancer and other breast-related conditions, by achieving high local concentrations with reduced systemic impact. These methods collectively provided a comprehensive understanding of drug penetration levels and the potential for localized drug delivery through the nipple (24).

Administration of Cytotoxic Therapies to Breast Tumors via Local Iontophoretic Administration

The iontophoretic delivery of cisplatin was evaluated using SUM149 human xenograft and T11 syngeneic orthotopic breast cancer models. The study compared device-administered cisplatin, IV cisplatin, and a combination of both. Both IV cisplatin and device effectively inhibited tumor growth compared to controls, with device cisplatin demonstrating superior efficacy compared to combined treatment.

Moreover, the study investigated enhancing cislatin's efficacy with radiation therapy. Mice with T11 tumors received treatments: device + radiation, IV + radiation, device + cisplatin, or device + cisplatin + IV + radiation over five days post-tumor inoculation. Three main groups emerged: Those receiving radiation alone, device cisplatin, or IV cisplatin showed similar survival and tumor growth rates (17 days), all better than untreated controls. Combination therapies (device cisplatin plus radiation, IV cisplatin plus radiation, or device + IV cisplatin) resulted in similar outcomes (23 days). The most favorable results were observed in the device + IV cisplatin + radiation group, with the highest tumor inhibition and survival (26 days) (p<0.0002, log-rank test). The study concluded that integrating systemic treatment, device therapy, and radiation significantly enhances survival and inhibits tumor growth in breast cancer models (28).

Studies on the *In Vitro* Permeation of α-Santalol Across the Epidermis of the Breast and Nipple

Dave et al. (29), investigated the *in vitro* viability of administering an α-santalol formulation transdermally to rodents. They assessed the permeability of porcine, rat, and human breast tissues (nipple and breast skin), combining data from pig/human tissues. Rat breast tissue showed a reduced lag time compared to pig and human tissues, with significantly diminished tissue retention. However, the cumulative amount of α-santalol infiltrating the breast tissue over 24 hours (122-236 g/mL) was seven to fifteen times more than the IC50 value for human breast cancer cells.

The chemopreventive efficacy of the α-santalol formulation was tested using an experimental 7,12-dimethylbenz anthracene (DMBA) model of breast cancer. After a 12-week treatment period, the vehicle and control groups each had three tumors, while the α-santalol treatment group had only one tumor. This indicates that α-santalol significantly reduced tumor incidence and multiplicity. The study concludes that developing an effective and safe transdermal chemoprevention approach for breast cancer using α-santalol was feasible (29).

Emu Oil Transfersomes Delivered Locally via Transdermal Route

Oral tamoxifen for estrogen-positive ductal carcinoma *in situ* (DCIS) is poorly accepted due to adverse effects, though its effectiveness comes from its metabolite, 4-OHT. Sundralingam et al. (30), used a mouse breast cancer model to compare 4-OHT transfersomal formulations (without and with emu oil) to oral tamoxifen. They found that both transfersomal formulations were as effective as oral tamoxifen in reducing tumor volume and necrosis. However, these formulations had significantly lower plasma concentrations of 4-OHT compared to the oral tamoxifen group (10.24±0.07 and 32.45±0.48 ng/mL, respectively). The study suggests that emu oil-enhanced transdermal formulations could treat breast cancer effectively while minimizing the adverse effects of oral tamoxifen (30).

Liposome Nanoparticles of Raloxifene

In an effort to improve the binding and antitumor efficacy of raloxifene (RXF) as a prospective therapy for breast cancer, Salem et al. (31), developed a stable deformable liposome formulation. In order to investigate deformable liposomal penetration, RLDL formulation was incorporated into a carbopol gel in order to assess penetration and antitumor efficacy.

The anticancer activity was assessed by weekly measuring of the quantity and diameter of papillomas greater than 1 mm in female rodents injected with a single dose of the tumor initiator DMBA. The ideal gel formulation demonstrated 2.77 times greater bioavailability than oral RXF and, as a result, exerted a substantial antitumor effect. In light of the author's conclusion, the optimal RLDL gel may represent an effective breast cancer treatment (31).

Nanogel Topically Applyable Tamoxifen Citrate

The objective of the research conducted by Alyami et al. (20), was to develop a water-insoluble nanoemulgel (NEG) formulation of the potent anticancer drug tamoxifen citrate (TAM) in order to improve topical delivery, induce substantial accumulation at the tumor site, and preserve healthy tissues. The nanoemusion system was designed and developed with the objective of optimizing the therapeutic efficacy of topical breast cancer treatment through enhancements in the anticancer TAM lipophilic agent's solubility, skin deposition, and permeation. The assessment of the formulations' *ex vivo* skin penetrability properties was conducted on albino rats. Consequently, the researchers reached the conclusion that the recently developed TAM-NEGs functioned as a potentially effective vehicle for enhancing the transdermal effectiveness of poorly diffusable TAM medications, particularly in the context of long-term breast cancer management, primarily by eliminating systemic adverse effects induced by oral TAM administration (20).

Modification of Microneedles and Microemulsions for Augmenting the Topical Delivery of Celecoxib

In addition to optimizing microemulsions for transdermal delivery of celecoxib to the breast surface, Mojeiko et al. (32) evaluated the efficacy of their formulation in conjunction with microneedles. The assessment of encapsulation's impact on the cytotoxicity of celecoxib towards MCF-7 breast cancer cells was conducted via cytotoxicity assays. By reducing the IC50 of celecoxib in MCF-7 cells by 3.3-fold, microemulsion incorporation suggests that the drug's cytotoxicity may be enhanced by the presence of formulation components in the breast tissue. In breast tissue, the presence of formulation components may mitigate the cytotoxicity of the drug. The potential for microneedle application to increase the delivery of microemulsion components to mammary tissue and facilitate the cytotoxic effects of drugs in cancer cells was attributed to its ability to penetrate the epidermis (32).

Targeted Delivery of Resveratrol-Loaded Nanostructured Lipid Carriers via Microneedle Assistance

Gadag et al. (33) devised nanostructured lipid carriers (NLCs) containing resveratrol (RVT) in order to enhance the efficacy of localized drug delivery to breast tissues via microneedle arrays. When compared to unadulterated RVT, the RVT-NLCs administered via microneedle array 1200 exhibited enhanced transdermal RVT penetration while minimizing skin retention. Based on cell viability studies, RVT-NLCs exhibited greater cytotoxicity compared to purified RVT. Preclinical studies conducted on rodents demonstrated that the bioavailability and localized effect of RVT were enhanced when combined with the benefit of microneedle arrays, in contrast to pure RVT administered orally. This finding established the superior treatment efficacy of RVT-NLCs in the context of breast cancer (33).

Clinical Efficacy of 4-OHT Percutaneous Gel in a Study of Breast Cancer

Rouanet et al. (34) conducted a randomized trial with 55 postmenopausal women diagnosed with invasive estrogen receptor-positive breast cancer to compare the efficacy of oral tamoxifen (20 mg/day) and 4-OHT gel (0.5, 1, or 2 mg/day) applied percutaneously. The study lasted two to three weeks. The oral tamoxifen group had higher plasma levels of 4-OHT compared to the gel groups. There was no dose-dependent effect on progesterone or estrogen receptor levels, and the topical gel was well tolerated. Both the higher gel concentrations and tamoxifen induced hot flashes at similar rates. The study concluded that percutaneous 4-OHT gel effectively regulates local tumor proliferation (34).

Transdermal 4-Hydroxytamoxifen Gel Compared to Oral Tamoxifen

Lee et al. (35) conducted a phase II randomized, double-blind, placebo-controlled trial comparing oral tamoxifen (20 mg/day) with topical 4-OHT gel (4 mg/day) in 27 pre- and post-menopausal women with DCIS. Treatment lasted six to ten weeks before surgery, with tamoxifen and metabolite levels measured in plasma, nipple aspirate fluid, and breast adipose tissue using liquid chromatography. The primary outcome, Ki-67 staining in DCIS lesions, showed post-therapy decreases of 3.4% in the 4-OHT group and 5.1% in the oral tamoxifen group (p = 0.03, between-group p = 0.99). Mean 4-OHT concentrations in mammary adipose tissue were comparable (5.4 ng/g for oral *vs.* 5.8 ng/g for 4-OHT, p = 0.88), while plasma levels differed significantly (0.2 ng/mL oral *vs.* 1.1 ng/mL 4-OHT). Oral tamoxifen increased plasma sex hormone binding globulin, factor VIII, and von Willebrand factor, and decreased plasma insulin-like growth factor-1 levels. The study suggests exploring local transdermal therapies for breast cancer prevention and DCIS treatment (35).

A Phase II Placebo-Controlled Trial of Telapristone Acetate Local Transdermal Delivery

In a phase II trial, Lee et al. (36) randomized women considering mastectomy to receive a progesterone receptor antagonist, telapristone acetate (TPA), either orally (12 mg/day) or transdermally (12 mg/breast) for 4±1 weeks. Tissue and plasma concentrations were measured using liquid chromatography at five locations within the mastectomy specimen. The breast-to-plasma concentration ratio was higher in the transdermal group (2.73 *vs.* 1.44, p = 0.02). Oral TPA significantly decreased serum EST and progesterone, while transdermal TPA did not affect these hormones because of low systemic levels. Despite limited dermal penetration, drug distribution in the breast was consistent across both groups, unaffected by tissue adiposity. The study demonstrated that transdermally applied drugs can effectively traverse the entire breast with distribution similar to the oral route (36).

Increased scientific attention has been devoted to the development of novel therapeutic agents via the application of nanotechnology. Various drug delivery systems, including transfersomes, microemulsions, nanogels, microneedles, and iontophoresis (Figure 1) can efficiently transport drugs to breast cancer cells. These systems are capable of traversing biological barriers, such as the stratum corneum in the skin.

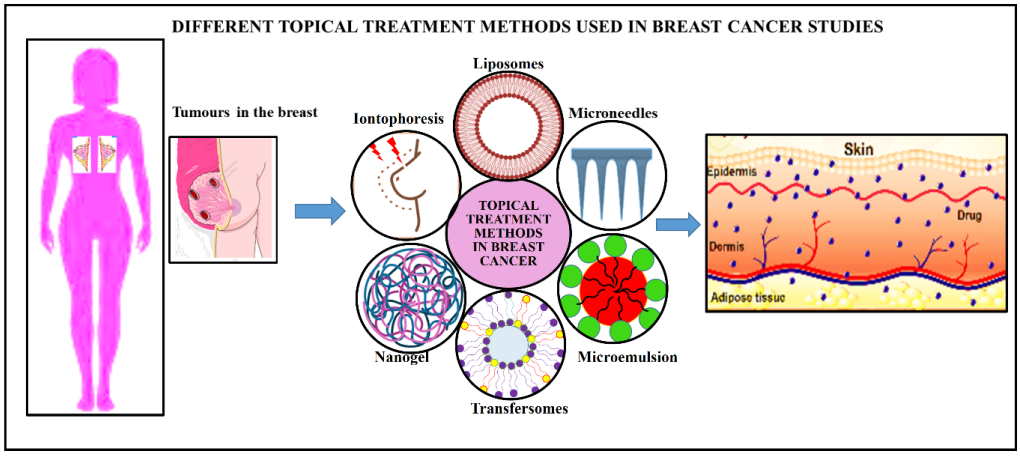

Figure 1. Different topical drug delivery system used in breast cancer studies

Furthermore, their capability to deliver components to the intended site is especially beneficial when co-delivering substances or combining treatments.

Future Prospective Aspects of Topical Treatment for Breast Cancer

Elevated local drug concentrations may be achieved through the direct administration of medication to the breasts, thereby potentially improving efficacy, safety, and acceptability. Local transdermal treatment administered via the breast skin has been hypothesized to increase drug concentrations in the breast tissue as a consequence of both deep and percutaneous absorption and local penetration (29).

Advances in topical and TDD techniques have facilitated the precise administration of remedies to the intended site of action, resulting in enhanced penetration of the stratum corneum and increased bioavailability. The significance and potential of natural drug discovery are expanding at a rapid rate. Phytoconstituents are experiencing a surge in prominence due to their reduced toxicity in comparison to synthetic compounds. Through modulation of signaling pathways and gene expression, these phytochemicals have the capability to impede cancer cell proliferation and surmount resistance (37).

A multitude of studies have reported that the concurrent administration of phytochemicals and chemotherapy resulted in reduced toxicity, a synergistic effect, and an enhanced response against multidrug-resistant breast cancer (38). The constraints of traditional treatment act as an ongoing impetus for the advancement of optimized and refined transdermal and TDD systems. Compared to conventional therapy, these may provide numerous advantages, including enhanced solubility for highly hydrophobic pharmaceuticals and improved drug stability. By employing a constant formulation, multiple agents can be delivered concurrently to a single site, ensuring synergy and facilitating the more accurate determination of the optimal medication ratio and dose for maximum therapeutic effect (39).

When contrasting topical therapy with systemic agents, the former potentially facilitates increased drug concentrations at the tumor site while minimizing overall toxicity. Furthermore, the co-administration of numerous drugs possessing diverse physicochemical properties may potentially exert a synergistic influence on cancerous cells, potentially overcoming the therapeutic barrier to the treatment (40). As a result, numerous novel prospects exist regarding the identification, development, and application of novel pharmaceuticals intended for topical treatment of breast cancer.

Discussion and Conclusion

Previous research studies have demonstrated that local transdermal formulations for the treatment of breast cancer are just as effective as oral approaches, with no or minimal adverse effects. In addition, topical gel applied to the breast surface has been shown in clinical trials to have an antiproliferative effect comparable to that of oral medications. A multitude of novel compounds and inventive amalgamations are undergoing clinical evaluation; should any prove efficacious, they could potentially be implemented in real-world environments, providing a ray of optimism for the efficient management of breast cancer. This review has summarized the substantial body of research that has been conducted thus far and anticipates the advancement of novel pharmaceuticals delivered transdermally via topical means. These have the potential to mitigate adverse effects, improve user safety, and elevate overall quality of life.

Footnotes

Authorship Contributions: Concept: N.B.S.T.,V.P.K., R.G., C.S.; Design: N.B.S.T.,V.P.K., R.G., C.S.; Data Collection or Processing: N.B.S.T.; Analysis or Interpretation: N.B.S.T.,V.P.K., R.G., C.S.; Literature Search: N.B.S.T.; Writing: N.B.S.T.

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Review

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An Investigation into Psychological Aspects of Patients Diagnosed with Breast Cancer: A Review Study of Postgraduate Theses Prepared in Turkey

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ABSTRACT

A significant number of scientific data concerning breast cancer is generated in Turkey. The present research reviewed postgraduate theses examining the psychological evaluation of breast cancer patients conducted in Turkey. The objective of the review study was to ascertain the focal topics of the theses, identify commonly examined psychological variables, determine research gaps, compare the frequency of experimental and intervention studies with other kinds of research, and provide recommendations for literature. A retrospective descriptive study was designed by performing a search on the YÖK Thesis Center website with the keywords "breast cancer" and "psychology" (in Turkish and English) between 2000 and 2024. The criteria for inclusion in the review study required that the dissertation be a master's or doctoral thesis in psychology, involve breast cancer patients as participants, focus on patients who are not in remission, and be available as open access. Twenty-seven postgraduate theses were selected. Of the theses 88.9% were classified as master's theses, while 11.1% were categorized as doctoral theses. Although the variables included in the these studies were numerous, some were investigated more often. "Post-traumatic growth" was evaluated by 12 theses, "perceived social support" by 6, "depression-anxiety-stress" by 15, and "coping" by 8. more frequently observed factors include metacognition, ruminative thinking, schemas, body perception/image, and self-esteem. Most of the studies were relational and non-interventional. Only three studies used psychological intervention. It is suggested that thesis studies should include more participant characteristics, control for them in analyses, and be more experimental and effectiveness focused.

Keywords: Breast cancer; psychology; postgraduate thesis; review

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Key Points

- The theses examined were mostly prepared descriptively and cross-sectionally.
- The characteristics of the participants who had breast cancer were not homogeneous. The participants need to be limited according to their medical and socio-demographic characteristics.
- The number of psychological intervention studies produced for breast cancer patients has increased with the theses conducted in recent years.

Introduction

Breast cancer is defined as a disease with different subtypes and different characteristics (1). Characterized by a tumor found in the breast tissue, this disease can usually be seen in the lobules and milk ducts that produce milk (2). According to World Health Organization data, breast cancer has been reported as the most common type of cancer in women worldwide, and approximately 2.3 million people have been diagnosed with this disease as of 2023 (3). Although it is known to be mostly common among women, the incidence of this disease in men is between 0.5% and 1% (3). When breast cancer statistics in Turkey were examined, the most up-to-date information was from 2018, and it was reported that the lifetime probability of contracting this disease is 1 in 8 (4). The fact that 1 in 4 women diagnosed with cancer have breast cancer and that the age of onset is decreasing (4) shows that this disease should be considered a public health concern in Turkey.

Recent literature indicates advances in the diagnosis, prognosis, and therapy of breast cancer. Surgical and oncological treatments (radiotherapy, chemotherapy and hormone therapy) are the most widely used methods for this disease (5). In addition to all the physical effects after a cancer diagnosis, another important consideration for the patient is survival (6). Naturally, psychological variables come into play in this process and can affect the prognosis of the disease, the quality of life and the psychological state of the patient (7). The most common psychological processes are depressive symptoms, anxiety,

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stress and trauma symptoms (8). Their levels may vary depending on individuals, the stage of cancer, the type of treatment and the person's environmental support (9).

Another area at the intersection of breast cancer and psychology is psychological intervention. The importance of adding psychological treatments to all treatment protocols in addition to medical treatments for breast cancer patients has been highlighted (10). Both types of treatment can improve the quality of life by treating the patient holistically (11).

The information reviewed above is the results of scientific studies. Academic knowledge is produced in a certain systematic order and presented to the literature in different forms (12). Theses are one form of academic knowledge production. These studies, which are conducted as part of postgraduate education, both improve students' academic knowledge and skills and expand the academic literature (13). While breast cancer literature is rapidly developing both internationally and nationally, it may be seen that some variables are frequently repeated and similar methods are used, especially in postgraduate theses in the national literature. In addition, when preparing postgraduate theses, what kind of studies (knowledge gaps) are needed may be overlooked.

Evaluation of these problems were the aim of the current study. Postgraduate theses prepared in universities in Turkey examining the psychological characteristics of breast cancer patients were reviewed and the results obtained within the scope of the above information constituted the output of this review. Especially in the field of breast cancer, the psychology literature is increasing, and it is necessary to identify the knowledge gaps with a more general view for the studies to be carried out. Thus, psychology theses including breast cancer patients were reviewed. By reviewing both general information about the theses (such as the year the thesis was written, the type of the thesis, the title of the academic advisor) and the content information of the theses, questions emerged as to which areas the studies were concentrated in the theses, which variables and methods were less often addressed in the studies, and what the distribution was in terms of participant characteristics.

The findings obtained through this review will guide future studies to areas of need, will provide methodological strengthening of new thesis studies, and will demonstrate the accumulation of knowledge revealed over the years by presenting a summary of the postgraduate theses conducted to date. With this review, a general scope assessment will be made for future studies and points to be considered will be highlighted.

Literature Search Strategy

A review was created for the purpose of retrospectively examining postgraduate theses written in Turkey and registered with the YÖK Thesis Center, which included the subject of breast cancer. For this purpose, the research was designed in a retrospective descriptive method. To provide the data for the current study, a search was conducted between 10.06.2024 and 10.07.2024 on the web page of the Council of Higher Education Thesis Center (2024). The keywords "breast cancer" and "psychology" were first used for the search (in Turkish and English) between the years 2000 and 2024. Then, from the advanced search tab, the department was limited to "Psychology Department", "General Psychology Department" and "Clinical Psychology Department".

Inclusion/Exclusion Criteria

The review includes studies that were published prior to July 2024. The inclusion criteria were:

1. Language: Theses written in Turkish or English.

2. Population: Breast cancer patients.

3. Intervention, comparator, and outcome: postgraduate psychology theses that accept breast cancer patients as participants and investigate psychological processes.

4. Study design: Quantitative or qualitative designs.

The exclusion criteria were: (1) closed to access; (2) population: participants were breast cancer patients in remission; (3) main field: a field outside the department of psychology.

Procedure

The examined theses were accessed via the YÖK Thesis Center web page. For theses uploaded to this system, authors can manage whether to give approval for sharing the information of theses while logging into the system. Therefore, theses that have been approved can be examined. For this reason, it was not necessary to obtain approval from the authors of the theses and the ethics committee.

The abstracts and titles of the acquired studies were subsequently assessed. Studies eligible for open access were determined by the analysis of the abstract and title. The qualifying theses were identified subsequent to the study review. The author extracted data from each study. This data encompasses the study's author, year, title, country, objective, participants, data collection method, scales, research design, methodologies, and research findings.

In the review it was found that the studies were quite heterogeneous about method, even though only quantitative and qualitative studies were examined. The investigations exhibited significant variations in several aspects, including the socio-demographic and medical attributes of the participants, the instruments utilized, and the variables analyzed. This may complicate the meta-analysis procedure. Consequently, it was posited that narrative synthesis would be appropriate for analyzing psychological characteristics in studies involving breast cancer patients (14).

In the initial search, there were 1769 theses, of which 1728 were from other fields (medicine, social work etc.) and were removed. The author screened the titles and abstracts of the 41 remaining theses by considering the inclusion and exclusion criteria. After screening the titles and abstracts, an additional 14 were removed for the following reasons: Six included participants in remission period; five included both breast cancer patients and relatives; two were on breast cancer but without a diagnosis from the participants; and one was inaccessible. This resulted in 27 these being included (Figure 1).

The data of the studies evaluated were entered into SPSS for Windows, version 25.0 (IBM Inc., Armonk, NY, USA). A separate column was defined for each variable to be examined. A separate table was created for the findings of the theses examined and the findings of the theses were summarized.

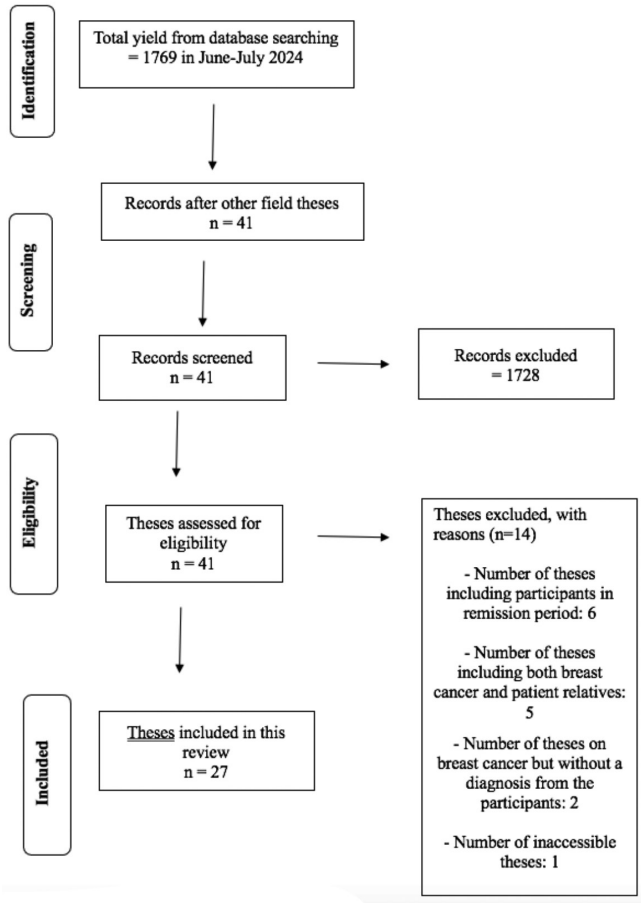

Figure 1. Inclusion flow chart diagram

Results

The characteristics of the theses selected for the present study are summarized in two tables. Table 1 contains general information about the theses, while Table 2 contains summary information about the theses' contents.

A total of 27 postgraduate theses that met the specified criteria were examined. Of these, 24 (88.89%) were master's theses and only 3 (11.11%) were doctoral theses. The examined studies were published in the YÖK Thesis Center between 2011 and 2023. When the characteristics of the candidates' advisors were examined, 2 (7.40%) had two advisors (Asst. Prof. Dr. and Assoc. Prof. Dr.), 13 (48.14%) had one Assoc. Prof. Dr., 2 (7.40%) had an advisor with the title of Prof. Dr. and 10 (37.03%) had an advisor with the title of Asst. Prof. Dr.

In terms of the methods used, 10 (37.03%) were descriptive and cross-sectional, 2 (7.40%) used descriptive and cross-sectional methods together with scale adaptation studies, 9 (33.33%) were of the causal comparative type, 2 (7.40%) used the longitudinal type, 3 (11.11%) were of randomized controlled design examining the effectiveness of a psychological intervention and 1 (3.70%) was prepared using the qualitative method. The number of participants varied between 3 and 201. There were 10 (37.03%) that included a control/comparison group. In 20 (74.07%) data and applications were conducted face-to-face, in 4 (14.81%) online and in 4 more (14.81%) both face-to-face and online applications were conducted (Table 1).

Although the variables examined in the theses were several, some variables were investigated more frequently. In particular, the post-traumatic growth variable was examined by 12 theses, perceived social support by 6 theses, depression-anxiety-stress by 15 theses, and coping variable by 8 theses. In addition to these, metacognition, ruminative thinking, schemas, body perception/image and self-esteem are among the variables encountered more frequently than others. Most of the studies were relational in design and did not include intervention. However, three of the studies included psychological intervention.

The stages of breast cancer, whether they had undergone surgery, whether they received complementary treatment, and whether they had metastases and other cancer diseases were all assessed in the context of the participants' characteristics. This showed that 12 (44.44%) did not provide information on the stage of cancer in the participants; only 1 study (3.70%) had stage 1 and 2 breast cancer in the participants, 6 studies (22.22%) had stage 1, 2 and 3 breast cancer in the participants, and 8 studies (29.62%) accepted patients in stage 1, 2, 3 and 4 as participants. When the additional treatment status of the participants was examined, 5 (18.51%) did not provide information about the participants' status, 14 studies (51.85%) included patients who received radiotherapy, chemotherapy and hormone therapy, 6 (22.22%) included patients who received radiotherapy and chemotherapy, 1 (3.70%) included patients who received only chemotherapy and 1 (3.70%) included patients who received only hormone therapy. While participants were those who had undergone surgery in 24 studies (88.9%), patients who had not undergone surgery were recruited in 1 thesis (3.70%). In addition, information was not obtained about whether patients had undergone surgery in 2 studies (7.40%). In 21 of the examined thesis studies (77.8%), no information was given regarding the metastasis status of the participants, while in 6 studies (22.22%), information was collected regarding metastasis status. In addition, in 23 studies (85.15%), no information was found regarding whether the participants had cancer other than breast cancer; in the remaining 4 studies (14.81%), information was available on this subject (Table 2).

Discussion and Conclusion

In the present study, postgraduate theses produced in Turkey that examine the psychological processes of breast cancer patients were reviewed. Also, the criteria determined for the selection of theses and the findings obtained are discussed together with the relevant literature and suggestions for future studies are presented.

First, some criteria were determined in the selection of theses to be used in the review study. These are detailed in the method section (Figure 1). Thesis studies that accepted patients in remission as participants, which is considered an important criterion, were excluded. Especially in the field of oncology, the meaning of the word remission is the decrease in cancer symptoms and burden. It is also emphasized that a single method-based decision will not be sufficient for the decision of the remission period in cancer, and that the results obtained only with pathological and radiological measurable tools will not provide a complete prediction (15). Therefore, cancer survival is related to some psychosocial processes. In this survival phase, the psychological needs and characteristics of the individual may differ from the disease period (15). For these reasons and because it was suitable for the purpose of the study, studies conducted with patients in remission were determined as an exclusion criterion for the review.

Table 1. General information about theses

	Author	Type of thesis and year written	Title	University	Thesis advisor title	Type of study	Number of participants (person diagnosed with breast cancer)	Control group (healthy female participants) Number	Where data is collected
1	Yola (31)	Master	The mediating roles of coping styles and perceived social support between dispositional hope and posttraumatic growth/PTSD relationships among postoperative breast cancer patients: A longitudinal study	Middle East Technical University	Asst. Prof.	Longitudinal	73	None	Ankara
2	Önder (16)	Master	The mediating role of coping strategies in the basic personality traits PTG and locus of control PTG relationships in breast cancer patients	Middle East Technical University	Assoc. Dr.	Descriptive and cross-sectional	114	None	Ankara
3	Sarısoy (22)	Master	An investigation of posttraumatic growth rate and factors that predict posttraumatic growth in breast cancer patients	Hacettepe University	Prof. Dr.	Descriptive and cross-sectional, scale adaptation	63	None	Ankara
4	Olgar (32)	Master	The relationship between locus of control and posttraumatic growth in women diagnosed with breast cancer	Okan University	Asst. Prof.	Descriptive and cross-sectional	91	None	Ankara
5	Coşar (23)	Master	An investigation of the predictors of post traumatic growth among post-operative breast cancer patients	Uludağ University	Assoc. Dr.	Descriptive and cross-sectional	66	None	İstanbul
6	Bellur (33)	Master	The relationship of environmental personal and event related factors with post - traumatic growth in breast cancer patients	Mersin University	Asst. Prof.	Descriptive and cross-sectional, scale adaptation	134	None	Mersin
7	Dönmez (34)	Master	The relationships between illness perception and metacognition, early maladaptive schemas, negative automatic thoughts among cancer patients	Ankara University	Prof. Dr.	Descriptive and cross-sectional	122	None	Ankara
8	Aydoğdu (35)	Master	Factors related with psychological distress and posttraumatic growth in women with breast cancer: Core beliefs, rumination and type C personality	Dokuz Eylül University	Prof. Dr.	Descriptive and cross-sectional	201	None	İzmir
9	Alamış (36)	Master	The relationship between illness perception,anxiety,depression and marital adjustment in patients with breast cancer: A controlled study	Işık University	Prof. Dr.	Causal comparative	35	35	Eskişehir

Table 1. Continued

	Author	Type of thesis and year written	Title	University	Thesis advisor title	Type of study	Number of participants (person diagnosed with breast cancer)	Control group (healthy female participants) Number	Where data is collected
10	Güler (37)	Master	Examination of body image perception and sexual experiences of women treated with breast conserving surgery and mastectomy for breast carcinoma	Üsküdar University	Asst. Prof.	Descriptive and cross-sectional	100	None	Hatay
11	Geyikçi (38)	Master	Anxiety and depression level of breast cancer patients who completed the first year and their coping attitudes with the disease	Çağ University	Prof. Dr.	Descriptive and cross-sectional	94	None	Mersin
12	Mike (39)	Master	Investigate the depression and hopelessness levely in women with mastectomy and those without mastectomy	İstanbul Gelişim University	Asst. Prof.	Causal comparative	93	None	İstanbul
13	Özer (40)	Master	Examination of the relationship between depressive symptoms and early maladaptive schemes in breast cancer patients	İstanbul Gelişim University	Asst. Prof.	Descriptive and cross-sectional	100	None	Denizli
14	Kamsız (41)	Master	Psychology of mastectomy in breast cancer: A comparison between women diagnosed with breast cancer and healthy women	Üsküdar University	Prof. Dr.	Causal comparative	78	78	İstanbul
15	Özdem (17)	Master	The effects of gestalt contact styles on coping styles in breast cancer patients before and after surgical intervention	İstanbul Arel University	Asst. Prof.	Descriptive, longitudinal	100	None	İstanbul
16	Özdemir (42)	Master	The effect of chemotherapy on self-esteem and psychological wellbeing in individuals diagnosed with breast cancer	University of Health Sciences Turkey	Asst. Prof. & Assoc. Dr.	Causal comparative	60	59	İstanbul
17	Kanmaz (43)	Master	Investigation of effect of mastectomy and reconstructive operation after mastectomy on depression, self-esteem, and self-efficacy among breast cancer patients	Hasan Kalyoncu University	Prof. Dr.	Causal comparative	107	133	Mersin
18	Kantarcı (44)	Master	Examination of psychic functioning of women who associated breast cancer through projective tests	İstanbul Arel University	Asst. Prof.	Qualitative, descriptive	3	None	İstanbul
18	Küçükkavradım, (45)	Master	Investigation of the relationship between body and social support perception to depression level in a group of women with mastectomy	Işık University	Asst. Prof.	Causal comparative	75	125	İstanbul & Antalya

Table 1. Continued

	Author	Type of thesis and year written	Title	University	Thesis advisor title	Type of study	Number of participants (person diagnosed with breast cancer)	Control group (healthy female participants) Number	Where data is collected
20	Aras (46)	Master	Investigation of factors affecting the development of post-traumatic growth in breast cancer patients	İbn Haldun University	Asst. Prof.	Descriptive and cross-sectional	68	None	İstanbul
21	İğci (47)	Master	Comparison of the effects of pre- and postoperative meta-cognitive beliefs on depression, anxiety levels and fear of recurrence levels of women with breast cancer	İstanbul Kent University	Asst. Prof.	Causal comparative	45	None	İstanbul
22	Arıtürk (26)	Doctorate	Adaptation and effectiveness of mindfulness based cognitive therapy program for improving quality of life in breast cancer patients	Ege University	Prof. Dr.	Effectiveness	38	18	İzmir
23	Kaplan (48)	Master	The relationship between self-compassion and traumatic growth in female patients diagnosed with breast cancer	Nişantaşı University	Asst. Prof.	Causal comparative	77	77	Mersin
24	Taş (49)	Master	Determinants of psychological distress and post-traumatic growth levels of breast cancer survivors during the COVID-19 pandemic: A controlled study	Işık University	Assoc. Dr. & Asst. Prof.	Causal comparative	95	87	İstanbul
25	Babadostu (50)	Master	An invastigation of the relationship between fear of cancer recurrence, intolerance of uncertainty, metacognitions and coping strategies among breast cancer survivors	Maltepe University	Asst. Prof.	Descriptive and cross-sectional	130	None	Türkiye
26	Yastıbaş-Kaçar (25)	Doctorate	An investigation of the effectiveness of an online group therapy focused on post-traumatic growth in women with breast cancer	Dokuz Eylül University	Prof. Dr.	Effectiveness	32	17	Eskişehir
27	Ülbe (24)	Doctorate	Developing and testing effectiveness of an online individual intervention program to make meaning of experiences after a breast cancer diagnosis	Dokuz Eylül University	Prof. Dr.	Effectiveness	41	21	İzmir

Table 2. Informations on the contents of theses

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
1	Face to face	Ways of Coping Scale, Multidimensional Scale of Perceived Social Support, Hope Scale, Posttraumatic Growth Scale, Impact of Event Scale	No	1,2, 3, & 4	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	No mediating effects of problem-focused coping strategy and perceived social support and its sources were found in the relationship between hope orientation and post-traumatic growth and its subscales. Similarly, emotion-focused coping strategy did not have a mediating effect in the relationship between hope orientation and post-traumatic stress disorder and its subscales. However, perceived social support and perceived social support from friends were reported to have a moderating effect in the relationship between hope orientation and post-traumatic growth.
2	Face to face	Basic Personality Traits Inventory, Locus of Control Scale, Turkish Ways of Coping Scale and Post-Traumatic Growth Scale	No	1,2,3, & 4	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	Problem-focused coping was found to have a significant mediating effect on the relationships between some basic personality traits (extraversion, openness to experience, conscientiousness, agreeableness) and post-traumatic growth and external locus of control. However, emotion-focused coping was a significant mediating variable in the relationships between some personality traits (conscientiousness, agreeableness, openness to experience) and external locus of control. Social support seeking also significantly mediated the relationship between post-traumatic growth and external locus of control.
3	Face to face	Traumatic Stress Symptom Scale, Ways of Coping Inventory, Posttraumatic Growth Inventory, Hospital Anxiety and Depression Scale, Cancer Patient Social Support Scale, Cancer Thoughts Scale	No	1,2, & 3	Radiotherapy Chemotherapy Hormone therapy	Yes	Yes	Yes	The internal consistency of the Cancer Thoughts Scale and the Negative Thoughts and Positive Thoughts subscales of the scale was found to be satisfactory. For the total score of post-traumatic growth and the Interpersonal Relations subscale, time since diagnosis, helpless coping approach and positive thoughts about cancer were found to be predictors. For the Self-Perception subscale of post-traumatic growth, time since diagnosis, traumatic stress symptom level and confident coping approach were found to be predictors. For the Value of Life subscale of post-traumatic growth, time since diagnosis and negative thoughts about cancer were found to be predictors. For the New Options subscale of post-traumatic growth, time since diagnosis and confident coping approach were found to be predictors.

Table 2. Continued

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
4	Face to face	Rotter's Internal-External Locus of Control Scale and Posttraumatic Growth Scale	No	No information	Radiotherapy Chemotherapy Hormone therapy	Ye	No information	No information	A negative and significant relationship was found between locus of control and post-traumatic growth. In terms of post-traumatic growth, the pre-diagnostic examinations such as ultrasound, treatment methods such as radiotherapy and surgery, family history of disease and breast self-examination were found to have significant effects.
5	Face to face	Self-Evaluation Scale, Social Support Scale, Ruminative Thinking Style Scale, Coping Styles Scale, Locus of Control Scale, Post-Traumatic Growth Inventory	No	1,2,3, & 4	Hormone therapy	Yes	Yes	No information	The stage of the disease significantly predicted the total post-traumatic growth level and the subscale of change in interpersonal relationships. After controlling for the stage of the disease, social support was found to be associated with total posttraumatic growth and change in interpersonal relationships. Breast cancer patients with higher social support showed greater total post-traumatic growth and change in interpersonal relationships. The increased use of a self-confident approach as a coping strategy was found to be associated with an increase in change in philosophy of life.
6	Face to face	Dyadic Adjustment Scale-Revised, Impact of Event Scale-Revised Form, Posttraumatic Growth Scale, Ways of Coping Inventory, Multidimensional Scale of Perceived Social Support, General Self-Efficacy Scale	No	No information	No information	No information	No information	No information	It was observed that perceived social support from family increased as the time passed since the diagnosis. Participants who had experienced trauma before being diagnosed with breast cancer used a helpless coping style more, while those who had not experienced trauma before diagnosis used a problem-focused coping style more. In addition, those who had not experienced any trauma before diagnosis showed more post-traumatic development. In the mediation tests conducted, the mediating effect of coping methods on the relationship between environmental, individual and event-related factors and post-traumatic development was examined.

Table 2. Continued

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
7	Face to face	Illness Perception Scale, Metacognition – 30 Scale, Young Schema Scale – Short Form 3 and Negative Automatic Thoughts Scale	No	No information	Radiotherapy Chemotherapy	Yes	Yes	No information	It was concluded that the sub-dimensions of illness perception and illness causes did not differ significantly in terms of these variables. It was observed that the variables predicting the duration acute/chronic sub-dimension were personal attributions, lifestyle attributions and the impaired boundaries schema area. When evaluated in terms of metacognition, it was reported that the duration acute chronic variable and positive beliefs about anxiety showed a positive correlation. It was understood that the variables predicting the schema areas differed.
8	Face to face	Core Beliefs Inventory, Event-Related Rumination Inventory, Type C Behavior Scale, Depression Anxiety Stress Scale, and Posttraumatic Growth Inventory	No	1,2,3, & 4	Radiotherapy Chemotherapy Hormone therapy	Yes	Yes	No information	It was determined that the change in core beliefs and type C personality significantly and positively predicted depression, anxiety and stress. It was also concluded that the relationship between the change in core beliefs and depression, anxiety and stress was partially mediated by involuntary rumination. It was determined that the change in core beliefs significantly and positively predicted both the sub-dimensions of PTG, “change in relationships with others”, “change in self-perception” and “change in philosophy of life” and the total PTG level.
9	Face to face	Couples Adjustment Scale, Hospital Anxiety and Depression Scale and Illness Perception Scale	No	No information	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	The compliance levels were found to be lower in women diagnosed with breast cancer than in the control group. When the anxiety and depression levels in both groups were compared, they were found to be significantly lower in patients diagnosed with breast cancer. The total score of the disease perception and the scores from all three sub-dimensions were found to be higher in patients diagnosed with breast cancer than in the control group.

Table 2. Continued

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
10	Face to face	Golombok-Rust Sexual Satisfaction Scale, Arizona Sexual Experiences Scale and Body Image Scale	No	No information	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	Sexual satisfaction scores were found to be significantly different in terms of education level and family communication variables. However, sexual satisfaction and sexual experience scores were found to be significantly different in terms of breast cancer surgical operation type, and women who had mastectomy were found to have significantly more complaints in terms of sexual satisfaction and experience than women who had breast-conserving surgery. A significant relationship was found between body image and sexual satisfaction sub-dimensions.
11	Face to face	Beck Anxiety Inventory, Beck Depression Inventory and Coping Attitudes Assessment Scale	No	No information	Radiotherapy Chemotherapy	Yes	No information	No information	A positive and highly significant relationship was found between depression and anxiety. The group with the highest depression scores were those whose anxiety and fear increased after the surgery. The group with the lowest mean depression scores were those who were quite satisfied with the surgery. A negative significant relationship was found between depression and the coping attitude sub-dimensions. A positive significant relationship was found between anxiety and the use of emotional social support, one of the coping attitude sub-dimensions.
12	Face to face	Beck Depression Inventory, Beck Hopelessness Inventory	No	No information	No information	Yes	No information	No information	No significant differences were found between participants with and without mastectomy in terms of depression and hopelessness. A positive correlation was reported between levels of depression and hopelessness.

Table 2. Continued

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
13	Face to face	Beck depression inventory and Young schema scale	No	No information	No information	Yes	No information	No information	As the participants' depression scores increase, their scores from the sub-dimensions of failure, pessimism, social isolation, enmeshment/ underdeveloped self, self-sacrifice, abandonment/instability, defectiveness/shame, and vulnerability to harm or illness increase. Those who use prosthesis have been found to have a stronger inadequate self-control/self-discipline schema compared to those who do not. Those who have had breast tissue removed have significantly higher scores on the sub-dimensions of punitiveness and self-sacrifice than those who do not have breast tissue removed, while those who do not have breast tissue removed have significantly higher scores than those who do have breast tissue removed.
14	Face to face	Rosenberg Self-Esteem Scale Short Form, Body Image Scale and Golombok-Rust Sexual Satisfaction Scale	No	No information	No information	Yes	No information	No information	The self-esteem and body image levels of women who have had mastectomy are significantly lower than healthy women. However, among the factors related to sexual satisfaction, the levels of avoiding sexual intercourse are significantly higher in women who have had mastectomy, while the frequency of sexual intercourse and sexual satisfaction are significantly lower. In healthy women, it has been reported that there are similar relationships between body image and the frequency of sexual intercourse, satisfaction with sexual intercourse and touching during sexual intercourse.
15	Face to face	Gestalt Contact Barriers Scale	No	1,2,3, & 4	No information	No information	No information	No information	The psychiatric history of the individuals was not found to have a significant effect on the full contact items. There was a significant relationship between the mean tertiary full contact scores of individuals with a history of psychiatric disease and the mean scores of patients without a psychiatric history. It is observed that individuals with contact and full contact disabilities are not aware of their emotions and cannot express their emotions in a healthy way.

Table 2. Continued

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
16	Face to face	Self-Esteem Assessment Scale Short Form, Multidimensional Psychological Well-Being Scale Short Form	No	1, 2, & 3	Radiotherapy Chemotherapy	No	Yes	Yes	No significant differences were found between the chemotherapy group and the other groups in terms of self-esteem and psychological well-being. Psychological well-being and self-esteem were positively correlated in all three participant groups. Psychological well-being was predicted by self-esteem.
17	Mixed	General Self-Efficacy Scale, Self-Esteem Scale and Beck Depression Inventory	No	No information	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	Patients who had mastectomy were found to have higher levels of depression than patients who had reconstructive procedures after mastectomy. Patients who had mastectomy were also found to have lower self-esteem and self-efficacy beliefs than patients who had reconstructive procedures after mastectomy.
18	Face to face	Rorschach Test and Thematic Apperception Test	No	1,2,3, & 4	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	Participants stated that they had difficulty processing their impulses and emotions. Although they used different defense mechanisms, they were reported to be affectively depressed and to have traumatic events in their life stories.
19	Face to face	Beck Depression Inventory, Body Image Scale, and Multidimensional Scale of Perceived Social Support	No	1,2,3, & 4	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	For mastectomy patients, a negative relationship was found between depression and body image total score, perceived social support friend sub-dimension and total score. It was determined that body image and perceived social support total score were a significant predictor of depression in the negative direction. Body image, depression and perceived social support family, friend, special person sub-dimensions and total score of women who underwent breast reconstruction after mastectomy did not differ significantly compared to those who did not undergo reconstruction surgery.
20	Mixed	Post-Traumatic Stress Disorder Checklist, Hospital Anxiety and Depression Scale, Core Beliefs Inventory, Appreciation Scale, and Post-Traumatic Growth Inventory	No	1,2,3, & 4	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	It has been reported that as the levels of core beliefs, shock and post-traumatic stress symptoms increase, the level of post-traumatic growth increases. According to hierarchical regression analysis, it was found that the levels of core beliefs, shock and appreciation, have a predictive effect on increasing the level of post-traumatic growth.

Table 2. Continued

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
21	Face to face	Metacognition Scale, Hospital Anxiety and Depression Scale, and Fear of Cancer Recurrence Inventory	No	1, 2, & 3	Chemotherapy	Yes	No information	Yes	There is a positive correlation between anxiety, depression, metacognition and fear of recurrence scores in the preoperative and postoperative periods. In addition, a significant decrease in anxiety scores and a significant increase in the functional impairment subscale score of fear of recurrence were observed after surgery compared to preoperative levels. Level of education, presence of psychopathology, anxiety level and positive beliefs were reported as significant predictors.
22	Face to face	Mindfulness Scale, Cognitive and Emotional Mindfulness Scale – Revised, Hospital Anxiety Depression Scale, Perceived Stress Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and Post-Traumatic Growth Inventory	Yes	1 &2	Radiotherapy Chemotherapy	Yes	No information	No information	As a result of two-way variance analyses for mixed designs conducted with pre-tests and post-tests, statistically significant differences were found within-group and/or between-groups in the sub-dimension of mindfulness, depression, stress and general well-being of the quality of life scale. Due to the decrease in the number of participants in the post-test and follow-up measurements, Intention to Treat analysis was conducted and it was seen that the effect observed in the sub-dimension of mindfulness, depression, stress and general well-being of the quality of life scale continued in a similar way.
23	Online	Post-Traumatic Growth Scale, Self-Compassion Scale, Body Image Scale	No	No information	Radiotherapy Chemotherapy	Yes	No information	No information	No significant difference was found between the levels of self-compassion between the diagnosis and healthy participant groups. The diagnosed group was found to have a higher level of body perception than the other. It was determined that the level of self-compassion of women diagnosed with breast cancer positively predicted the change in self-perception, change in relationships with others, change in philosophy of life and body perception.

Table 2. Continued

	Data collection method	Scales	Does it include psychological intervention?	Cancer stage	Additional treatments	Surgical intervention	Metastasis	History of cancer	Thesis results
24	Mixed	Depression Anxiety Stress Scale, Post-Traumatic Growth Inventory, Social Support Scale, Intolerance of Uncertainty Scale, Short Form of Coping Strategies Scale	No	No information	Radiotherapy Chemotherapy Hormone therapy	Yes	Yes	No information	It has been reported that breast cancer diagnosis has no significant effect on women's depression and anxiety levels during the Covid-19 pandemic, but is associated with decreased stress levels, and being diagnosed with breast cancer is associated with increased PTG levels. Variables that increase PTG levels have been identified as increased social support levels, increased intolerance of uncertainty, and increased problem-focused coping.
25	Online	Fear of cancer recurrence inventory, Intolerance of uncertainty scale-short form, Metacognition scale-30, Coping strategies scale short form, Covid-19 fear scale	No	1,2, & 3	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No	A positive significant relationship was found between fear of cancer recurrence, intolerance of uncertainty and metacognition values of women who survived after breast cancer. The moderating effect of metacognition was found to be significant in the relationship between intolerance of uncertainty and fear of cancer recurrence.
26	Online	Post-Traumatic Growth Scale, Depression Anxiety Stress Scale, Multidimensional Scale of Perceived Social Support, Event-Related Rumination Inventory, Cognitive Emotion Regulation Scale, Core Beliefs Inventory, Self-Disclosure Scale and Group Meeting Evaluation Form	Yes	1, 2, & 3	Radiotherapy Chemotherapy	Yes	No information	No information	It is stated that the intervention program showed significant differences in some psychological adjustment variables, especially post-traumatic growth and depression, and these differences were maintained in the follow-up measurements. It was determined that the intervention developed to increase post-traumatic growth in people diagnosed with breast cancer was effective.
27	Online	Meaning in Life Scale, Posttraumatic Growth Inventory-X, Stress Rating Scale, Global Impairments Scale, Impact of Events Scale-Revised Form, Acceptance and Action Scale-II, Hospital Anxiety and Depression Scale	Yes	1,2, & 3	Radiotherapy Chemotherapy Hormone therapy	Yes	No information	No information	Compared to the control group, the intervention group showed significant improvements in the presence of meaning, post-traumatic growth, seeing the breast cancer diagnosis as an opportunity to challenge, and anxiety levels. In the final measurement of the intervention group, it was determined that the improvements in the presence of meaning, intrusive thoughts, and psychological rigidity were maintained in the follow-up measurement.

The initial observation was the absence of homogeneous structures when the studies were analyzed in terms of participant characteristics, even though the theses under review made contributions to related literature. For example, the characteristics of the participants' cancer and treatment stages were not separated in many studies. It is suggested that this should be considered as a limitation. There are studies supporting this suggestion (16, 17). In the study by Costa-Requena et al. (18), patients showed different characteristics in terms of social, familial, emotional well-being and psychological stress at different stages. Although there are studies showing that the psychological characteristics of individuals do not change according to the cancer stages in terms of psychological needs and characteristics, it is recommended that this be checked and analyzed. Another striking finding was that the participants' complementary treatment information (radiotherapy, chemotherapy, hormone therapy, etc.) and information on the metastasis status of the cancer were not considered or provided. This is an additional limitation. The fact that this information regarding the medical conditions of the participants in the theses is not considered or is incomplete may be related to the fact that education in psychology does not include sufficient health-disease information. An estimated cause for the lack of information on this variable, which should be adjusted for, is the prevalence of relationship designs in research, which often neglect the gathering of information based on cancer history. However, it is thought that conducting analyses by controlling such participant characteristics in these correlational studies will reveal more accurate findings. For example, depression and anxiety levels can differ in metastatic and non-metastatic breast cancer patients, and different factors can affect these psychological symptoms (20). Therefore, it is recommended to obtain information about these two characteristics and control for them in future theses.

When the methodology was examined, descriptive and cross-sectional studies were predominant. Following this, there were theses comparing diagnosed and healthy groups. The characteristics of the participants in both groups in these investigations were not equivalent. For example, many characteristics of the participants, such as their ages, education levels, and socio-economic levels should be as similar as possible. In such designs, it is recommended that the groups be similar to each other in order to see the most accurate results of the difference or manipulation (21). The least common research method was scale development and effectiveness studies. Although the number of scales translated into Turkish is increasing, introducing scales that prioritize breast cancer will yield more reliable results. In the reviewed theses, the validity and reliability of the Cancer-Related Thoughts scale (22) and the Self-Evaluation scale (23) were examined in Turkish. In Coşar's (23) study, the validity and reliability of a previously translated scale was reanalyzed in a breast cancer patient sample and the scale was adjusted according to this group. In this example a scale that can be used in studies involving other breast cancer patients has been added to the national literature. Other important information added to the literature will be produced through effectiveness studies. Three effectiveness studies were included, two online psychological interventions (24, 25) and one face-to-face psychological intervention (26) were described for breast cancer patients and their effectiveness was tested. These three intervention programs are potentially valuable for the national literature, once the findings are validated by other studies. Psychological interventions developed for breast cancer patients are frequently encountered in the international literature (27). In a meta-analysis study by Guarino et al. (28), it was reported that psychological interventions developed for breast cancer are mostly in the cognitive behavioral therapy school and create positive psychological results for patients. The intervention studies examined in the current study were also cognitive behavioral therapy-centered and have achieved effective results. Considering the increasing prevalence of breast cancer (4), it will be beneficial to develop more Turkiye-specific psychological interventions for breast cancer patients and add them to treatment protocols.

The subjects and variables considered most often included post-traumatic growth, anxiety-depression-stress, psychological coping and perceived social support. Post-traumatic growth, in particular, has an important place in psychology literature. Positive psychological changes that occur after a negative experience are seen as important, especially in the psychological treatment of chronic patients (29). The description of the post-traumatic growth characteristics of breast cancer patients in Turkey reveals potentially important findings and can guide experts working in the field. In addition, examining perceived social support by adding it to the post-traumatic growth models of patients diagnosed with breast cancer can be considered as a suggestion for future studies. Another striking element was that positive psychological variables related to the psychological aspect of cancer are frequently investigated in international literature (30). Since the positive psychological growth of individuals is also seen to be related to post-traumatic growth, perhaps examining positive psychology variables (finding meaning, acceptance, awareness) in post-traumatic development models and examining the relationship and effects of these variables with other psychological processes in national studies will reveal important findings.

The current review examined post-graduate theses studies investigating the psychological aspect of breast cancer in Turkey. In the evaluation, it was noted that although the participants included in the theses were breast cancer patients, they were not homogeneous in terms of socio-demographic and medical characteristics. In most of the theses, patients with different disease stages were evaluated together. This limits the generalizability of the results. It is recommended that future studies be structured with more homogeneous participant groups.

In addition, the fact that the scales used in theses are scales adapted for breast cancer patients is another factor that will affect the research findings. Although the validity and reliability of the scales used in the national context are among the sufficient criteria, conducting their validity and reliability with breast cancer patients may reveal more accurate results. In addition, developing culture-specific scales will the quality of findings.

Another suggestion for future studies is consistency in the psychological variables examined in breast cancer. The examined theses generally addressed the relationships between psychological symptoms and post-traumatic growth in relation to breast cancer. When the current literature is examined, positive psychology topics and Third Wave CBT are now associated with post-traumatic growth. Thus, it can be suggested that the literature be expanded with studies examining these variables in Turkey.

A further recommendation for future research is the design of the studies. Cross-sectional and descriptive studies were frequently conducted. In particular, experimental designs and effectiveness studies of psychological interventions, which have been published more frequently in recent years, have attracted attention. Future studies

developing psychological interventions and testing their effectiveness in breast cancer patients will be beneficial for both the literature and patients.

One of the strengths of the current study is that it is the first article at the national level to review postgraduate theses examining the psychological characteristics of breast cancer patients. In addition, in the light of the findings, research into identified knowledge gaps will be possible in the future.

Footnotes

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Original Article

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Artificial Intelligence in Diagnostic Breast Ultrasound: A Comparative Analysis of Decision Support Among Radiologists With Various Levels of Expertise

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ABSTRACT

Objective: To investigate integrating an artificial intelligence (AI) system into diagnostic breast ultrasound (US) for improved performance.

Materials and Methods: Seventy suspicious breast mass lesions (53 malignant and 17 benign) from seventy women who underwent diagnostic breast US complemented with shear wave elastography, US-guided core needle biopsy and verified histopathology were enrolled. Two radiologists, one with 15 years of experience and the other with one year of experience, evaluated the images for breast imaging-reporting and data system (BI-RADS) scoring. The less-experienced radiologist re-evaluated the images with the guidance of a commercial AI system and the maximum elasticity from shear wave elastography. The BI-RADS scorings were processed to determine diagnostic performance and malignancy detections.

Results: The experienced reader demonstrated superior performance with an area under the curve (AUC) of 0.888 [95% confidence interval (CI): 0.793–0.983], indicating high diagnostic accuracy. In contrast, the Koios decision support (DS) system achieved an AUC of 0.693 (95% CI: 0.562–0.824). The less-experienced reader, guided by both Koios and elasticity, showed an AUC of 0.679 (95% CI: 0.534–0.823), while Koios alone resulted in an AUC of 0.655 (95% CI: 0.512–0.799). Without any guidance, the less-experienced reader exhibited the lowest performance, with an AUC of 0.512 (95% CI: 0.352–0.672). The experienced reader had a sensitivity of 98.1%, specificity of 58.8%, positive predictive value of 88.1%, negative predictive value of 90.9%, and overall accuracy of 88.6%. The Koios DS showed a sensitivity of 92.5%, specificity of 35.3%, and an accuracy of 78.6%. The less-experienced reader, when guided by both Koios and elasticity, achieved a sensitivity of 92.5%, specificity of 23.5%, and an accuracy of 75.7%. When guided by Koios alone, the less-experienced reader had a sensitivity of 90.6%, specificity of 17.6%, and an accuracy of 72.9%. Lastly, the less-experienced reader without any guidance showed a sensitivity of 84.9%, specificity of 17.6%, and an accuracy of 68.6%.

Conclusion: Diagnostic evaluation of the suspicious masses on breast US images largely depends on experience, with experienced readers showing good performances. AI-based guidance can help improve lower performances, and using the elasticity metric may further improve the performances of less experienced readers. This type of guidance may reduce unnecessary biopsies by increasing the detection rate for malignant lesions and deliver significant benefits for routine clinical practice in underserved areas where experienced readers may not be available.

Keywords: Breast cancer; breast ultrasound; elastography; artificial intelligence

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Key Points

- Artificial intelligence (AI) decision support software, can enhance the characterization of preselected ultrasound lesions by providing breast imaging-reporting and data system scoring and associated cancer risk predictions.
- AI systems can support radiologists, particularly those with less experience.
- The integration of AI-guided systems with shear wave elastography measurements demonstrates potential for reducing unnecessary biopsies.

Introduction

Breast cancer is the second most common cancer among women worldwide (1). It is a complex disease with varying types and stages, necessitating early detection and accurate diagnosis for effective treatment. Mammography has been at the forefront as the first modality of breast cancer detection for years. However, more refined, accessible, and less invasive modalities have led to significant advances in imaging technologies. Among these, breast ultrasound (US) has emerged as a vital diagnostic tool, offering substantial benefits, especially when used alongside other imaging modalities (2). Its non-invasive nature, absence of radiation exposure, and ability to visualize

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dense breast tissue make it an excellent option for a wide range of patients, including those for whom radiation is a concern (3).

The advent of sophisticated artificial intelligence (AI) systems has further enhanced the capability of breast US (4). Research indicates that AI, known for its high accuracy and sensitivity, holds great promise in assisting radiologists and breast specialists (5). Particularly for those with less experience, AI can serve as a valuable tool, helping to reduce the rate of misdiagnosis and ensure patients receive timely and appropriate treatment (6). Despite its low specificity, the potential of AI in improving US diagnostics cannot be understated, underlining the need for ongoing research in this exciting intersection of technology and medicine. Commercially available AI systems for breast US are designed to enhance diagnostic accuracy, streamline workflow, and improve the overall efficiency of breast cancer detection (7). The Koios decision support (DS) system has been designed to assist radiologists in classifying and diagnosing breast lesions using US imaging. Koios DS uses deep learning algorithms to analyze US images and provides a breast imaging-reporting and data system (BI-RADS) classification to help determine the necessity of a biopsy (8). S-Detect for Breast US is another software integrated into US devices that uses an advanced AI algorithm to analyze and classify the characteristics of breast lesions in US images, aiming to increase diagnostic accuracy and efficiency. S-Detect™ provides standardized reporting, similar to Koios DS, and can assist in reducing variability among different examiners (9). QVCAD is a computer-aided detection system designed for use in both breast US and mammography. It aids radiologists by highlighting areas that may warrant a closer look, thus potentially improving detection rates and reducing the time taken to review images (10, 11). Each system brings a unique approach to integrating AI into breast US imaging. The common goal is to support radiologists by providing a second opinion, reducing the chance of missed diagnoses, and improving the specificity and sensitivity of breast cancer detection through US, serving as an adjunct to the radiologist's expertise (6, 12). This can potentially decrease unnecessary biopsies and allow for a more accurate and timely diagnosis of breast cancer (8).

Continual advances in AI technology and ongoing research ensure AI systems become increasingly sophisticated, further revolutionizing breast cancer diagnostics using US imaging. The aim of the current study was to assess the role of Koios DS in augmenting the capabilities of experienced and less experienced radiologists and improving efficiency and accuracy in diagnosing breast lesions.

Materials and Methods

Study Population

The institutional review board approved the study (İstanbul Bilgi University, Committee on Ethics in Research on Humans with the approval number of 2024-50162-062, date: 04.03.2024), and written informed consent was obtained from participants. Initially, a cohort of 80 patients was considered who had been admitted to our institute with a suspicion of breast cancer and had undergone diagnostic breast US imaging and US-guided core needle biopsy between September 2022 and August 2023. The exclusion criteria applied were being pregnant or breastfeeding, undergoing neoadjuvant chemotherapy, having a prior history of US-core needle biopsy of the target lesion, and having poor-quality US images. Finally, seventy patients with a total of seventy suspicious breast lesions (53 malignant and 17 benign) were enrolled in this retrospective study.

Breast US Imaging and Ultrasound-Guided Biopsy

The breast US imaging was conducted using the GE LOGIQ E9 system (GE Healthcare, USA). The imaging covered conventional B-mode and color Doppler imaging using a high-frequency broad-bandwidth linear matrix array transducer (ML6-15 transducer, GE Healthcare) and shear wave elastography (SWE) using a linear array probe (9-L probe, GE Healthcare). During SWE imaging, patients were instructed to stop breathing for five seconds to reduce motion artefacts. Lesions were imaged in their longest diameter with minimal pressure applied to the breast. The imaging display featured a side-by-side panel for B-mode and SWE images, allowing real-time breast lesion evaluation. A circular region of interest was positioned on the stiffest part of the lesion, and the maximum elasticity was measured in kilopascals (13, 14). The two orthogonal transverse and sagittal grayscale US images and maximum elasticity measurement for lesions were stored in the picture archiving and communication system.

US-guided biopsy procedures were performed with an automated biopsy gun equipped with a 14-gauge needle (Bard Peripheral Vascular, Inc., USA). This technique combined the real-time imaging capabilities of US with the precision of an automated biopsy gun to collect tissue samples from inside the body, which improved the accuracy of diagnoses, reduced the risk of complications, and often requires only local anesthesia, making it a preferred option for many patients and healthcare providers alike (15). The obtained biopsy specimens were subsequently dispatched for standard histopathological evaluation, considered the gold standard diagnosis for the analyses in the current study.

AI Augmented Image Evaluation

The orthogonal transverse and sagittal grayscale breast US images of lesions were inputted into an AI-incorporated computerized image analysis software implemented in the PACS system, which is not available on the US machine, the Koios DS study tool (version 2.3.0; Koios Medical Inc., IL, USA). The user marked the centers of the lesions on the images, and the tool then automatically segmented the lesions. The user had the option to correct the segmentation manually. Finally, the tool extracted morphological features for the lesions and used them to provide a risk indicator for the likelihood of malignancy. The risk indicator fell into four categories: "Benign," which indicated BI-RADS 2 assessment; "Probably Benign," which referred to BI-RADS 3 assessment; "Suspicious," which designated BI-RADS 4A/B assessment; and "Probably Malignant," which stated BI-RADS 4C+ assessment (for illustrations, see Figures 1, 2).

Image Evaluation by the Readers

The orthogonal transverse and sagittal grayscale breast US images of a mass lesion were reviewed by two readers blinded to the patient's clinical data. Among the two readers, one had 15 years of experience (F.C.), whereas the other had one year of experience (M.O.) in breast US imaging. The experienced reader conducted real-time US, while the less-experienced reader assessed the images stored in the PACS system. The readers evaluated for differences in echotexture of mass lesions, and evaluated various aspects of mass lesions, including shape and margin, size, echogenicity, posterior features, elasticity, and vascularity based on the US characteristics; the lesions were classified using BI-RADS (16).

After evaluating the images, the less experienced reader was allowed to revise their previous BI-RADS assessments one month later. This

deliberate temporal gap was to diminish any potential bias and enhance the repeated assessment's objectivity. In a two-stage review, the reader was informed about the categorizations by the Koios AI system first and second, informed about the categorizations due to the maximum elasticity in adjuncts. In each stage, the alterations in their assessments were marked.

The BI-RADS assessments by the two readers and the AI system were recorded for use in enumerating overall diagnostic performances. They were processed to quantify detection performances by performing dichotomization into benign or malignant detection as follows: BI-RADS 2 and 3 were designated as benign, while BI-RADS 4A/B and 4C+ were considered malignant.

Statistical Analysis

Youden's analysis was performed to determine the optimum lower and upper thresholds for the maximum elasticity measure, ensuring sensitivity and specificity at a level of 95%. The lesions with elasticity lower than the lower threshold were categorized as benign, while those with elasticity higher than the upper threshold were categorized as malignant. The lesions with elasticity between the lower and upper thresholds were acknowledged as non-specific.

Overall diagnostic performance was enumerated by plotting the receiver operator characteristics (ROC) curve and calculating the area under the curve (AUC). The performance according to an AUC was attributed excellent, good, fair, poor, and fail if the AUC was 0.90–1.00, 0.80–0.89, 0.70–0.79, 0.60–0.69, and 0.50–0.59, respectively. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy metrics were used to evaluate the detection performances. They were considered very high, high, moderate, low, and very low if their values were 95–100%, 85–94.9%, 75–84.9%, 65–74.9%, and 0–64.9%, respectively. All analyses were performed using SPSS, version 25.0 statistical software (IBM Inc., Armonk, NY, USA).

Results

Seventy women aged between 32 and 87 years (mean, 50.4 years) were included in the study. There were seventy breast masses, of which fifty-three were malignant (75.7%) and seventeen were benign (24.3%). Among the malignant masses, the predominant pathology was invasive ductal carcinoma (61.4%), while it was fibrosis among the benign masses (14.3%). The mass diameter ranged from 5 to 65 mm [mean, 19.9 mm; standard deviation (SD), 12.6 mm]. The mass elasticity varied from 10 to 184 kPa (mean, 87.8 kPa; SD, 45.6 kPa) (Table 1).

Figure 3 shows the plot for Youden's statistics that reveals the sensitivity and specificity for the maximum elasticity of the SWE. On this plot, consideration of 95% sensitivity and specificity gives the lower and the upper thresholds of 20 kPa and 138 kPa for the elasticity, which quantifies the stiffness of tissues as an indicator in differentiating between benign and malignant breast lesions (malignant lesions tend to be stiffer compared to benign ones). Consequently, the masses with E_{max} ≤20 kPa were classified as benign, 20 kPa < E_{max} <138 kPa were classified as non-specific, and E_{max} ≥138 kPa were classified as malignant.

Table 2 tabulates the BI-RADS categorizations of the breast masses by the experienced reader, the less-experienced reader alone, the Koios DS AI system alone and the less-experienced reader with either AI system support or AI system and elasticity data. The AI system decision guidance led to four upgrades (BIRADS 3 to BIRADS 4A) and one downgrade (BIRADS 4A to BIRADS 3). Moreover, incorporating the elasticity classification upgraded two lesions while downgrading two lesions though one of the lesions was malignant.

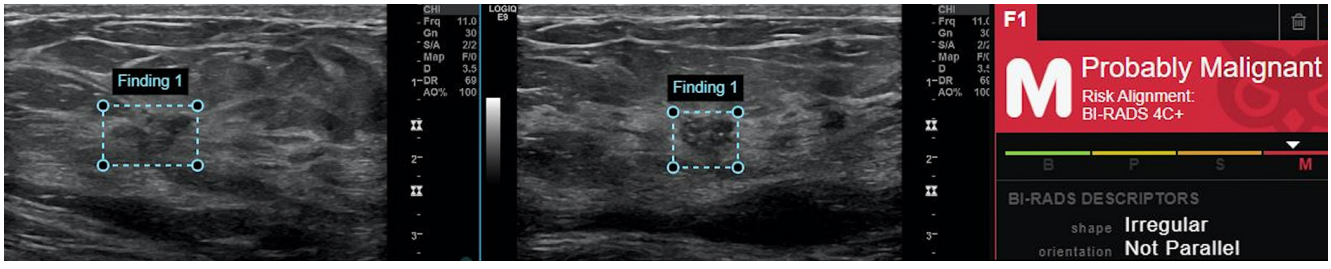

Figure 1. A malignant breast mass with a diameter of 9 mm, histologically proven IDC. Orthogonal transverse and sagittal ultrasound images, the categorical assessment by Koios DS that reports "Probably Malignant" with "BI-RADS 4C+" risk

DS: Decision support; BI-RADS: Breast imaging-reporting and data system

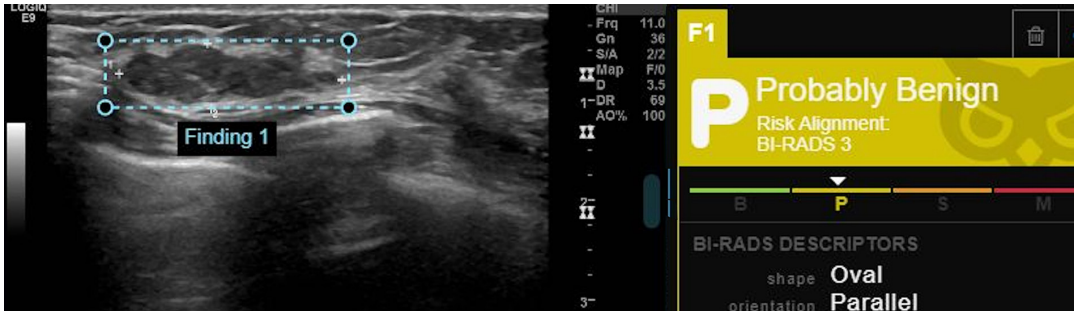

Figure 2. A benign breast mass with a diameter of 2.2 cm, histologically proven fibroadenoma. Orthogonal transverse ultrasound image, the categorical assessment by Koios DS that reports "Probably Benign" with "BI-RADS 3" risk

DS: Decision support; BI-RADS: Breast imaging-reporting and data system

Figure 4 shows the plots for the ROC curves illustrating the overall diagnostic performances of the readers and the AI system considering the BI-RADS categories and the histopathological assessments. The experienced reader showed good overall diagnostic performance (AUC=0.888), and the Koios DS AI system attained fair overall diagnostic performance (AUC=0.693). The less-experienced reader showed poor to fair performances impacted by the guidance. The performance was poor when no guidance was considered (AUC=0.512). However, it improves when the reader received guidance from the AI system (AUC=0.655). Further improvement in the performance was accomplished when the reader was guided by both the AI system and the maximum elasticity from elastography (AUC=0.679) (Table 3).

The BI-RADS assessments by the two readers and the Koios DS AI system were dichotomized into benign or malignant detection (BI-RADS 2 and 3 were designated as benign, while BI-RADS 4A, 4B, and 4C+ were designated malignant). Table 4 tabulates the diagnostic performances of the experienced reader, the AI system, and the less-experienced reader due to the dichotomization. Corresponding bar plots are shown in Figure 5. The experienced reader correctly diagnosed 52 out of the 53 malignant lesions and 10 out of the 17 benign lesions. The one misdiagnosed malignant lesion was an invasive ductal carcinoma. The misdiagnosed benign lesions were three fibrosis, two fibroadenomas, one atypical ductal hyperplasia (ADH), and one sclerosing adenosis. Subsequently, the experienced reader achieved 98.1% sensitivity, 58.8% specificity, 88.1% PPV, 90.9% NPV, and 88.6% accuracy in the diagnosis. The AI system correctly identified 49 of the 53 malignant lesions and 6 of the 17 benign lesions. The misclassified lesions were two invasive ductal carcinoma, two ductal carcinoma *in situ* (DCIS), six fibrosis, three fibroadenomas, and two sclerosing adenosis. The AI system demonstrated a sensitivity of 92.5%, specificity of 35.3%, PPV of 81.7%, NPV of 60.0%, and overall accuracy of 78.6%. The less-experienced reader correctly diagnosed 45 out of 53 malignant lesions and 3 out of 17 benign lesions without any guidance. The misdiagnosed lesions included seven invasive ductal

Table 1. Breast mass characteristics

Mass diameter (mm)	**19.9±12.6[a] (5–65)[b]**	
Mass elasticity (kPa)	87.8±45.6 (10–184)	
Number of masses	Malignant	Benign
	53 (75.7%)	17 (24.3%)
	Histopathology	
	43 IDC (61.4%)	10 Fibrosis (14.3%)
	3 ILC (4.3%)	4 Fibroadenoma (5.7%)
	5 DCIS (7.1%)	1 ADH (1.4%)
	2 apocrine carcinoma (2.9%)	2 sclerosing adenosis (2.9%)

[a]: Mean ± SD; [b]: Minimum-maximum; SD: Standard deviation; ADH: Atypical ductal hyperplasia; DCIS: Ductal carcinoma *in situ*

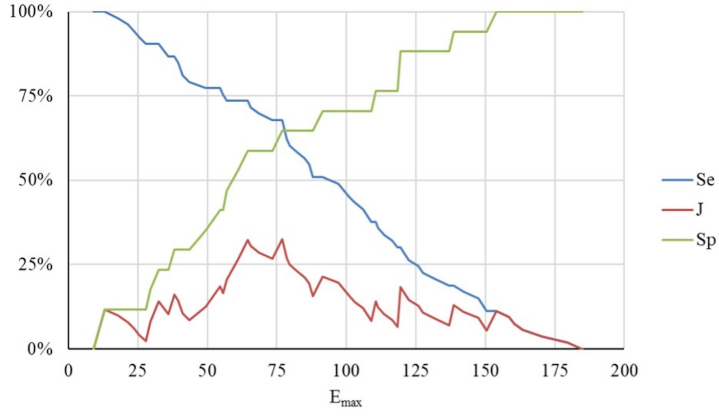

Figure 3. Plots for the Youden J index for the maximum elasticity, E_{max}

Sp: Specificity; Se: Sensitivity

Table 2. BI-RADS categorizations of breast masses

	BI-RADS 2	BI-RADS 3	BI-RADS 4A/B	BI-RADS 4C+
Experienced reader	0	11	24	35
Koios DS	3	4	40	23
Less experienced reader Koios and elasticity guided	0	8	34	28
Less experienced reader Koios guided	0	8	34	28
Less experienced reader	0	11	38	21

BI-RADS: Breast imaging-reporting and data system; DS: Decision support

carcinomas, one DCIS, seven fibrous lesions, four fibroadenomas, two cases of sclerosing adenosis, and one ADH. Consequently, the less experienced reader achieved 84.9% sensitivity, 17.6% specificity, 76.3% PPV, 27.3% NPV, and 68.6% accuracy. When informed of the AI system classification, the less-experienced reader diagnosed 48 of the 53 malignant lesions and 3 of the 17 benign lesions. This practice slightly improved the performance: 90.6% sensitivity, 17.6% specificity, 77.4% PPV, 37.5% NPV, and 72.9% accuracy. When the less-experienced reader made a diagnosis knowing both the decision of the AI system and the detection regarding the maximum shear wave velocity, 49 out of the 53 malignant lesions and 4 out of the 17 benign lesions are correctly diagnosed. This practice markedly improved the performance: 92.5% sensitivity, 23.5% specificity, 79.0% PPV, 50.0% NPV, and 75.7% accuracy.

Discussion and Conclusion

The current work reveals that the sensitivity and specificity of the AI system were lower than those accomplished by an experienced reader but higher than the less-experienced reader. In accordance with our study, Chabi et al. (12) showed that the contribution of computed aided diagnosis (CAD) varied according to the level of experience of the radiologists, increasing sensitivity from approximately 88% to 99%. Similar to their results, the Koios DS AI system increased

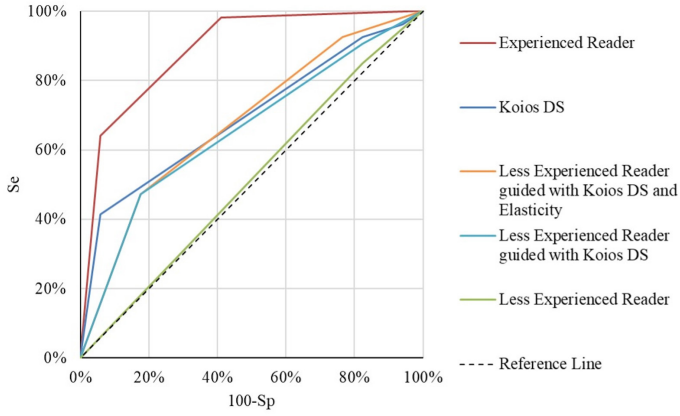

Figure 4. Plots for the ROC curve

ROC: Receiver operator characteristics; DS: Decision support; Sp: Specificity

Table 3. Results of the ROC analysis

	AUC	Standard error	95% CI	
			Lower bound	Upper bound
Experienced reader	0.888	0.049	0.793	0.983
Koios DS	0.693	0.067	0.562	0.824
Less experienced reader Koios and Elasticity guided	0.679	0.074	0.534	0.823
Less experienced reader Koios guided	0.655	0.073	0.512	0.799
Less experienced reader	0.512	0.082	0.352	0.672

ROC: Receiver operator characteristics; AUC: Area under the curve; DS: Decision support; CI: Confidence interval

Table 4. Diagnostic performances

	TP	TN	FP	FN	Se (%)	Sp (%)	NPV (%)	PPV (%)	Acc (%)
Experienced reader	52	10	7	1	98.1	58.8	90.9	88.1	88.6
Koios DS	49	3	14	4	92.5	35.3	60.0	81.7	78.6
Less experienced reader Koios and elasticity guided	49	3	14	4	92.5	23.5	50.0	79.0	75.7
Less experienced reader Koios guided	48	3	14	5	90.6	17.6	37.5	77.4	72.9
Less experienced reader	45	3	14	8	84.9	17.6	27.5	76.3	68.6

NPV: Negative predictive value; PPV: Positive predictive value; Acc: Accuracy; Sp: Specificity; Se: Sensitivity; DS: Decision support

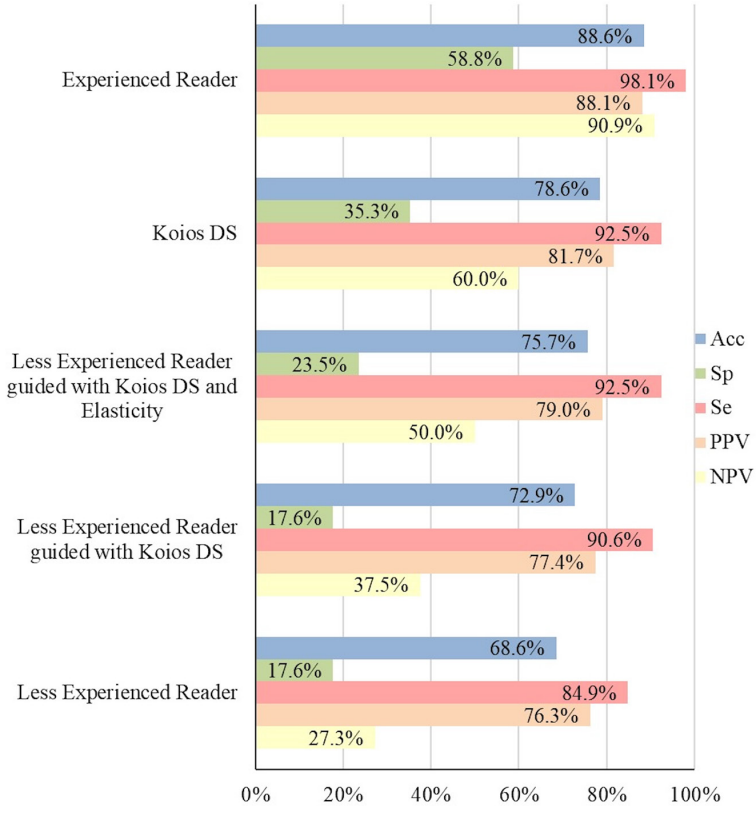

Figure 5. The bar plots for detection performances

Sp: Specificity; Acc: Accuracy; Se: Sensitivity; DS: Decision support; NPV: Negative predictive value; PPV: Positive predictive value

the sensitivity of the less-experienced reader to 90.6% from 84.9%, although the specificity remained the same in our study (12). Lee et al. (6) demonstrated that the diagnostic performance of the inexperienced group did not differ from or was lower than that of CAD, and adjunct use of CAD enhanced the performance from 0.65 to 0.71, similar to our findings, which showed an improvement from 0.512 to 0.650. Compared with a single S-Detect or conventional ultrasound, S-Detect combined with elastography showed higher accuracy and specificity (17).

Park et al. (18) demonstrated a significant enhancement in both PPV, increasing from 53.3% to 76.2%, and AUC, rising from 0.623 to 0.759, through the integration of CAD, which is consistent with our findings.

To the best of our knowledge, few published studies have compared AI with radiologists at varying levels of expertise and incorporate SWE measurements into their findings. Our results demonstrated that the implementation of SWE along with KOIOS has been shown to enhance the AUC and specificity. Sun et al. (19) found that their combined AI model achieved an AUC of 0.89 and a specificity of 92%, exceeding the performance of individual models, including clinical, ultrasonic, elastography, and AI-only approaches. Similarly, our results support these findings. While US is a crucial imaging modality for detecting primary breast malignancies, recent studies have increasingly focused on AI-based advances. AI is advantageous for identifying internal textures; there exists a lack of notable studies about the diagnosis of breast lesions, including DCIS, and the AI-assisted assessment of BI-RADS exceeding the capabilities of radiologists and standardizing assessments, BI-RADS categories (20). Determining DCIS and other breast lesions through US is important for early preventive treatment measures. Yin et al. (21) showed that US radiomics-based AI can effectively differentiate between DCIS and benign fibroadenomas. However, Berg et al. (22) highlighted that AI software has not been trained on a sufficient number of US images of masses in the context of DCIS and that there is a need for improvement in this area. Our study also found that the AI missed two DCIS cases, both of which were correctly diagnosed by an experienced reader, while one was overlooked by a less-experienced reader, although not all the other lesions were benign. These results suggest that the AI's diagnostic performance does not match that of an experienced reader in recognizing DCIS as malignant.

There are some limitations of the current study. Firstly, it was limited by its retrospective, single-center design and a relatively small number of patients. In addition, the evaluation of breast US images was conducted by two radiologists, which may impact the generalizability of the findings to the broader population. Furthermore, the use of Koios DS in the study was limited as it is not integrated within the US device and was only implemented in the PACS system for the second evaluation by an inexperienced radiologist. This setup prevents simultaneous evaluation with the Koios results by the experienced radiologist during lesion assessment. Moreover, the study focused on lesions directed to biopsy, which may introduce a bias towards higher BI-RADS categories. Finally, it is important to keep in mind the low specificity of the AI system to minimize unnecessary biopsies of benign lesions.

In conclusion, evaluating suspicious masses on breast US images requires experience, and the experience level determines the diagnostic performance. Experienced readers may show performance categorized as good, but the performance of the less experienced may only be categorized as fair and thus should be improved. AI-based guidance may improve the lower performances. However, adopting the elasticity metric into the guidance may lead to further improvements in the performances of less experienced readers. This type of guidance may reduce unnecessary biopsies by increasing the detection rate for malignant lesions and deliver significant benefits for routine clinical practice in underserved areas where experienced readers may not be available. The findings advocate for further exploration of AI guidance to improve diagnostic accuracy and patient outcomes in diagnostic breast US.

Ethics

Ethics Committee Approval: The institutional review board approved the study (İstanbul Bilgi University, Committee on Ethics in Research on Humans with the approval number of 2024-50162-062, date: 04.03.2024)

Informed Consent: Written informed consent was obtained from participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.Ç.; Concept: F.Ç., T.D., G.E.; Design: F.Ç., T.D., G.E.; Data Collection or Processing: F.Ç., O.T., M.O., G.E.; Analysis or Interpretation: F.Ç., O.T., M.O., G.E.; Literature Search: F.Ç., T.O., G.E.; Writing: F.Ç., O.T., T.O., G.E.

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

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Original Article

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Evaluation of Long-Term Lymphedema Rate in Patients With Subclinical Lymphedema Diagnosed in the Preoperative Period via Bioimpedance

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ABSTRACT

Objective: The aim of this study was to evaluate the relationship between subclinical lymphedema identified prior to surgical intervention and clinical lymphedema observed in the late period, the incidence of lymphedema in our cohort, and the associated risk factors.

Materials and Methods: This prospective study was conducted with early-stage breast cancer patients who had been enrolled in a previous study. For diagnosing lymphedema, physical examination, L-Dex® score, and circumferential measurement was used. The L-Dex® score was used as a screening test for preoperative, subclinical lymphedema since there were no clinical findings. Patients with subclinical lymphedema were provided with education and followed up more frequently with regular monitoring.

Results: The mean age of the 217 participants was 56.7±12.7 years (range 29–90), and the mean body mass index was 27.7±3.3 kg/m^2 (range 19.3–36.9). Among the 217 patients, lymphedema was detected in 31 (14.7%) at a median follow-up period of 89 months (range 73–108 months). Multivariable analysis of factors associated with late-stage lymphedema revealed positive lymph node count and capsular invasion as significant factors (p = 0.001 for both). Forty (18.4%) had preoperative subclinical lymphedema. At the end of the follow-up period, lymphedema persisted in 11 patients (27.5%) and resolved in 29 patients (72.5%). In multivariable analysis, the positive lymph node count was identified as an independent variable in these patients.

Conclusion: Identifying high-risk patients, regular monitoring, and early intervention can significantly reduce the risk of clinical lymphedema through timely treatment.

Keywords: Breast cancer; lymphedema; risk factors; early detection

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Key Points

- This study identified lymphedema risk factors (positive lymph node count and capsular invasion) based on a median 89-month follow-up in 217 patients who were followed-up for lymphedema from the preoperative period.

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Introduction

Lymphedema, commonly observed following breast cancer therapy, is a significant complication affecting quality of life. Due to the increasing incidence of breast cancer globally-making it the most frequent type of cancer-and the success of modern treatments that have significantly improved survival rates, early detection and effective management of lymphedema have become increasingly important (1). Breast cancer-related lymphedema results from the accumulation of protein-rich lymphatic fluid in the extracellular compartment due to reduced lymphatic circulation capacity (2). This condition presents as a severe problem for breast cancer patients, causing swelling, pain, fatigue, susceptibility to infections, and impaired daily activities. It also induces psychological distress, including anxiety and depression, which can evoke memories of cancer (3). Currently, there is no definitive treatment for this condition. Early detection and treatment of lymphedema during the early stages, where subcutaneous fibrosis or fat tissue development has not occurred (stages 0 and 1), have been shown to improve patient outcomes (4). Close monitoring of high-risk patients is central to early detection. Thus, identifying risk factors and calculating the risk of developing lymphedema are of clinical importance.

Risk factors for lymphedema have ben reported to include axillary lymph node dissection (ALND), radiotherapy, a high number of dissected lymph nodes, and obesity. Chemotherapy, genetic predisposition, and hypertension are being investigated as potential risk factors (5). Early-stage risk calculation based on these factors allows the inclusion of high-risk patients in close monitoring programs (6).

In our breast center, subclinical lymphedema was detected preoperatively in 21.3% of patients using bioimpedance spectroscopy (L-Dex®) among 245 breast cancer surgery patients between 2012 and 2015 (7). Obesity and positive lymph node count post-surgery were identified as independent risk factors for lymphedema. The aim of the present study was to evaluate the relationship between preoperative, subclinical lymphedema and late-stage clinical lymphedema, the incidence of lymphedema in our patients, and the associated risk factors. A predictive model for high-risk patients is also proposed.

Materials and Methods

Patients from the previous study (7) on preoperative lymphedema were included in the current study. These patients underwent surgery for early-stage breast cancer (cT1-3, N0-3, M0) at a single center between 2012 and 2015 and were regularly monitored for lymphedema every three months during the first postoperative year and every six months thereafter. Patients monitored between 2012 and 2021 with a minimum follow-up of six years were enrolled.

Inclusion criteria were participation in the previous study; no contraindications for bioimpedance analysis; unilateral breast cancer; and consent to participate in the study. The exclusion criteria were conditions causing edema such as cardiac or renal failure; bilateral breast cancer; refusal to participate; and patient mortality.

Patient examinations were conducted by an experienced physiatrist. Clinical, histopathological and treatment findings, and preoperative bioimpedance measurements were recorded. In the pre-operative period, an L-Dex score of 7.1 was used as the threshold for bioimpedance analysis, as previously described (8).

Lymphedema diagnosis was based on circumferential measurements and bioimpedance analysis during physical examinations. A difference of more than 2 cm between arms was defined as lymphedema. L-Dex® scores ≥7.1 were used to diagnose lymphedema (8).

Patients with subclinical lymphedema received training on self-drainage methods, arm usage principles, and early lymphedema symptoms. Clinical lymphedema patients underwent manual lymph drainage and compression therapy.

The İstanbul Bilim University Clinical Research Ethics Committee approved the study (decision no: 30.04.2014/19-136, date: 30.04.2014). Informed consent was obtained from all participants.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 22 was used for statistical analyses (IBM Inc., Armonk, NY, USA). The Kolmogorov-Smirnov test assessed data distribution. Independent variables were analyzed using independent samples t-test, Mann-Whitney U, and chi-square tests, as appropriate. Logistic regression was used to develop a risk model. Receiver operator characteristics curve analysis determined cut-off values. Graphs were created using SPSS and Excel. Statistical significance was set at $p<0.05$.

Results

A total of 277 patients who had been included in our previous study on preoperative lymphedema were eligible. Among these, 28 (10.1%) were lost to follow-up for various reasons, and 32 (11.5%) could not be followed up. Thus, the study was completed with 217 patients. The mean age of the 217 participants was 56.7±12.7 years (range 29–90), and the mean body mass index (BMI) was 27.7±3.3 kg/m^2 (range 19.3–36.9). Lymphedema was observed in 31 (14.7%). The median duration of follow-up was 89 months (range 73–108). The demographic characteristics are presented in Table 1 and Figure 1.

In long-term follow-up, multivariable analysis revealed that positive lymph node count and capsular invasion were independent factors affecting lymphedema development (Table 2). The probability curve generated using these variables enabled the calculation of long-term lymphedema risk (model accuracy: 85.3%). This calculation is shown in Figure 2.

Among the 217 patients who underwent preoperative bioimpedance analysis, 40 (18.4%) were diagnosed with subclinical lymphedema (7). At the end of a mean follow-up period of 89 months, lymphedema persisted in 11 patients (27.5%) and resolved in 29 patients (72.5%). In multivariable analysis of these patients with preoperative subclinical lymphedema, the positive lymph node count was identified as the only independent variable for persistent lymphedema. The model's accuracy was calculated at 75% (Table 3, Figure 2).

In the descriptive evaluation of the 29 patients who had pre-operative subclinical lymphedema but later showed regression, the mean BMI was 28.4±3.2, 51.7% underwent axillary dissection, 17.2% received axillary radiotherapy, and 20.6% underwent neoadjuvant chemotherapy.

When considering risk factors for early-term lymphedema, the cut-off value was found to be 4 positive lymph nodes. The area under the curve for 4 positive lymph nodes (sensitivity: 72%, specificity: 86%) was higher compared to positive lymph node counts of 3, 5, and 6 (0.795 *vs*. 0.770-0.749-0.749) (Figure 3).

Table 1. Demographic, pathological and treatment characteristics, and lymphedema rates of patients with long-term follow-up

Characteristics		Lymphedema		
		No LE (n=186)	**LE present (n=31)**	***p*-value**
Age (mean ± SD)		56.24±12.9	60±10.9	0.081
BMI (mean ± SD)		27.5±3.1	28.7±3.9	0.085
Axillary intervention	SLNB alone	114 (61.3)	4 (12.9)	**≤0.001**
	SLNB+ALND	72 (38.7)	27 (87.1)	
Pathological lymph node status	N0	114 (61.3)	4 (12.9)	**≤0.001**
	N1	54 (29.0)	11 (35.5)	
	N2	10 (5.4)	4 (12.9)	
	N3	8 (4.3)	12 (38.7)	
Radiation Therapy	Breast	158 (84.9)	17 (54.8)	**≤0.001**
	Breast+AX	28 (15.1)	14 (45.2)	
Pre-operative LE	Absent	157 (84.4)	20 (64.5)	**0.008**
	Present	29 (15.6)	11 (35.5)	
Obesity	BMI ≥30	49 (26.3)	15 (48.4)	**0.013**
	BMI <30	137 (73.7)	16 (51.6)	
*Systemic chemotherapy	Absent	73 (39.2)	2 (6.4)	**≤0.001**
	Presence	113 (60.8)	29 (93.6)	

All data given as count and percentage [n (%)] unless otherwise stated
*Among the patients who received systemic chemotherapy, 14.3% underwent neoadjuvant chemotherapy
SD: Standard deviation; BMI: Body mass index; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection; AX: Axillary lymph nodes; LE: Lymphedema

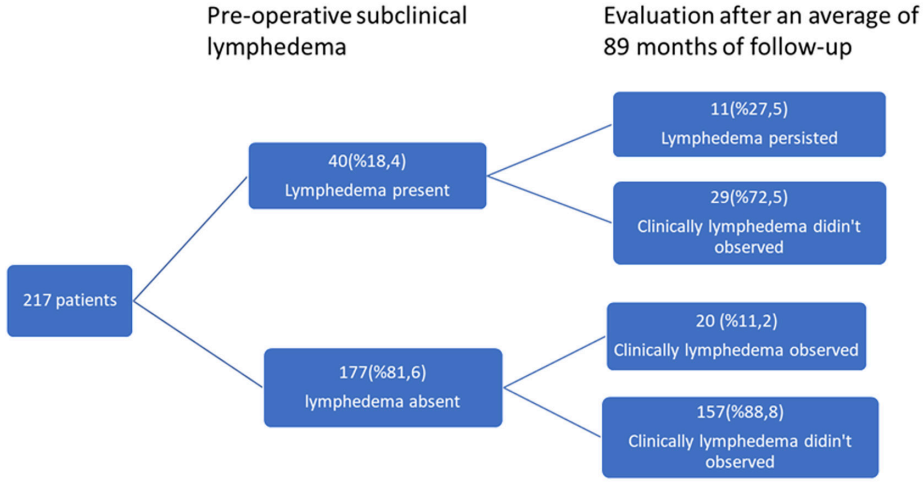

Figure 1. Changes in lymphedema over the follow-up period

Lymphedema was diagnosed at a median of 11 months (range 1–84 months) in patients with no preoperative lymphedema who later developed the condition (n = 20). The mean BMI in this group was 27.5±3.2, with daily arm usage reported as 4–6 hours. Infection in the operated arm was observed in only two (10%) patients. In multivariable analysis, capsular invasion, positive lymph node count, and a high L-Dex® score measured preoperatively were identified as independent variables.

At the time of the first study, the L-Dex® cut-off value was set at 10. However, using new data, the L-Dex® cutoff was adjusted to 7.1, increasing its sensitivity (8). The positive predictive values of L-Dex® 7.1 and L-Dex® 10 in detecting long-term clinical lymphedema were 23.5% and 26%, respectively. The negative predictive values were 89.9% and 88.8%, respectively.

Table 2. Logistic regression analysis of the factors affecting lymphedema in the long-term

Single-variable analysis					**Multi-variable analysis**			
		95% CI EXP (B)				**95% CI EXP (B)**		
	OR	**Lower**	**Upper**	***p*-value**	**OR**	**Lower**	**Upper**	***p*-value**
**BMI	1.124	0.998	1.267	0.054				0.364
Positive lymph node count	**1.226**	**1.126**	**1.335**	**≤0.001**	**1.162**	**1.064**	**1.269**	**0.001**
Dissected lymph node count	1.118	1.069	1.169	≤0,001				0.142
Capsular invasion	**8.750**	**3.821**	**20.035**	**≤0.001**	**4.882**	**1.967**	**12.115**	**0.001**
Radiotherapy	4.651	2.060	10.04	≤0.001				0.329
Axillary intervention (SLNB/AD)	10.687	3.592	31.811	≤0.001				0.082
Pre-operative LE present/absent)	2.978	1.291	6.867	0.010				0.986
Obesity (present/absent)	2.621	1.206	5.697	0.015				0.161
Chemotherapy	2.702	1.405	5.923	0.01				0.225

**: BMI ≥30; CI: Confidence interval; OR: Odds ratio; BMI: Body mass index; SLNB: Sentinel lymph node biopsy; AD: Axillary dissection; LE: Lymphedema

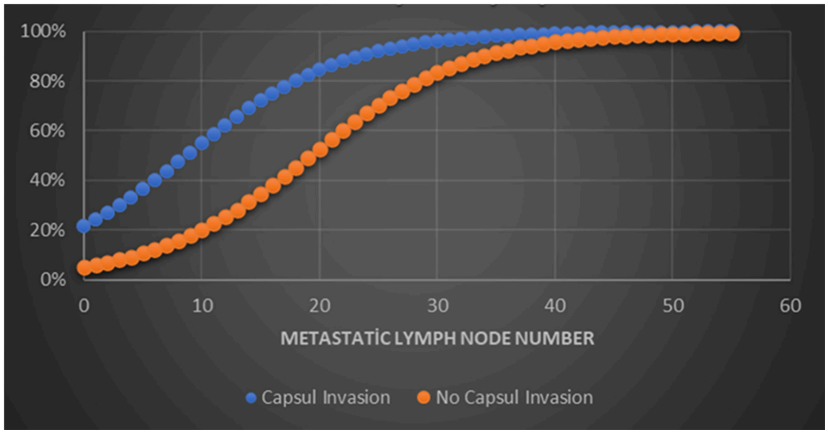

Figure 2. Estimated lymphedema risk based on the probability model

Discussion and Conclusion

The preliminary findings of this study revealed that preoperative, subclinical lymphedema was detected in 21.3% of early-stage breast cancer patients (cT1-3, N0-3) using bioimpedance spectroscopy (7). During a mean follow-up of 89 months, the clinical lymphedema rate was 14.7%. Of note, in patients who underwent ALND the lymphedema incidence was 27.3%, while it was only 3.4% in patients who underwent sentinel lymph node biopsy (SLNB).

Compared to other studies, the lymphedema rate in ALND patients in our study was similar, while the rate in SLNB patients was lower (3, 9, 10). The absence of clinical lymphedema in 29 of 40 patients (72.5%) diagnosed with preoperative, subclinical lymphedema may be attributed to early lymphedema education and timely intervention after surgical treatment. Kilgore et al. reported that lymphedema regressed to a subclinical stage in 82% of patients monitored with bioimpedance, while clinical lymphedema was observed in patients with N2/N3 stages (10).

In the present study, positive lymph node count and capsular invasion were independent predictors of persistent lymphedema, consistent with findings from other studies (11, 12). While BMI, radiotherapy, and taxane-based chemotherapy were significant risk factors in univariate analysis, they were not identified as independent risk factors in multivariable analysis. N2/N3 patients likely received more aggressive chemotherapy and radiotherapy, making these variables dependent on lymph node count and capsular invasion.

The lower risk observed for BMI, chemotherapy, and radiotherapy in our study may be attributed to patient education, regular monitoring, and early interventions. These factors may mitigate the extracellular fluid buildup and reduced lymphatic flow caused by these variables.

Table 3. Multi-variable analysis of the patients (n=40) who had preoperative sub-clinical lymphedema, patients whose lymphedema continued (n=11) and patients whose lymphedema resolved (n=29)

Single-variable analysis					**Multi-variable analysis**			
		95% CI EXP (B)				**95% CI EXP (B)**		
	OR	**Lower**	**Upper**	***p*-value**	**OR**	**Lower**	**Upper**	***p*-value**
BMI	1.425	1.023	1.984	0.036				0.079
Positive lymph node count	**1.150**	**1.034**	**1.278**	**0.010**	**1.150**	**1.034**	**1.278**	**0.001**
Dissected lymph node count	1.108	1.018	1.206	0.018				0.225
Capsular invasion	4.364	0.950	20.036	0.058				0.276
RT (present/absent)	6.708	1.460	30.733	0.014				0.133
Axillary intervention SLNB/AD)	9.333	1.054	82.635	0.045				0.135
Obese*	4.821	0.884	26.300	0.069				0.201
Chemotherapy (present/absent)	2.638	1.105	6.735	0.006				0.117

*: Classified as BMI ≥30 *vs.* BMI<30; CI: Confidence interval; OR: Odds ratio; BMI: Body mass index; RT: Radiotherapy; SLNB: Sentinel lymph node biopsy; AD: Axillary dissection

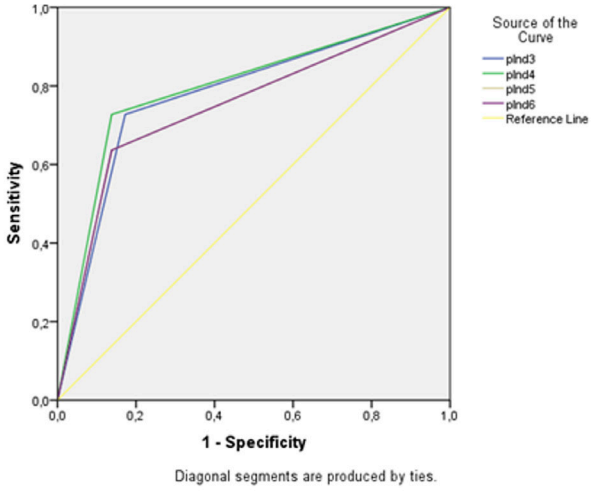

Figure 3. Effect of lymph node positivity on early-term lymphedema. Cut-off value calculations were performed sequentially according to 3, 4, 5, and 6 positive lymph nodes (PLND3, PLND4, PLND5, PLND6)

Byun et al. (13) identified BMI, lymph node dissection count, taxane-based chemotherapy, lymph node radiotherapy, and total mastectomy as independent risk variables for lymphedema. While these parameters were significant in our univariate analysis, they were not significant in multivariable analysis. Other studies conducted in our center found BMI to be an independent variable, along with lymph node dissection count (7, 14). The focus on weight management, dietitian support, and a mean BMI of <30 kg/m2 in our cohort probably contributed to these results.

According to previous research, early detection and treatment of lymphedema positively impacts treatment outcomes (15, 16). In our model, positive lymph node count and capsular invasion were the key predictors of lymphedema risk. Unlike symptom-based risk calculations (17), our model allows for risk assessment before chemotherapy and radiotherapy, enabling better follow-up and early treatment initiation. The long follow-up period and prospective design further strengthen our findings (18).

Positive lymph node count and capsular invasion were effective predictors of long-term lymphedema risk in early-stage breast cancer patients. Educating this high-risk patient group, initiating early treatment, and maintaining regular follow-up are crucial for reducing clinical lymphedema incidence.

Ethics

Ethics Committee Approval: The İstanbul Bilim University Clinical Research Ethics Committee approved the study (decision no: 30.04.2014/19-136, date: 30.04.2014).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Pracites: Z.E.İ., S.İ., E.Ö., F.Ç., A.Ö., Ç.O.; Concept: Z.E.İ., T.O., S.İ., E.Ö., A.Ö., G.S.; Design: Z.E.İ., T.O., S.İ., E.Ö., A.Ö., Ç.O., G.S.; Data Collection and/or Processing: Z.E.İ., S.İ., C.N., E.Ö., F.Ç., Ç.O.; Analysis and/or Interpretation: Z.E.İ., T.O., S.İ., C.N., E.Ö., F.Ç.; Literature Search: Z.E.İ., E.Ö., F.Ç., Ç.Ü., A.Ö., G.A., Ç.O., G.S.; Writing: Z.E.İ, T.O., S.İ., C.N., E.Ö., F.Ç., Ç.Ü., A.Ö., G.A., Ç.O., G.S.

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Original Article

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Assessment of Tumor Response to Neoadjuvant Chemotherapy in Breast Cancer Using MRI and ^{18}F-FDG PET/CT

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ABSTRACT

Objective: Neoadjuvant chemotherapy (NACT) has been the primary treatment method for patients with local advanced breast cancer. A pathological complete response (pCR) to therapy correlates with better overall disease prognosis. Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) have been widely used to monitor the response to NACT in breast cancer. The aim of this study was to assess tumor response to NACT by MRI and PET/CT, to determine which imaging modality is more accurate in detecting tumor response post NACT in breast cancer.

Materials and Methods: A retrospective review of our database revealed 34 women with breast cancer that had MRI and PET/CT performed prior to and after NACT, followed by definitive surgery. For response assessment, we calculated the difference in maximum diameter of the tumor in MRI and difference in standard uptake values in PET/CT. The correspondence rate between the imaging modalities and pCR were calculated. For the prediction of pCR, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy where analyzed.

Results: The assessment of tumor response to NACT showed 11 cases with pCR (32%), 15 pathological partial response (44%) and eight pathological no response (24%). The correspondence rate between MRI and pathological response was 50% (17/34), compared to 65% (22/34) for PET/CT. For prediction of pCR, MRI showed higher specificity compared to PET/CT (78.2% *vs.* 73.9%, $p = 0.024$), while the accuracy of PET/CT was significantly higher (79.4% *vs.* 70.5%, $p = 0.004$). PET/CT also had a higher NPV compared to MRI (94.4% *vs.* 78.2%, $p = 0.002$). There were no differences in terms of sensitivity and PPV between MRI and PET/CT.

Conclusion: Compared to MRI, PET/CT was more likely to correlate with the pathological response after NACT. For the prediction of pCR, PET/CT proved to be a more accurate imaging modality to monitor response after NACT than MRI.

Keywords: Breast cancer, MRI; neoadjuvant chemotherapy; pathological response; PET/CT

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Key Points

- The aim of neoadjuvant chemotherapy (NACT) is to achieve pCR, which correlates well with the overall prognosis.
- Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are increasingly used to monitor the tumor response after NACT, with certain limitations.
- There are no recommendations as to which imaging modality is the gold standard for assessing tumor response after NACT.
- This study showed that while PET/CT was more accurate than MRI for predicting pCR, combined use of both imaging modalities optimizes prediction of residual disease.

Introduction

Neoadjuvant chemotherapy (NACT) has been widely accepted as the primary treatment method for patients with locally advanced and inoperable breast cancer (1). Additional recommendations include its use in triple-negative or human epidermal growth factor receptor 2 (HER2) -positive breast cancers that are node-positive and/or larger than 2 cm, as it influences adjuvant therapy decisions in these patients (2). Moreover, NACT allows time to delay surgery, while waiting for genetic testing results or considering reconstructive options (3). The aim of NACT is to downstage tumors and to de-escalate the extent of surgical treatment, facilitating breast conserving surgery (BCS) and less aggressive axillary surgery (4). Having a pathological complete response (pCR) following NACT correlates with better overall prognosis, with an improved five-year survival rate of 89% reported in those receiving NACT compared to those not achieving pCR (5).

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Accurately identifying tumor response to therapy can only be made after final histological examination following definitive surgery (4). This leads to a delay in identifying the response to NACT during the course of treatment, either by excessive or deficient combination therapy, or by exposing patients to a prolonged treatment course with unwanted chemotherapy effects and might even result in incomplete or more aggressive surgery. Therefore, in order to evaluate the tumor response earlier during the course of neoadjuvant therapy and prior to definitive surgery, it is necessary to determine which imaging modality is more accurate (4, 5).

Tumor response has been traditionally evaluated by clinical examination, mammogram and ultrasound, with difficulty in differentiating fibrosis from residual tumor, limiting their efficacy (5, 6). Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) have been increasingly used to monitor response to NACT in breast cancer. They assess the morphological characteristic and the tumor function, respectively (6). There are many studies exploring the ideal imaging modality to evaluate the tumor response to NACT, but no consensus has been reached (5, 7). Moreover, the majority of the studies in literature evaluated MRI and PET/CT separately, in different cohorts of patients. Therefore, the aim of the present study was to assess the tumor response to NACT using both imaging modalities in the same group of patients with breast cancer, keeping pCR as the reference standard, in order to determine whether MRI or PET/CT was more accurate in detecting tumor response post NACT in breast cancer.

Materials and Methods

The study was approved by the Research Ethics Committee of the Government Hospitals in Bahrain (approval number: 65-230524, date: 23.05.2024). A retrospective review of our database revealed 209 female patients with biopsy-proven breast cancer who underwent NACT from January 2018 to December 2022. Patients were included if they had MRI and PET/CT performed prior to and after NACT, followed by definitive surgery. Patients who did not have both imaging modalities and those with missing data were excluded. Only 34 patients met the inclusion criteria and were analyzed.

The following data were collected from the patients' medical records: age at diagnosis; tumor type; tumor size; tumor grade; oestrogen receptor; progesterone receptor and HER2 status; Ki-67 index; clinical stage; NACT regimen and cycles; type of surgery; and final histopathological stage.

In order to evaluate tumor response in MRI, the maximum diameter of the tumor (Dmax) before and after chemotherapy were recorded. For assessment of tumor response in PET/CT, the tumor maximum standardized uptake value (SUV) before and after chemotherapy were recorded. The pathological response to chemotherapy was kept as the reference standard. Absence of invasive tumor was considered as pCR, however, ductal carcinoma *in situ* (DCIS) may be present. A change in the stage of the tumor following NACT was considered a pathological partial response (pPR). Tumors that did not show pCR or pPR were considered as pathological non-responder tumors (pNR). A radiological complete response (rCR) in MRI was absence of tumor enhancement in imaging after chemotherapy. A radiological partial response (rPR) was at least a 30% reduction in the Dmax of the tumour following therapy and the others were considered as radiological no response (rNR). In PET/CT, absence of flourine-18 fluorodeoxyglucose (^{18}F-FDG) uptake was considered as rCR. A reduction of at least 50% in SUV was considered as rPR and all others were considered as rNR.

Statistical Analysis

Changes in the Dmax were calculated using the following equation: [(Dmax_pre – Dmax_post)/Dmax_pre] x 100, where Dmax_pre was the maximum tumor diameter in pre-chemotherapy MRI and Dmax_post was post-chemotherapy. Changes in SUV were calculated as: [(SUVpre – SUVpost)/SUVpre] x100, where SUVpre and SUVpost were the maximum SUV uptake in PET/CT pre- and post-chemotherapy, respectively. The correspondence rates of tumor response between both imaging modalities and the final histopathological diagnosis were calculated. Demographic data were analyzed using means and percentages. To predict pCR, we compared the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy between both imaging modalities using the McNemar test. Statistical analysis were performed using Statistical Package for the Social Sciences software, version 29.0 (IBM Inc., Chicago, IL, USA) and $p < 0.05$ values were considered to be significant.

Results

The mean age of the patients was 46 years (range 33-66 years). The clinical stages of the patients at the time of presentation were: stage I in one patient (2.9%); IIA in 10 patients (29.4%); IIB in 10 patients (29.4%); IIIA in seven patients (20.6%); IIIB in four patients (11.8%); and IIIC in two patients (5.9%). Most (91.2%) had invasive ductal carcinoma. The NACT regimen was determined by tumor biology and the clinical stage. Of the 34 patients, 58.8% of patients where HER2-positive and therefore received six cycles of a combination of docetaxel, carboplatin, trastuzumab and pertuzumab. The remaining 14 patients received four cycles of doxorubicin, cyclophosphamide and paclitaxel. Chemotherapy was started within two weeks following initial imaging. The mean time interval between completion of chemotherapy and breast MRI was 17 days. The mean time interval between completion of chemotherapy and PET/CT was 18 days. The mean time interval between breast MRI and PET/CT after chemotherapy was 5 days. All patients underwent surgery approximately six weeks following NACT. Types of surgical procedure were: modified radical mastectomy n=13; mastectomy with sentinel lymph node biopsy (SLNB) n=7; BCS and axillary clearance n=5; and BCS with SLNB n=9.

Furthermore, the mean tumor size on pre-chemotherapy MRI was 5.75 cm (range 1.3–16 cm), with mean reduction in Dmax following treatment of 63%, ranging from 11% to complete reduction. One patient showed 87% increase in size following chemotherapy, indicating disease progression. The mean tumor SUV in the pre-chemotherapy PET/CT was 12.3 (range 2.8–30.8), with the mean reduction in SUV following treatment was 85.4% (range 3–100% reduction).

The histopathological characteristics and tumor response following NACT are shown in Table 1. Of the 34 patients, 23 (68%) had residual invasive tumor seen on final histopathology. The pathological tumor responses were as follows: 11 pCR (32%), 15 pPR (44%) and 8 pNR (24%). The correspondence rate between MRI and pathological response was 50% (17/34), compared to 65% (22/34) between PET/CT and pathological response, as shown in Table 2. MRI correctly assessed 6 of the 11 pCR (54.5%) cases, whereas PET/CT accurately assessed 10 of the 11 patients with pCR (90.9%). One pCR case was

Table 1. Histopathological characteristics and tumor response following neoadjuvant chemotherapy

Pathological complete response (n=11)		Pathological partial response (n=15)		Pathological no response (n=8)	
Age		**Age**		**Age**	
48 (35-62)		45 (33-55)		47 (33-66)	
Histological subtype		**Histological subtype**		**Histological subtype**	
IDC	10	IDC	13	IDC	8
ILC	1	ILC	0	ILC	0
MC	0	MC	2	MC	0
Tumor grade		**Tumor grade**		**Tumor grade**	
Grade 1	1	Grade 1	0	Grade 1	0
Grade 2	7	Grade 2	4	Grade 2	8
Grade 3	3	Grade 3	11	Grade 3	0
ER status		**ER status**		**ER status**	
Positive	8	Positive	9	Positive	7
Negative	3	Negative	6	Negative	1
PR status		**PR status**		**PR status**	
Positive	8	Positive	8	Positive	6
Negative	3	Negative	7	Negative	2
HER2 status		**HER2 status**		**HER2 status**	
Positive	8	Positive	8	Positive	4
Negative	3	Negative	7	Negative	4
Ki-67 index		**Ki-67 index**		**Ki-67 index**	
<20%	3	<20%	2	<20%	1
>20%	8	>20%	13	>20%	7
MRI response		**MRI response**		**MRI response**	
CR	6	CR	4	CR	1
PR	5	PR	9	PR	5
NR	0	NR	2	NR	2
PET/CT response		**PET/CT response**		**PET/CT response**	
CR	10	CR	3	CR	3
PR	1	PR	11	PR	4
NR	0	NR	1	NR	1

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; MC: Mucinous carcinoma; CR: Complete response; PR: Partial response; NR: No response; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography

Table 2. Correlation of pathological tumor response with response in MRI and PET/CT

			MRI			PET/CT		
		Patients	**rCR**	**rPR**	**rNR**	**rCR**	**rPR**	**rNR**
Pathological response	pCR	11	6	5	0	10	1	0
	pPR	15	4	9	2	3	11	1
	pNR	8	1	5	2	3	4	1
	Total	34	11	19	4	16	16	2

pCR: Pathological complete response; pPR: Pathological partial response; pNR: Pathological no response; rCR: Radiological complete response; rPR: Radiological partial response; rNR: Radiological no response; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography

assessed as rPR in PET/CT, which correlates with the residual DCIS seen on histopathology. For the 15 pPR cases, the correspondence rate of MRI was 60% (9/15) and PET/CT 73% (11/15). For the 8 cases of pNR, the correspondence rate of MRI was 25% (2/8) and PET/CT was 12.5% (1/8).

Prediction of the pCR by PET/CT and MRI is shown in Table 3. While PET/CT showed a higher sensitivity (90.9% *vs.* 54.5%) and PPV (62.5% *vs*. 54.5%) compared to MRI, this was not significantly better (p = 0.130 and p = 0.722, respectively). The specificity of MRI was significantly higher than PET/CT (78.2% *vs.* 73.9%, p = 0.024). PET/CT showed a significantly greater NPV (94.4% *vs.* 78.2%, p = 0.002) and accuracy (79.4% *vs.* 70.5%, p = 0.004) in predicting pCR than MRI.

Discussion and Conclusion

In recent years, NACT has been an essential aspect of the treatment plan for locally advanced and inoperable breast cancers, in order to provide patients with the possibility of BCS, and to increase the rate of negative margins in the final histopathological specimen (1, 2). The ultimate aim of NACT is to achieve pCR, which correlates positively with the patient prognosis (4, 8).

In order to assess tumor response to NACT in breast cancer during therapy or prior to surgery and for early identification of non-responders, so as to switch to different regimens, many imaging modalities have been used, with certain advantages and limitations (5, 6). Currently, there are no established guidelines as to which modality is the gold standard to evaluate tumor response (7). The National Comprehensive Cancer Network (NCCN) guidelines recommend physical examination and repeating the initial imaging modality that detected an abnormality in the staging process (9). Traditionally, physical examination and conventional imaging modalities, such as mammogram and ultrasound, have been used, with a reported accuracy of 57%, 74% and 79%, respectively. Physical examination may be limited, where, in a palpable lesion, it is not possible to differentiate fibrosis from residual disease and the absence of a palpable lesion does not confirm CR (10). Mammogram is more sensitive than physical examination to detect residual disease, but the presence of architectural distortion and microcalcifications may underestimate the treatment response (11).

Breast MRI has been widely used to evaluate the local extent of the primary disease, multicentricity, bilaterality and to differentiate scarred tissue from local recurrence in patients who previously underwent BCS (12). MRI, done before and after therapy, is an optional recommendation in the NCCN guidelines (13). MRI is superior to ultrasound and mammogram in evaluating response to NACT (14). Contrast enhanced MRI is based on neo-angiogenesis. Tumors have more blood vessels and higher permeability compared to normal cells and so have increased contrast uptake. An enhancing lesion correlates with a viable tumor. Tumor necrosis due to therapy results in inflammation and formation of granulation tissue, which enhances in MRI, resulting in overestimation of the tumor size. Also, certain chemotherapeutic agents have anti-angiogenic effects without necrosis, resulting in lack of enhancement and underestimation, thereby limiting its accuracy (12).

Furthermore, PET/CT can be used in staging and re-staging of stage III, locally advanced, inflammatory, recurrent or metastatic breast cancer, or if there are suspicious results in conventional staging investigations, as per the recent NCCN guidelines (9, 15). ^{18}F-FDG is a glucose analogue, and undergoes the same initial pathway of glucose metabolism, but due to the lack of a hydroxyl group, it does not get metabolized further and gets trapped in the cell. Malignant cells have higher glucose metabolism, resulting in an increased uptake and entrapment of ^{18}F-FDG, increasing their detection through PET/CT scan. Nevertheless, increased glucose metabolism is seen physiologically; in the brain and muscles, and in inflammatory and infectious processes, limiting its specificity (15). Many published studies and meta-analyses were done to evaluate the superiority of either MRI or PET/CT in assessing the tumor response to therapy, with variable results (5, 7).

NACT usually starts two to four weeks after diagnosis and completion of initial staging imaging, while surgery should not be delayed beyond eight weeks following last chemotherapy cycle for accurate assessment of tumor response. For an effective correlation between MRI and PET/CT, it is recommended that the time interval between the two modalities must not exceed two weeks (1, 6), as in our study. In order to evaluate the radiological response to treatment, the pathological response has been used as a reference standard in all previous studies so the same criterion was applied in our study.

The rCR rate assessed by MRI was 32.4% (11/34) and PET/CT was 47% (16/34), with similar results reported in literature (6). In addition, the rate of false rCR by MRI was higher compared to that by PET/CT in our study. One reason for this discrepancy is that, MRI interpretation is limited by fibrosis and scar formation, resulting in higher false positive results (12). For the prediction of pCR after NACT, several studies have concluded that PET/CT was superior to MRI, showing similar results to our study (16-18). However, two studies reported that the performance of MRI was similar to PET/CT (7, 19). Therefore, the combined use of these two imaging modalities may increase the possibility to evaluate pCR accurately. PET/MRI is a

Table 3. Prediction of the pCR by MRI and PET/CT

Parameter	MRI	PET/CT	*p*-value
Sensitivity %	54.5 (6/11)	90.9 (10/11)	0.130
Specificity %	78.2 (18/23)	73.9 (17/23)	**0.024**
Positive predictive value %	54.5 (6/11)	62.5 (10/16)	0.772
Negative predictive value %	78.2 (18/23)	94.4 (17/18)	**0.002**
Accuracy	70.5 (24/34)	79.4 (27/34)	**0.004**

pCR: Pathological complete response; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography

new imaging modality that was first introduced in 2010. It combines the advantages of both PET and MRI, by assessing the metabolic activity of the tumor and its vascularity, with higher contrast resolution compared to PET/CT (9, 20). Studies showed that the addition of MRI to PET scans significantly improves its sensitivity and specificity, which opens an area for future research (21, 22).

Limitations of our study include its retrospective nature and single-center experience. Although our sample size was relatively small, this is probably because not all of our patients who underwent NACT had the indications for both MRI and PET/CT to be performed. Furthermore, our study focused on the tumor response to therapy without evaluating axillary lymph node involvement, which could be explored in a future study.

In conclusion, this study demonstrated that, after NACT for breast cancer, the use of PET/CT had a better correlation with the pathological response than MRI in terms of assessing the tumor response. For the prediction of pCR, PET/CT was a more accurate method, while MRI was a more specific imaging modality. The complementary value of combined use of both imaging modalities is perhaps the most important way to improve diagnostic performance in the setting of NACT. Nevertheless, further larger prospective studies, including randomized controlled trials, are needed to evaluate other methods, which should include PET/MRI.

Ethics

Ethics Committee Approval: The study was approved by the Research Ethics Committee of the Government Hospitals in Bahrain (approval number: 65-230524, date: 23.05.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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Original Article

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Level of Awareness, Screening Practices, and Self-Detection Among Breast Cancer Patients

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ABSTRACT

Objective: Having good knowledge and performing regular pre-tests under physician supervision play a crucial role in the early detection of breast cancer. The aim of this study was to investigate the level of awareness, frequency of performing routine screening, types of screening methods prior to detection, and who detected the case, among women diagnosed with breast cancer.

Materials and Methods: A cross-sectional study that used a designed questionnaire applied to investigate demographic data and four other aspects: level of awareness, screening practices, type of screening methods used, and who detected the case for the first time. Women who were diagnosed with breast cancer and registered at Nanakali Hospital were included.

Results: A total of 150 women participated. Most of the participants (80%) had no previous knowledge regarding causes, signs and symptoms, or detection methods, while only 20% had little information. Among the participants, most (87.3%) did not undergo any pre-tests before the time of diagnosis, while only 12.7% did pre-test at least once. The screening methods used prior to the diagnosis were: breast self-exam (n=9); ultrasonography (n=8), and only two had mammography. Detecting the case for the first time, 68.7% of the cases were detected by chance or accidentally, and 31.3% were detected by physicians.

Conclusion: The level of awareness and performance of routine screening differ greatly among different populations and countries. Women in Erbil, generally have a low level of awareness and insufficient knowledge regarding breast cancer; most women do not undertake any regular screening for early detection of this cancer compared to Western countries. Having previous knowledge and doing pre-tests regularly play a key role in the early detection of this cancer, which minimizes the consequences.

Keywords: Breast cancer; level of awareness; pre-tests; screening methods; self-detection

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Key Points

- Having sufficient knowledge regarding breast cancer (BC) is important for all women, of all ages.
- Performing a pre-test enables the early diagnosis of BC.
- Women in the northern part of Iraq, like other low- and middle-income countries, have little information and very poor screening practices before being diagnosed with BC.
- Increasing awareness and encouraging women to undergo regular screening to enable the early detection of BC.

Introduction

Breast cancer is a neoplasm that affects the breast tissue, and it is the most common type of cancer among women. Annually, more than two million new cases of breast cancer are diagnosed, which causes about 685,000 deaths globally. About two-thirds of these deaths were recorded in low- and middle-income countries (1-3). Women's awareness of breast cancer is very important and plays a key role in its early diagnosis, which increases overall survival. In high-income countries, the overall five-year survival rate is over 80%, while in low-income countries, like India, it is less than 70%, and in South Africa, it is less than 50%. The United States achieved a 36% reduction in breast cancer mortality rates between 1989 and 2012. The high survival rate in developed countries results from advanced strategies for early detection, access to early diagnosis, and effective treatments (1, 4, 5). The degree of awareness and levels of knowledge about the disease differ among different countries and societies and generally women in low- and middle-income countries have less awareness and knowledge of breast cancer (6, 7). Several factors, such as education, socioeconomic status, health care levels, and geographical distribution, contribute to the level of awareness among women in different countries and populations (6).

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Diagnosis of any cancer type at its early stages plays a key role in the treatment strategies, control of the disease, and reduction of morbidity and mortality of the cancer (8). Diagnosis of breast cancer at earlier stages will reduce the likelihood of a poor outcome, and the approach to treatment will be easier and more varied than when detecting the cancer at advanced stages (9, 10). Unfortunately, women in low- and middle-income countries do not perform screening as a pre-test regularly, compared to women in Western countries (11, 12). There are different methods that can be used for screening breast cancer, such as mammography (MG), ultrasonography (USG), magnetic resonance imaging (MRI), biopsy, molecular based methods, flow cytometers, and breast self-examination (BSE). The simplest way is BSE that women can perform at home at any time and it costs nothing; however, women should be trained well to be able to do BSE effectively and regularly (13, 14). It should be noted that BSE is not able to detect the cancer at its preliminary stages, so regular MG screening is highly recommended for its ability to detect this cancer even at its first stage (15, 16).

The initial detection of breast cancer may be by the patient or by physicians and health care workers. Self-detection of cancer is encouraged, especially in low- and middle-income countries where there are poor screening practices for early detection (17). Breast cancer in Iraq has become a pressing public health concern as the number of cases rises every year (18, 19). There is a shortage of studies covering these issues regarding breast cancer in our region. The aim of this study was to investigate the level of awareness and prior knowledge of breast cancer, investigating the frequency of performing pre-tests for the early detection, the types of screening methods that were used, and how the case was detected for the first time among women with breast cancer in the Erbil governorate of Iraq.

Materials and Methods

Study Design, Sample Collection, Parameters

Iraqi Kurdish women who had an existing diagnosis of breast cancer were included in the study. Samples were collected at Nanakali Hospital for Blood Diseases and Cancer, Erbil, Iraq. After obtaining their agreement, they were included in this study.

The present study was a cross-sectional study that used a structured questionnaire to investigate parameters related to the aim of the present study. Four parameters were investigated. The first was level of awareness and prior knowledge regarding breast cancer, such as information about the cancer, risk factors, early signs, and screening methods. The second was performance of any pre-test before the time of diagnosis and how many times the individual underwent screening. Then the type of screening method used, if any, was investigated. Finally, how the case was detected for the first time, by the patients or by the physician was collected. Demographic data including age, education level, place of residence (rural/urban), and marital status were also collected.

Inclusion and Exclusion Criteria

Women who were diagnosed with breast cancer and belonged to the Iraqi Kurdish population were included in the present study. Women who did not meet these criteria or who declined to participate were excluded.

Ethics Consideration

All participants were fully informed about the aim and objectives of the study through a written consent form, and after obtaining their agreements, they were included as participants in accordance with the Helsinki Declaration. The research was approved by the Medical Ethics Committee of Erbil Polytechnic University (approval no: 23-0011, date: 30/10/2023).

Statistical Analysis

To compare between different groups, a chi-square test was used. Statistical analysis was performed using GraphPad Prism, version 9.0.0 (121) (GraphPad Software LLC, www.graphpad.com). A p -value less than <0.05 was considered significantly different.

Results

Demographic Data

A total of 150 women were included in the study, with a mean age of 53.7 years, ranging from 29 to 75 years. Most (76.7%) were 50 years of age or older. In terms of level of education, 42.7% were illiterate and 70%, lived in urban areas. The marital status showed that the majority, 87.3%, were married. The details and results of the statistical analysis of these parameters are shown in Table 1.

Level of Awareness and Having Previous Knowledge of Breast Cancer

Among 150 participants, only 30 (20%) had some previous knowledge about some aspects of breast cancer, while 120 (80%) had no previous knowledge about breast cancer ($p < 0.0001$; Table 2).

Table 1. Demographic parameter of the participants (n=150)

Parameter	Categories	n	%	*p*-value
Age, years	<50	35	23.3	<0.0001
	≥50	115	76.7	
Education	Illiterate	64	42.7	0.01
	Primary or Secondary School	45	30	
	Institute or University	41	27.3	
Rural / Urban	Urban	105	70	<0.0001
	Rural	45	30	
Marital State	Single	19	12.7	<0.0001
	Married	131	87.3	

Performing Routine Test for Pre-diagnosis of Breast Cancer

Only 19/150 (12.7%) reported that they had undergone a pre-test at least once before being diagnosed with breast cancer, while the majority, 131 (87.3%), did not undergo any pre-tests before the time of diagnosis ($p < 0.0001$; Table 2).

Type of Pre-screening

Among the 19 participants who did have a pre-test, the screening methods were: BSE (n=9; 47.4%); USG (n=8; 42.1%); and only two (10.5%) underwent MG ($p = 0.03$; Table 2).

How the Cancer was Detected for the First Time and by Who

Most of the cases, 103 (68.7%) reported that the case was detected at first through self-detection, feeling abnormal mass, or by chance, while 47 (31.3%) of the cases were detected by physicians ($p < 0.0001$; Table 2).

Discussion and Conclusion

Among the participants in the current study, 80% reported having no previous knowledge of breast cancer. The 30 participants who reported prior knowledge of breast cancer knew little about the causes, risk factors, diagnosis, or screening methods. An earlier study from Iraq that included educated participants from two different universities, found about 50% of the participants had poor knowledge regarding breast cancer and only 14.3% were graded as "good" (20). Thus, the findings of the current study are not surprising as nearly half were illiterate and only just over a quarter had post-secondary school education. Another study carried out in 2015 in Baghdad, included 508 women, of whom 61.2% had poor knowledge about breast cancer (21). A recent study carried out in 2021 in Al-Hilla province, Iraq, reported that 68.4% of the participants didn't know or were not sure about risk factors for breast cancer, and 95% didn't know or were not sure about symptoms of breast cancer (22). The results of the current study are in line with the findings of these earlier studies from Iraq. Having poor knowledge of breast cancer among women in developing countries is not limited to Iraq. According to research carried out in Bangladesh, 61.5% of the women were unaware of the causes and risk factors of this type of cancer (23). In Delhi research carried out by Dey et al. (24) showed that 53.4% of the women had awareness, at different levels, about different aspects of breast cancer; their result differed from ours, indicating that geographical distribution plays a role in the level of awareness.

Several factors may play a role in having poor knowledge about breast cancer, including education, age, health care services, socio-demographic characteristics, community, religion, and the society the sample is taken from (25, 26). One possible explanation for the high proportion of our participants with insufficient information about breast cancer is the relationship between age and education. Around three quarter of the participants were of old age, and a similar proportion were either illiterate or had primary and secondary school education. Unfortunately, these high proportions of female illiteracy and poor education is not unusually in Iraqi society because until the mid-1970s to the early 1980s there were not enough schools, and many parents refused to send their daughters to school for cultural or traditional beliefs. Our findings and those of other researchers in Iraq and other developing countries suggest that urgent action is required, at national government level and through non-governmental organizations (NGOs), to increase awareness of breast cancer amongst women, given the severe morbidity and mortality associated with later diagnosis.

About 87% of women in the present study had not had any pre-test, while only 12.7% did pre-test at least once before being diagnosed with breast cancer. Of the 19 participants who had a pre-test, less than half used BSE despite this technique being among the easiest and most cost-effective ways that women can perform self-testing at home by themselves. It should be noted that BSE is not reliable and has limitations and should not replace the clinical breast exam. Unfortunately, women in Middle Eastern countries do not perform BSE (14). A study from Turkey showed that among 103 participants only 26.2% had knowledge about BSE, and only 4.3% of the participants performed BSE, in keeping with the findings of the present study (27). In Delhi, BSE was more commonly reported by Indian women with 34.9% performing BSE, while only 6.9% underwent clinical breast-examination through MG (24). Another study from Bangladesh in 2022 reported that only 14% of the participating women had information about screening tests for breast cancer, which again is supported by our findings (23). That only 12.7% of the participants in the present study performed any form of pre-test before being diagnosed with breast cancer is clinically worrying. Unfortunately, the majority of women in developing countries are not undergoing any pre-tests or screenings for breast cancer (28). Some reasons for this may be the low level of awareness and feeling of shame regarding this issue among women in these countries. We suggest that this situation is contributed to by the negligence of the competent authorities in the related ministries and directorates. NGOs have tried to increase

Table 2. Parameters of prior knowledge, screening, types of screening and who detected the diseae (n=150)

Parameter	Results	n	%	*p*-value
Level of awareness by having previous knowledge	Yes	30	20	<0.0001
	No	120	80	
Performing screening tests	Yes	19	12.7	<0.0001
	No	131	87.3	
Type of screening method	BSE	9	6	0.03
	Ultrasonography	8	5.3	
	Mammography	2	1.3	
Who detected the cancer at first	Self-detection	103	68.7	<0.0001
	Physicians	47	31.3	

awareness and the importance of screening for breast cancer among healthy women in recent years, but our findings show that this is still not enough.

Regarding the detection of a tumor in the breast and who detected it for the first time, among participants, 68.7% of them detected the tumor by themselves, mostly accidentally or by chance. According to research carried out in the USA that included 361 participants, 43% of the participants detected breast cancer by themselves, 18% detected it accidentally, and 25% detected it through BSE (29). In contrast, another study from the USA reported the reverse with, 88% of new cancer cases diagnosed in hospitals (30). This results from pre-test and screening policies because usually stage I cancer cannot be detected by women themselves, while it can be detected through screening and MG. This highlights the importance of routine screening for early detection of the disease. The detection of breast cancer by women rather than physicians or health care workers in the present study is logical, as most of them did not take any pre-tests or screenings for having breast cancer before being diagnosed with the disease. These results again show the significance of performing pre-tests periodically.

Finally, doing pre-tests among women to investigate breast cancer, especially among women at higher risk and those who have relatives with breast cancer, is highly recommended to minimize the consequences of the disease. Screening methods depending on MG are recommended among women to enable an early diagnosis (31, 32). The Ministry of Health and other relevant authorities must make greater efforts through an extensive awareness program and should offer free screening tests, as is done in other countries, to enable women, especially those who had low incomes, to conduct periodic and regular examinations under the supervision of physicians and specialists. This could be introduced to the public through general and social media channels to reach the largest possible number of women throughout society.

Women in Erbil, Iraq, like other low- and middle-income countries, have a very low awareness level and poor knowledge regarding aspects of breast cancer. Unfortunately, women in these countries do not perform routine pre-tests for breast cancer compared to Western countries. Performing pre-tests regularly is very important among women, especially after the age of forty years, to detect the disease in its early stages. Women are encouraged to undergo reliable pre-tests, such as MG under the supervision of physicians, and, if not applicable for any reason, BSE must not be neglected. Intensive programs by relevant authorities and health care providers are required to increase awareness levels among all women regarding breast cancer.

Study Limitations

The limitations include the small number of participants, the cross-sectional, questionnaire-based nature of the study and the single-center design.

Ethics

Ethics Committee Approval: The research was approved by the Medical Ethics Committee of Erbil Polytechnic University (approval no: 23-0011, date: 30/10/2023).

Informed Consent: All participants were fully informed about the purpose and objectives of the study through a written consent form, and their approval was obtained.

Footnotes

Authorship Contributions: Concept: A.N.H., M.S.A.; Design: A.N.H., M.S.A.; Data Collection and/or Processing: A.N.H.; Analysis and/or Interpretation: A.N.H.; Literature Search: A.N.H.; Writing: A.N.H.

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

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Original Article

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Carbonic Anhydrase IX Enzyme in Triple Negative Breast Carcinoma: Relationship With Prognostic Factors and Response to Neoadjuvant Chemotherapy

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ABSTRACT

Objective: Triple negative breast carcinoma (TNBC) is characterized by the absence of estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 receptor expression. Carbonic anhydrase IX (CA IX) is a tumor-associated cell surface glycoprotein that is involved in adaptation to hypoxia-induced acidosis and plays a role in cancer progression. The aim of this study was to investigate CA IX expression in TNBC and its relationship with treatment effect.

Materials and Methods: Immunohistochemical staining was performed on tru-cut biopsy materials with CA IX antibody. Positive staining was graded as low (<10%) and high (>10%). In addition, the relationship between tumor diameter, histological grade and the treatment effect on mastectomy materials performed after neoadjuvant treatment was evaluated.

Results: TNBCs with positive staining for CA IX exhibited higher histological grade, and higher Ki-67 index compared to TNBCs with negative staining ($p < 0.05$). The response to treatment decreased as the degree of CA IX staining increased. There was no significant difference between the high staining group and low staining group in terms of patient age, tumor diameter and breast localisation.

Conclusion: CA IX enzyme is a poor prognostic marker in TNBC cases. However, overexpression of CA IX was associated with reduced response to treatment.

Keywords: Triple negative breast carcinoma; carbonic anhydrase IX; treatment effect; Ki-67 proliferation index

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Key Points

- Understanding carbonic anhydrase-9 levels' affect on triple-negative breast cancer.
- Additionally it affects on the prognosis of the triple negative breast cancer cases.

Introduction

Breast cancer is the most common tumor in women and the second most common cause of cancer-related deaths. According to cancer data published in 2021, approximately 2,260,000 women were diagnosed with breast cancer, and 684,996 women died due to breast cancer (1, 2). Over the past 20 years, breast cancer has been recognized as a family of diseases with distinct pathological, molecular, and clinical characteristics. Various classification systems have been proposed, affecting prognosis and treatment. Breast cancer has been categorized into estrogen/progesterone receptor-positive (luminal), human epidermal growth factor receptor-2 (HER2) receptor-positive, and triple-negative breast carcinoma (TNBC), where all three receptors are negative (3). TNBCs account for approximately 15% of all breast cancer cases. They are more common in women under 40 years of age and have poorer survival rates compared to other types of breast cancer. Approximately 40% of women with TNBC die within the first five years after diagnosis. Distant metastasis is observed in around 46% of TNBC patients with a mean survival time of 13.3 months after metastasis (1, 3).

Since Warburg's (4) study in 1927 described the so-called Warburg effect, which is characterized by irregular glucose uptake and disruption of glycolytic metabolism in cancer cells, irregular energy metabolism has become known as an important part of the pathogenesis behind uncontrolled growth in cancer cells. Moreover, hypoxic areas are commonly found in more than half of breast tumors due to high metabolic proliferative rates and abnormal vascularization. In healthy breast tissue, the average oxygen pressure (pO_2) is 65 mmHg, whereas

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in breast tumors, it has been reported to be reduced to 10 mmHg. Tumor areas exhibit acidic pH (<6.5) (5). Hypoxia poses a life-threatening condition for all aerobic organisms, and they develop various adaptative mechanisms to survive in such conditions (6). The rapid proliferation of cancer cells increases the demand for oxygen, but the vessels supplying oxygen-carrying blood cannot keep up with this demand. Consequently, hypoxia occurs in rapidly growing tumor tissues, and tumor cells develop adaptive responses to cope with this stress (7).

Carbonic anhydrase IX (CA IX) is a tumor-associated cell surface glycoprotein enzyme that aids in adaptation to acidosis induced by hypoxia and plays a role in cancer progression. The active site of the CA IX enzyme in the catalytic domain is positioned towards the extracellular space, contributing to pH regulation across the plasma membrane by facilitating CO_2 hydration. This, in turn, enhances CO_2 diffusion and proton mobility in the tumor tissue. Simultaneously, CA IX exacerbates extracellular acidosis, which can activate proteases to degrade the extracellular matrix, promote epithelial-mesenchymal transition and invasion, reprogram metabolism, affect cell adhesion, and stimulate inflammation and angiogenesis. CA IX is more abundant in tumor tissues compared to normal tissues (8, 9).

Many tumor studies have reported CA IX overexpression as a poor prognostic marker. Previous clinical trials on invasive breast cancer have also demonstrated that CA IX is associated with poor outcomes, suggesting its relationship with an aggressive phenotype. CA IX overexpression has also been associated with shorter disease-free survival time in invasive breast cancer. However, there is little information regarding its role in TNBC (10).

TNBCs have poor prognoses and are resistant to chemo-radiotherapy, making them a focal point of cancer research. In this study, we investigated the relationship between CA IX expression and prognostic factors of TNBC, as well as its contribution to treatment. The aim was to identify the causes of poor prognosis and make recommendations for exploring new treatments.

Materials and Methods

This retrospective study was initiated after obtaining approval from the Ethics Committee of Fırat University (approval no: 2023/04-34, date:13.07.2023). One thousand seven hundred and fifty-three cut biopsy samples sent to our hospital laboratory between August 2018 and May 2023 were examined. These cases were compared, first by classifying according to their diagnosis with 541 cases diagnosed with carcinoma. Among these, 397 patients were diagnosed with invasive carcinoma NST were included in the study and those diagnosed with other carcinomas were excluded from the study. The 397 invasive carcinoma cases were evaluated according to estrogen, progesterone and HER 2 receptors. Triple negative tumor cases were thus identified. Among these cases, 40 cases who underwent breast resection in our hospital by receiving neoadjuvant chemotherapy (adriamycin, cyclophosphamide, and then paclitaxel for four cycles) were included in the study (Figure 1). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or ethical standards.

Hematoxylin-eosin stained preparations of tru cut biopsies and immunohistochemical staining preparations for estrogen, progesterone and HER2 receptors were re-examined using a Leica DM 2000 light microscope (Leica Biosystems 21440 W. Lake Cook Road Floor 5 Deer Park, IL 60010 United States). Patients with a score of +2 for HER2 antibody staining were excluded from the study, due to the unavailability of fluorescent *in situ* hybridization in our clinic. A total of 40 patients were included in the study, and histopathological evaluation was conducted on parameters which included histological type and histological grade. Histological grading was performed using the Nottingham score (Elston Ellis modification of Scarff-Bloom-Richardson grading system) (11). Tumor diameter evaluation was based on the measurements determined during radiological examinations.

Paraffin blocks of these cases were cut into 3 µm thick sections and placed on slides. The tissue samples were deparaffinized and treated with 3% H_2O_2 for 5 minutes, blocked with 10% serum in blocking solution for 1 hour, and incubated overnight at 4 °C with anti-CA IX antibodies (Leica Biosystems 21440 W. Lake Cook Road Floor 5 Deer Park, IL 60010 United States) at a 1/400 dilution in an antibody diluent. As CA IX is a transmembrane protein, it exhibits cytoplasmic membrane staining. Immunohistochemically positive cells were graded as "low staining" if they constituted <10% of the total or "high staining" if they constituted ≥10%, as previously described (12). Due to the small number of patients, in order to facilitate statistical comparison, the classification made by Zhu et al. (12), based on a previous meta-analysis of neck and head tumors, was chosen. Ogston et al. (13) grading was used to evaluate treatment effect after neoadjuvant chemotherapy in breast excision materials (Table 1).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 20 (IBM Corp., Armonk, NY, USA). All analyses were conducted based on the normality assumption and according to the low case count all the parametric values were accepted as non-normal distribution. Descriptive data are expressed as median (25–75

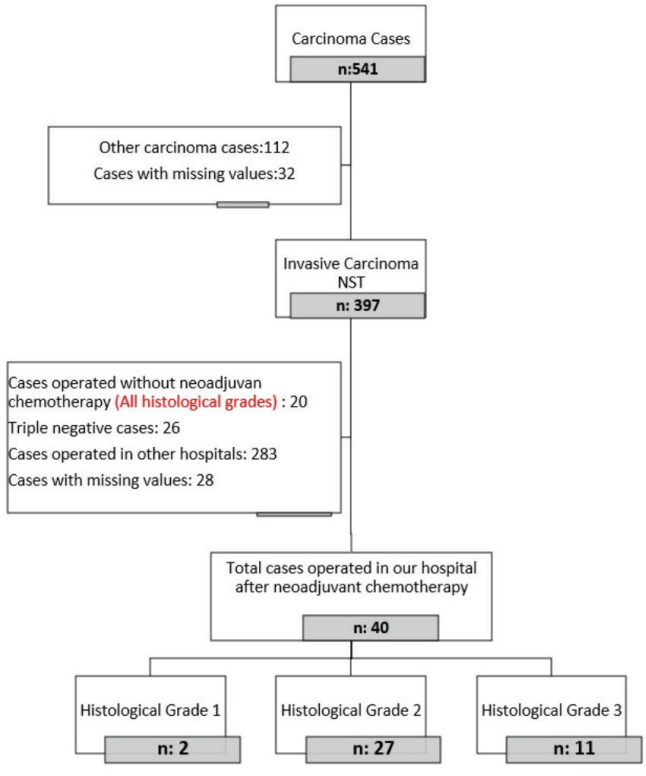

Figure 1. Flowchart of the study design

percentiles). The association between clinicopathological parameters, treatment effect and CA IX staining was tested using the chi-square test, Fisher's exact test or likelyhood ratio. Statistical significance was set at $p < 0.05$.

Results

All patients included in the study were female, with a mean age of 48.43±11.92, ranging from 33 to 84 years. The tumor was located in the right breast in 23 patients (57.5%) and in the left breast in 17 patients (42.5%). The median tumor diameter of all patients was 22.31 mm (5.5–100 mm). Based on histopathological grading, 2 patients (5%) were classified as Grade 1, 27 patients (67%) as Grade 2, and 11 patients (28%) as Grade 3. The median Ki-67 proliferation index was 40.62% (5–90%).

Immunohistochemical staining of CA IX in tumor tissues showed that 77.5% (n=31) had high staining (Figure 2) and 22.5% of patients (n=9) had low staining (Figure 3, Table 2). The tumor diameter of the low staining group was 17 mm (13–22 mm) and high staining group was 21 mm (17.5–25 mm) ($p = 0.337$).

Statistical analysis revealed a significant difference between CA IX staining level and histological grade of the tumor and Ki-67 proliferation index ($p = 0.003$, and $p = 0.008$, respectively) (Table 3). In other words, as the tumor histological grade and Ki-67 proliferation index increased, the CA IX staining level also increased. However, CA IX staining level showed no significant relationship with patient age, tumor diameter and tumor localization ($p = 0.975$, $p = 0.337$ and $p = 0.456$, respectively) (Table 4).

In the evaluation made using Miller Payne scoring (MPS), nine of the cases had a grade 2, 13 of them had a grade 3, 12 of them had a grade 4 and six of them had a grade 5 treatment effect. A significant difference was detected between MPS and CA IX expression ($p = 0.005$ (Table 3).

Discussion and Conclusion

Breast cancer is a complex disease with various histological types, natural courses, clinical behaviors, and treatment responses. In addition to classification based on histopathological characteristics, several molecular subtypes have been defined based on different expressions of cell surface receptors. TNBCs are breast carcinomas that test negative for estrogen, progesterone, and HER2 receptor and have worse prognoses compared to other breast carcinoma subtypes (14, 15). Conventional treatment methods remain valid for TNBCs, with systemic treatment being the primary protocol for both first-line and advanced treatments. However, patients often develop treatment resistance over time (16). Resistance to treatment leads to recurrence and distant metastasis in 40–80% of cases, resulting in death. The tumor microenvironment has been identified as one of the parameters influencing treatment response, emphasizing its importance in tumor development, growth, metastasis, recurrence, and treatment response (17). Recent studies have demonstrated that the hypoxic tumor microenvironment, influenced by CA IX, affects tumor growth, invasion, and treatment resistance (10). The hypoxia promotes an invasive phenotype characterized by decreased tumor

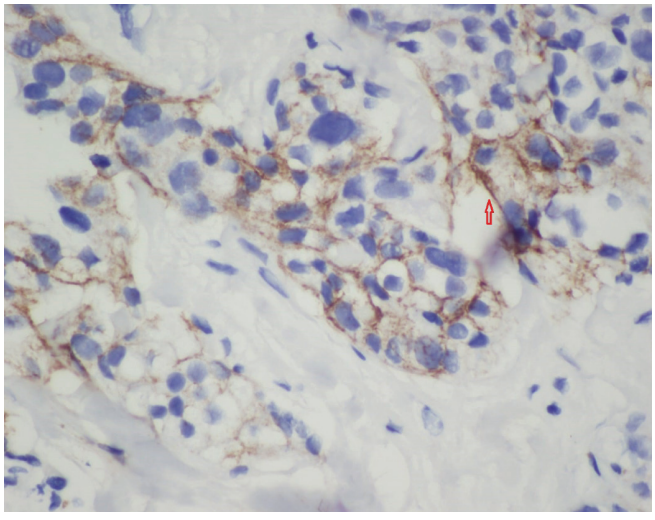

Figure 2. Membranous CA IX high staining x 400

CA IX: Carbonic anhydrase 9

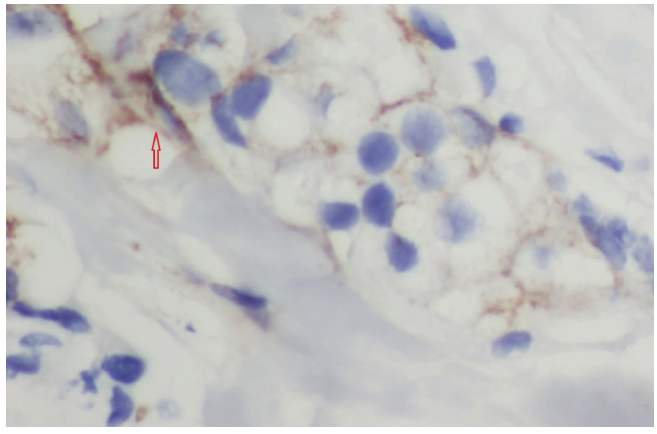

Figure 3. Membranous CA IX low staining x 400

CA IX: Carbonic anhydrase 9

Table 1. Miller and Payne histological grading system

Grade	Miller and Payne histological grading system
Grade 1	No change or some alteration to individual malignant cells but no reduction in overall cellularity.
Grade 2	A minor loss of tumour cells but overall cellularity still high; up to 30% loss.
Grade 3	Between an estimated 30% and 90% reduction in tumour cells.
Grade 4	A marked disappearance of tumour cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumour cells.
Grade 5	No malignant cells identifiable in sections from the site of the tumour; only vascular fibroelastotic stroma remains often containing macrophages. However, ductal carcinoma *in situ* (DCIS) may be present.

adhesion, increased invasion, mobility, migration, and stimulation of angiogenesis (18). This study investigated the relationship between CA IX expression and prognostic factors in TNBC. TNBCs with high CA IX staining exhibited higher histological grade, and higher Ki-67 index compared to TNBCs with negative staining.

Studies examining the relationship between breast carcinomas and CA IX overexpression have reported varying results (18). Few studies have specifically investigated the relationship between CA IX and TNBC, reporting that poor prognostic factors were common in TNBC patients with CA IX overexpression (19, 20). In the study conducted by Jin et al. (21) involving 270 TNBC cases, they observed that CA IX expression increased with higher histological grades. However, they found a negative correlation with lymphovascular invasion and disease-free survival (21). Ong et al. (22) found that positive CAIX membrane staining was associated with larger tumor size, higher histological grade, and worse survival rates. BRCA1 mutation was found to be present, especially in patients expressing CA IX in their TNBCs, which

Table 2. CA-IX expression according to histological grades

Histologic Grade	CA-IX		Total	*p*-value
	Low staining group	High staining group		
Grade 1, n (%)	1 (2.5)	1 (2.5)	2 (5.0)	0.029*
Grade 2, n (%)	8 (20.0)	19 (47.5)	27 (67.5)	
Grade 3, n (%)	0 (0.0)	11 (27.5)	11 (27.5)	
Total, n (%)	9 (22.5)	31 (77.5)	40 (100)	

*: According to likelyhood ratio
CA IX: Carbonic anhydrase 9

Table 3. Relationship of MPS and CA-IX expression degree

MPS	CA-IX		Total	*p*-value
	Low staining group	High staining group		
Grade 2, n (%)	0 (0.0)	9 (22.5)	9 (22.5)	0.005*
Grade 3, n (%)	1 (2.5)	12 (30.0)	13 (32.5)	
Grade 4, (n)	4 (10.0)	8 (20.0)	12 (30.0)	
Grade 5, n (%)	4 (10.0)	2 (5.0)	6 (15.0)	
Total, n (%)	9 (22.5)	31 (77.5)	40 (100)	

*: According to likelyhood ratio
CA IX: Carbonic anhydrase 9; MPS: Miller and Payne histological grading system

Table 4. Relationship of tumor localisation, Ki-67 proliferation index, age and tumor diameter with CA-IX

	CA-IX		*p*-value
	Low staining group	High staining group	
Tumor side			
Left	5 (12.5%)	12 (30.0%)	0.301*
Right	4 (10.0%)	19 (47.5%)	
Total	9 (22.5%)	31 (77.5%)	
Median (IQR) Ki-67 index (%)	20 (15-35)	40 (30-50)	0.008**
Median (IQR) age, (years)	45 (38-61)	46 (41-54)	0.975**
Median (IQR) diameter, (mm)	17 (12.5-24)	21 (17-26)	0.337**

*: According to Fischer's Exact Test
**: According to Mann Whitney U Test
CA IX: Carbonic anhydrase 9; IQR: interquartile range (25th to 75th percentiles)

hindered DNA repair (23). However, a study conducted by Ozretic et al. (24) found no significant relationship between CA IX expression and poor prognosis. In additionally, a small number of studies have reported that carbonic anhydrase inhibitors are a viable anticancer treatment, especially for TNBC (25).

In previous studies, pathological complete response (PCR) in TNBC was found to be between 15–30%. In this study, it was 15%, consistent with the literature. It is known that PCR after treatment increases the disease-free survival time in TNBCs. In previous studies investigating the relationship between CA IX expression and PCR, Aomatsu et al. (26) observed that high CA IX expression was associated with a low PCR rate and evaluated this protein as a marker of chemoresistance. However, Betof et al. (27) reported that PCR was higher in tumors showing high CA IX expression in tumor tissues before neoadjuvant chemotherapy. As a result of this study, it was shown that as CA IX expression increased, the pathological response decreased.

The most important limitation of the current study is the small number of cases. Since not all diagnosed patients were treated in our hospital, it was not possible to access the data. In addition, survival time and disease-free survival time could not be evaluated for this reason.

Significant advances have been made in understanding the biology of TNBCs in recent years. These tumors are now known to have more than one biological subtype, implying that there will be no single optimal treatment method. Considering the importance of the tumor microenvironment in treatment resistance, targeting the microenvironment that facilitates tumor growth, proliferation, and spread is likely to be a crucial factor in combating the tumor. Inhibiting the CA IX enzyme, which contributes to acidosis which benefits tumor survival and growth, may be a fundamental step in treatment. Our study showed that poor prognostic factors were more common and response to treatment was less in patients with TNBC and CA IX positive features. We believe that CA IX enzyme inhibition may be an important treatment approach. Studies involving larger patient groups with multicentric studies will provide more reliable results and help determine optimum treatment protocols.

Ethics

Ethics Committee Approval: This study was initiated after obtaining approval from the Ethics Committee of Fırat University (approval no. 2023/04-34, date:13.07.2023).

Informed Consent: This retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices: M.B.B., N.K., Ö.A.S.; Concept: M.B.B., N.K., Ö.A.S.; Design: M.B.B., N.K., Ö.A.S.; Data Collection and/or Processing: M.B.B., N.K., Ö.A.S.; Analysis and/or Interpretation: M.B.B., N.K., Ö.A.S.; Literature Search: M.B.B., N.K., Ö.A.S.; Writing: M.B.B., N.K., Ö.A.S.

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

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Original Article

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Bioinformatics Based Drug Repurposing Approach for Breast and Gynecological Cancers: *RECQL4/FAM13C* Genes Address Common Hub Genes and Drugs

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ABSTRACT

Objective: The prevalence of breast cancer and gynaecological cancers is high, and these cancer types can occur consecutively as secondary cancers. The aim of our study is to determine the genes commonly expressed in these cancers and to identify the common hub genes and drug components.

Materials and Methods: Gene intensity values of breast cancer, gynaecological cancers such as cervical, ovarian and endometrial cancers were used from the Gene Expression Omnibus database Affymetrix Human Genome U133 Plus 2.0 Array project. Using the linear modelling method included in the R LIMMA package, genes that differ between healthy individuals and cancer patients were identified. Hub genes were determined using cytoHubba in Cytoscape program. "ShinyGo 0.80" tool was used to determine the disease-specific biological KEGG pathways. Drug.MATADOR from the ShinyGo 0.80 tool was used to predict drug-target relationships.

Results: The RecQ Like Helicase 4 and *Family with Sequence Similarity 13 Member C* genes were found to be similarly expressed in breast cancer and gynaecological cancers. Upon KEGG pathway analyses with hub genes, Drug.MATADOR analysis with hub genes related to cancer related pathways was performed. We have determined these gene/drug interactions: NBN (targeted by Hydroxyurea), EP300 (targeted by Acetylcarnitine) and MAPK14 (targeted by Salicylate and Dibutyryl cyclic AMP).

Conclusion: The drugs associated with hub genes determined in our study are not routinely used in cancer treatment. Our study offers the opportunity to identify the target genes of drugs used in breast and gynaecological cancers with the drug repurposing approach.

Keywords: Breast cancer; gynaecological cancers; DEGs; hub genes; drug repurposing; RECQL4/FAM13C

Cite this article as: Ayna Duran G. Bioinformatics based drug repurposing approach for breast and gynecological cancers: *RECQL4/FAM13C* genes address common hub genes and drugs. Eur J Breast Health. 2025; 21(1): 63-73

Key Points

- The aim of the study is to determine the genes commonly expressed in both breast and gynaecological cancers and to identify the common hub genes and drug components.

In our study,

- Primarily, the *RecQ Like Helicase 4* and *Family with Sequence Similarity 13 Member C* genes were found to be similarly expressed in breast cancer and gynaecological cancers.
- Secondly, as a result of Drug.MATADOR analysis with hub genes, we have determined these gene/drug interactions such as NBN (targeted by Hydroxyurea), EP300 (targeted by Acetylcarnitine), and MAPK14 (targeted by Salicylate and Dibutyryl cyclic AMP).
- The drugs associated with hub genes determined in our study are not drugs routinely used drugs in cancer treatment.
- In summary, we offer the opportunity to identify the target genes of drugs used in breast and gynaecological cancers with the drug repurposing approach which is a novelty of our study. It brings together two women's cancer groups (breast and gynaecological cancers) that have not been clinically targeted in the literature and clinic and suggests common genes and new candidate drugs/therapeutics.

Introduction

Among all cancers, the most common and life-threatening cancer in women is breast invasive carcinoma (BRCA) (1). Another type of cancer that affects women's lives is gynecological reproductive system cancers. Although gynecological reproductive system cancers such as ovarian serous cystadenocarcinoma (OV), cervical squamous cell carcinoma (CESC) and uterine corpus endometrial carcinoma (UCEC) are not as common as breast cancer, they also threaten women's lives with increasing death rates (2). There are common risk factors (genetic

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predispositions, hormonal interactions, lifestyle factors) that trigger breast and gynecological cancers, which affect the mammary gland and female reproductive organs, respectively (3). For this reason, the probability of multiple primary cancers in the same breast cancer patient is up to %16 higher in women-related cancers due to common triggering factors and genetic predispositions. For example, a history of breast cancer has been shown to be a risk for the development of women's cancers. Additionally, the incidence of gynecological cancers is high in a woman with primary breast cancer (3, 4).

Due to the common biological and genetic mechanisms between breast cancer and gynecological cancers, we tried to identify the genes that are commonly upregulated or downregulated in these cancers through bioinformatic analysis using multiple and independent patient groups. Based on commonly expressed genes, hub genes were identified and drug components that could target these hub genes were tried to be predicted. According to our knowledge, any bioinformatics-based study has been found in which similarly expressed genes were detected using microarray data from both breast cancer patients and gynecological cancer patients. *RecQ Like Helicase 4 (RECQL4)* and Family with Sequence Similarity *13 Member C* (*FAM13C*) genes were detected as commonly expressed genes in gynecological and breast cancer patients.

RECQL4 and *FAM13C* genes were detected as commonly expressed genes in both gynecological and breast cancer patients in our study. *RECQ* genes encodes helicase enzymes that play roles in the DNA damage response. It has been summarized that expression level differences in the *RECQL4* gene, among other genes belonging to this family, play a role in the development of breast and gynecological cancers (5). It has been summarized that expression level differences in the *RECQL4* gene, among other genes belonging to this family, play a role in the development of breast and gynecological cancers (5-8). In addition, cross-sectional studies in patients with cervical cancer showed that the *RECQL4* gene was upregulated in tumour tissue (5, 9), while in a retrospective study, researchers found that the *RECQL4* gene was similarly expressed at higher levels in tissues of ovarian cancer patients than in normal tissue (5, 10).

The *FAM13C* gene, which was found to be downregulated in all cancer types in our study, is a gene belonging to the FAM family. Although the current literature shows that the *FAM13C* gene is downregulated in cervical and ovarian cancer patients compared to normal tissue (11-13), when the content of the studies is examined, it is seen that there is no study directly targeting the *FAM13C* gene. In addition, a study on endometrial cancers is the only study conducted on direct *FAM* genes to date, and as a result of bioinformatic analysis, it is emphasized that a group of FAM family genes, including FAM13C, may be an important prognostic marker in UCEC patients (14).There have been no studies in which the RECQL4 (upregulated) and FAM13C (downregulated) genes were simultaneously marked, and the common hub genes and possible drug-target components were attempted to be predicted in both breast cancer and all gynecological cancers (ovarian, endometrial and cervical). In this respect, our study has unique value.

Materials and Methods

Data Acquisition and Data Processing

Gene intensity values for BRCA (GSE42568, GSE20685, GSE54002), gynecological cancers such as CESC (GSE63514, GSE5787), OV (GSE54388, GSE14407, GSE27651) and UCEC (GSE17025) were obtained from the Affymetrix Human Genome U133 Plus 2.0 Array [HG-U133_Plus_2] project (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GPL570). GPL570 platform was used with 54.675 probes per patient in the Gene Expression Omnibus (GEO) database (15-23). Robust results were ensured by using independent and multiple datasets available for each cancer type. Gene intensity values of 17 healthy individuals (from GSE42568) and 24 healthy individuals (from GSE63514) were used as the control for gene intensities of breast and cervical cancer patients, respectively (24, 25). The data containing patient gene intensity data used in our study was selected from the data contained in the GPL570 platform in the NCBI GEO database because it is the platform with the highest number of probes per patient. We also aimed to include the highest number of patients as possible.

Statistical Analysis

Raw data of all datasets in the CEL format for each cancer type were utilized. Background correction and "Robust Multi-Array Average" normalization using the "oligo" package was done with the help of the Bioconductor R program (https://support.bioconductor.org/p/9148353/). The linear modelling method in the R LIMMA (version 4.3.1.) package was used separately for all datasets (https://www.bioconductor.org/packages/release/bioc/html/limma.html). By doing this, genes that show different gene expression (DEG) levels, either upregulated or downregulated when comparing healthy individuals and cancer patients were identified (26-28). To control the false discovery rate (FDR), The Benjamini-Hochberg method was used (29). Log2FC≥1 and log2FC≤−1 were accepted for the upregulation and downregulation of mRNA expression, respectively. The *p*-value was accepted as <0.05 for statistical significance.

Determination of Hub Genes and Protein-Protein Interactions (PPI) Network

After identifying DEG of interest, hub genes were investigated using the cytoHubba (30) program, which also identify important nodes and subnetworks of protein structures in the Cytoscape (31) program, an open-source software platform used to visualize complex molecular protein-protein interaction networks and integrate them with chosen attribute data. BioGRID 4.4 database was used to list the proteins interacting with *RECQL4* and *FAM13C* genes (32).

Gene Enrichment Analysis of Hub Genes

"ShinyGo 0.80" (known as a graphical gene-set enrichment tool for animals and plants) web-based tool was used to determine the disease specific functional biological pathways addressed by hub genes by selecting the "KEGG" pathway option (33). Furthermore, "ShinyGo 0.80" program was also utilized for gene annotations and probes that were not associated with any gene and were designated as NA were removed from the list. FDR cut-off was accepted as "0.05".

Predicted Drug-Target Interaction of Hub Genes

Drug.MATADOR, included in the ShinyGo 0.80 online tool, is used to predict drug-target relationships. MATADOR is a database used for predicting the interactions between proteins and chemicals. It is also a manually annotated list of relationships between protein products of such genes and chemicals (http://matador.embl.de) (34). In our study, this tool was used to predict the new candidate drug components.

Ethics Committee Approval

Publicly available data sets were utilized. Therefore, no approval from the ethics committee was required. Publicly available data sets were utilized. Therefore, patient consent was not required.

Results

The overall aim of our study was to determine the common DEGs between gynecological and breast cancers, which are women's cancers that can trigger each other in the clinic and have high hormonal interactions. Furthermore, we also aimed to determine hub genes that show gene interaction networks with defined DEGs. The final goal of the study was to determine which biological pathways that identified hub genes indicate and which drug-target interactions they address. Based on this purpose, firstly, genes commonly expressed in both BRCA, and all gynecological cancers were obtained. Furthermore, hub genes were identified, the biological pathways they indicate were determined, and predicted drug-target interactions were addressed (Figure 1).

Determination of Common DEGs of Both Breast Cancer and Gynecological Cancers

Types of cancers and their dataset numbers, healthy and patient numbers used in analysis and upregulated/downregulated gene numbers can be seen in Table 1. According to our findings, the *RECQL4* gene was shown to be commonly upregulated in all cancer types, including both BRCA and gynecological cancers, and the *FAM13C* gene was commonly downregulated in all cancer types (Table 2). Volcano plots of common DEGs for all cancers can be observed in Figure 2 a-i.

Identification of Hub-Genes and PPI Networks

A total of 3130 proteins, which interact with the protein products of the RECQL4 and FAM13C, were identified from the BioGRID 4.4 database. Using the obtained PPI protein list, hub genes were determined based on closeness (Figure 3a) and degree (Figure 3b) using the CytoHubba plugins of the Cytoscape program. According to these results, the top 20 nodes were identified according to both closeness and degree. Totally, 37 hub genes were determined (Figure 3). Furthermore, KEGG pathway analysis was performed for 37 hub genes. Pathways that may be associated with cancers were cellular senescence, FoxO signalling pathway, ubiquitin-mediated proteolysis and viral carcinogenesis and specifically annotated genes are shown in Figure 4 a-b and Table 3. Upon KEGG pathway analysis, among the 37 genes obtained, those related to defined KEGG pathways were determined and reduced to 11 genes.

Predicted Drug-Target Interactions by Using Common Hub Genes Determined for Breast and Gynecological Cancers

Drug.MATADOR analysis was performed using 11 hub genes *(RAD50, MAPK14, SIRT1, MRE11, NBN, EP300, USP7, DDB1, UBE2O, CDC16, and H2BC6)*. Drugs commonly associated with these hub genes and thus both breast and gynecological cancers were hydroxyurea; acetylcarnitine; salicylate; and dibutyryl cyclic AMP (Figure 5). In Table 4, there were three genes identified for these three drug components, and these were NBN, EP300 and MAPK14. For the gene NBN, hydroxyurea was the suggested interacting agent. However, for EP300, acetylcarnitine was suggested. Finally, both salicylate and dibutyryl cyclic AMP agents were suggested as interacting with the product of the *MAPK14* gene.

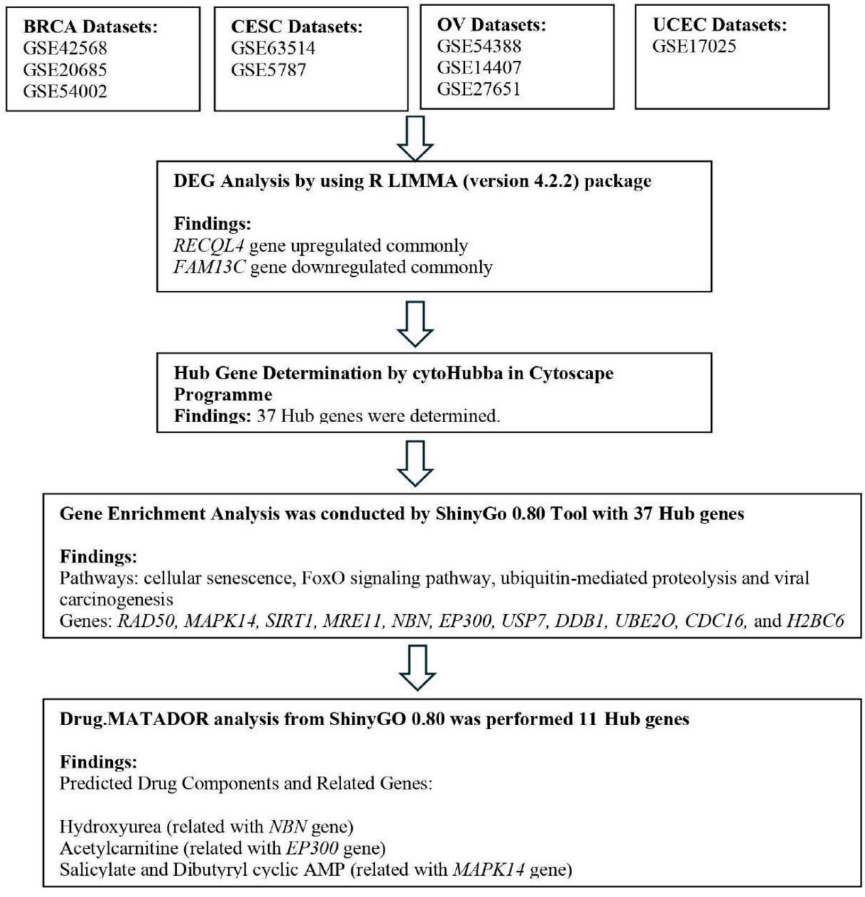

Figure 1. Outline of the study has been shown to clarify the setup of the research

Table 1. Information of breast and gynecological cancer datasets and DEG results

Cancer type	Breast cancer	Breast cancer	Breast cancer	Cervical cancer	Cervical cancer	Ovarian cancer	Ovarian cancer	Ovarian cancer	Endometrial cancers
GSE Code	GSE42568	GSE20685	GSE54002	GSE63514	GSE5787	GSE54388	GSE14407	GSE27651	GSE17025
Number of Samples (tumour/ healthy)	121 (104/17)	327 (327/17)	433 (417/16)	128(104/24)	33 (33/0)	22 (16/6)	24 (12/12)	49 (43/6)	103 (91/12)
Total number of samples	121	17	433	128	57	22	24	49	103
Tumour sample number	104	327	417	104	33	16	12	43	91
Healthy Sample number	17 healthy individuals (from GSE42568)		16	24 healthy individuals (from GSE63514)		6	12	6	12
Downregulated gene number	8563	27584	9919	5003	19460	4483	6161	6787	3311
Non-significant gene number	37872	11125	24141	44248	16550	45696	43224	42371	45724
Upregulated gene number	8240	15966	20615	5424	18665	4496	5290	5517	5640
Total gene number	54675	54675	54675	54675	54675	54675	54675	54675	54675

DEG: Differentially expressed genes

Table 2. Commonly expressed genes in both gynecological cancers (ovarian, cervical and endometrial) and breast cancers in women

Affy IDs of genes	Ensembl gene name (s)	Gene descriptions	Type	Expression pattern of genes in breast cancer	Expression pattern of genes in gynecological cancers
1553015_A_AT	RECQL4 (RECQ4)	RecQ like helicase 4	Protein coding	BRCA: upregulated	OV: upregulated CESC: upregulated UCEC: upregulated
1554547 AT	FAM13C (FAM13C1)	Family with sequence similarity 13 member C	Protein coding	BRCA: downregulated	OV: downregulated CESC: downregulated UCEC: downregulated

Discussion and Conclusion

In our study, the *RECQL4* and *FAM13C* genes were found to be similarly expressed in both breast cancer and gynecological cancers. Considering the proteins in the interaction network of the genes we focused on in our study, the hub genes obtained were primarily determined as 37. As a result of KEGG pathway analyses, pathways associated with cancers were determined as cellular senescence, FoxO signalling pathway, ubiquitin-mediated proteolysis and viral carcinogenesis, and hub genes indicating these pathways were focused on. After performing Drug.MATADOR analysis with the remaining 11 hub genes, we have 3 genes that both indicated a meaningful biological pathway and from which we can make drug-target predictions.

In the literature, instead of focusing on the common genes of breast cancer and all gynecological cancers, there are studies in the literature that analyse common DEGs between breast cancer, OV or UCEC separately. In this context, the only similar study conducted without using bioinformatic analysis is the study conducted by Naghizadeh et al. (35), and in group studies, researchers studied with 200 healthy individual and 200 female patients diagnosed with breast and gynecological cancer. In the study, only demographic data of the patients and statistical correlation data between cancer cases were obtained, with regional restrictions in the Iranian region. No analysis based on genetic-based bioinformatics methods was performed in the study (35). In addition, instead of focusing on the common genes of breast cancer and all gynecological cancers, there are studies in the literature that analyse common DEGs between breast cancer, OV and UCEC. In one study, DEG analyses and biological pathway predictions were made because it is not clear in the literature by which biological and genetic mechanisms breast cancer is associated with UCEC.

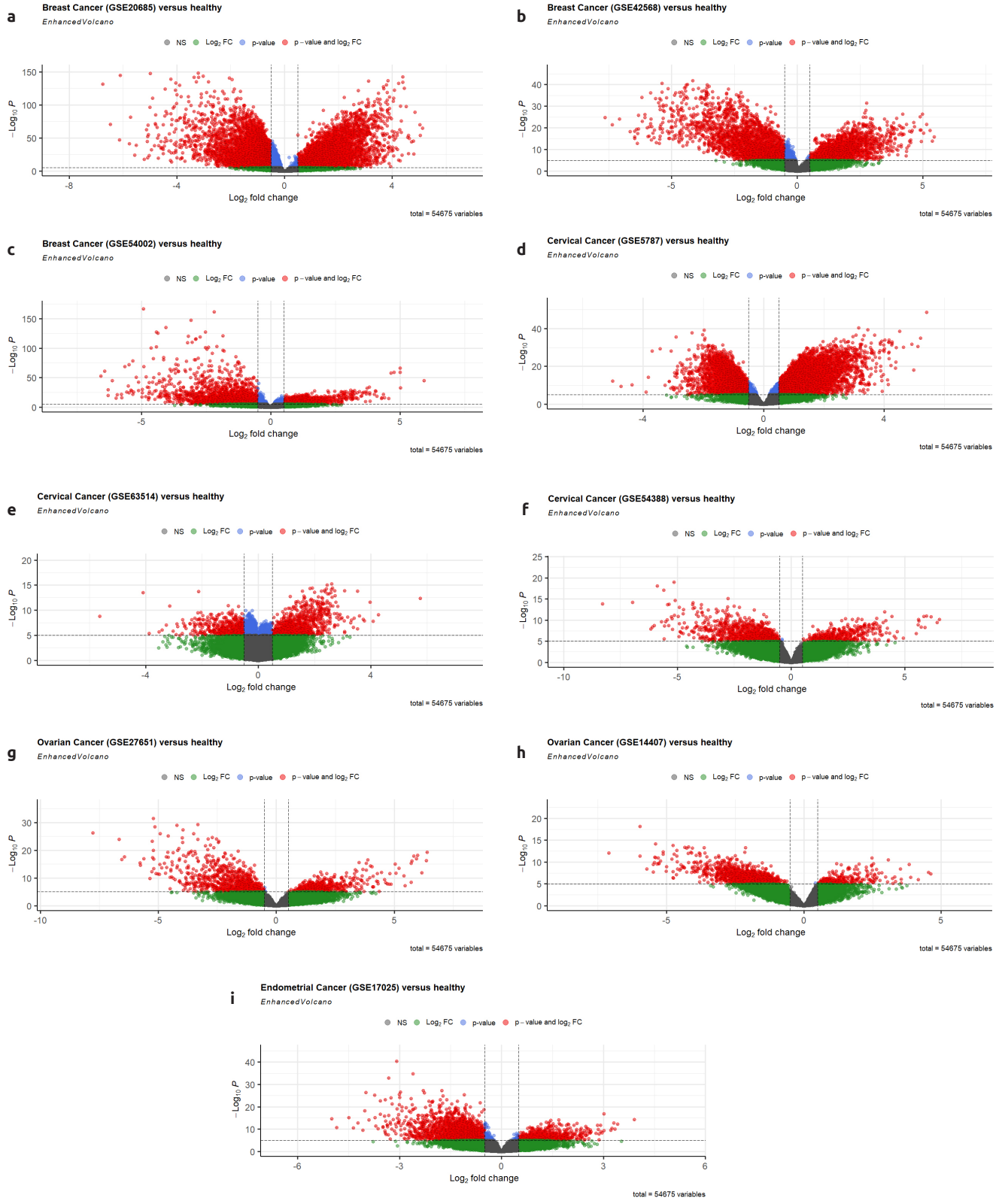

Figure 2. Volcano plot of breast and gynecological cancers. Blue dots indicate *p*-value 10e-6, green dots indicate Log2FC ≤ -1 and ≥1, and red dots show those that are below the p-value of 0.05 and Log2FC thresholds. Gray dots indicate insignificant genes. (a) breast cancer (GSE20685), (b) breast cancer (GSE42568), (c) breast cancer (GSE54002), (d) cervical cancer (GSE5787), (e) cervical cancer (GSE63514), (f) cervical cancer (GSE54388), (g) ovarian cancer (GSE27651), (H) ovarian cancer (GSE14407), (i) endometrial cancer (GSE17025)

Table 3. KEGG pathway genes specifically related to individual pathways

Enrichment FDR	Number of genes	Pathway genes	Fold enrichment	Pathway	Genes
0.019736446	2	41	39.86237	Homologous recombination	*MRE11, NBN*
0.000123199	5	156	26.19162	Cellular senescence	*RAD50, MAPK14, SIRT1, MRE11, NBN*
0.000972628	4	131	24.95202	FoxO signalling pathway	*MAPK14, EP300, SIRT1, USP7*
0.017618289	3	142	17.26434	Ubiquitin mediated proteolysis	*DDB1, UBE2O, CDC16*
0.003510585	4	202	16.18175	Viral carcinogenesis	*DDB1, EP300, USP7, H2BC6*
0.019736446	3	162	15.13294	Hepatitis B	*MAPK14, DDB1, EP300*

FDR: False discovery rate

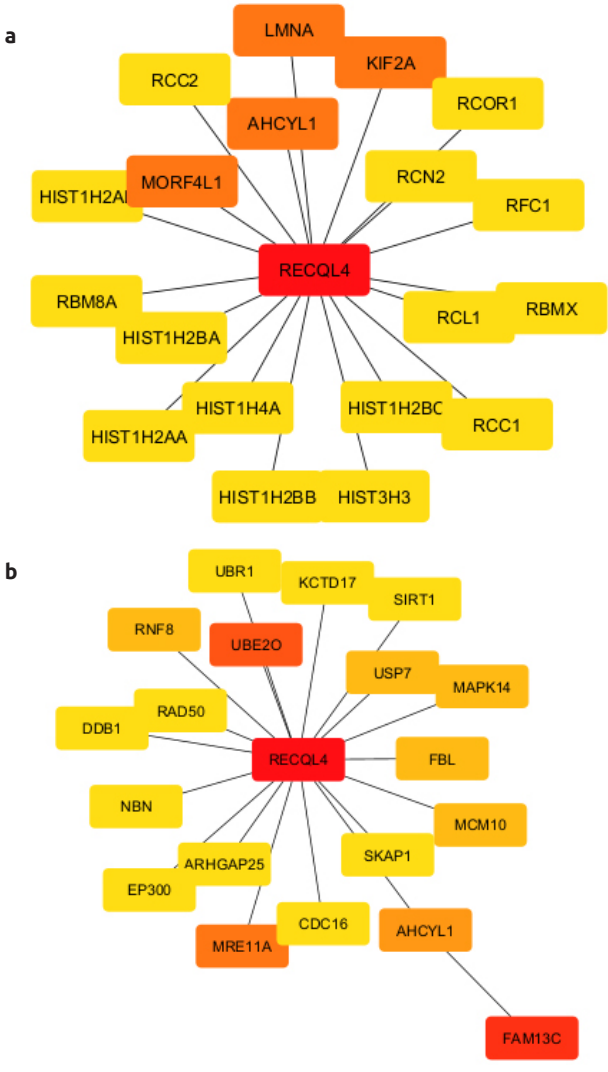

Figure 3. Network of hub-genes identified by closeness (a) and degree (b) in Cytoscape according to PPI network analysis done with CytoHubba plugins of the Cytoscape program, hub genes were determined based on closeness (a) and degree (b). The top 20 nodes were used according to both closeness and degree

PPI: Protein-protein interactions

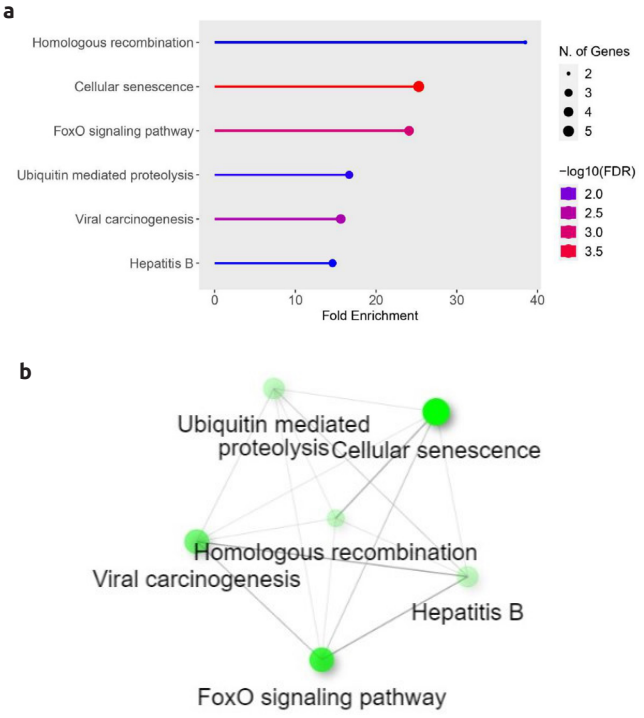

Figure 4. The lollipop chart (a) and network (b) of KEGG pathways in ShinyGO 0.80 According to KEGG pathway analysis from ShinyGO 0.80 online tool, biological pathways related commonly with breast and gynecological cancers are shown with lollipop chart (a) and network (b)

Fifty-seven DEGs were identified in the study, and among these genes, *RECQL4* and *FAM13C* genes, which were found to be commonly expressed in all cancers in our study, were not present (36). In another study, genes commonly expressed between breast cancer patients and both OV and UCEC patients were determined (37). In addition, another study in which bioinformatic analyses were performed using gene density data of breast cancer and ovarian cancer patients focused only on mutations of the BRCA gene (38). In addition, another study in which bioinformatic analyses were performed using gene density data of breast cancer and ovarian cancer patients focused only on mutations of the *BRCA* gene. In one of the current studies conducted

Table 4. Drug-target interaction prediction with common hub genes of both breast and gynecological cancers

Enrichment FDR	nGenes	Pathway genes	Fold enrichment	Drug component	Genes
0.02391172	1	11	189.0991736	Hydroxyurea	*NBN*
0.02391172	1	25	83.20363636	Acetylcarnitine	*EP300*
0.02391172	1	25	83.20363636	Salicylate	*MAPK14*
0.034966622	1	49	42.45083488	Dibutyryl cyclic AMP	*MAPK14*

FDR: False discovery rate

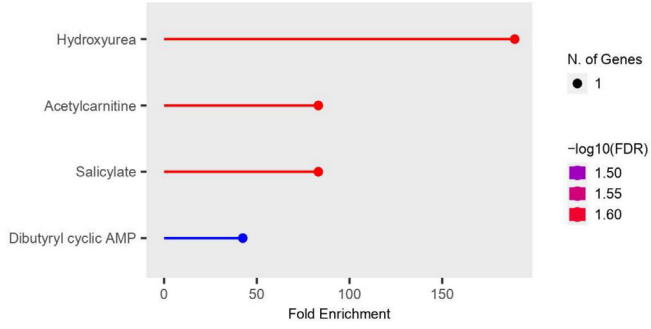

Figure 5. Predicted drug components commonly related to both breast and gynecological cancers. Using Drug.MATADOR analysis from ShinyGO 0.80 online tool, drug-gene target prediction has been made by using common hub genes determined for both breast cancer and gynecological cancers

among gynecological cancers without breast cancer, DEG analyses were performed in patients diagnosed with ovarian, endometrial and vulvar cancer (39). One of the most recent studies on this subject aimed to identify common genes in cervical, endometrial and ovarian cancers and to determined effective and dominant biological pathways through hub genes (40). None of the studies whose findings were summarized above focused on the DEGs we pointed out. For this reason, hub gene analysis and gene enrichment analysis results were also not similar. Additionally, these studies did not perform drug-target prediction analyses, which we focused on in our study.

It is known that the protein product of the *RECQL4* gene, one of the DEGs commonly detected in our study, is a protein that plays a role in the DNA repair mechanism, and it is known in the literature that it has more unique functions in replication and DNA breaks compared to other repair proteins (41). On the other hand, *FAM13C* gene and its protein product belongs to FAM family members and although it has been detected in cancer tissues, it should be further investigated.

Before discussing the drug, components obtained in our study and the hub genes they interact with, information will be given about all hub genes and enriched pathways obtained in the study. It has been well known that the MRN complex (MRE11-RAD50-NBN) creates a DNA damage repair site where there is double strand break. RAD50 (RAD50 double strand break repair protein) and Alterations in MRE11 (MRE11 homolog, double strand break repair nuclease) double strand break repair protein and variants of these genes have been observed in other cancers, including breast, ovarian and endometrial cancers (42, 43). In our study, we also showed MRN complex molecules among the hub genes indicated by DEGs obtained from breast and gynecological cancers.

SIRT1 protein has been shown to be an important protein in cancer progression however it has been newly shown that it contributes to the metastasis of breast cancer with the cooperation of (The Forkhead box O) FoxO protein (44). For instance, overexpression od *SIRT1* gene has been indicated in cervical cancer (45). Furthermore, based on the deacetylating effect of the *SIRT1* gene on histone and non-histone proteins, it is thought that it may contribute to DNA damage and repair, apoptosis, cell cycle regulation and inflammation in gynecological cancers (46). In our study, FoxO signalling pathway is enriched with our hub genes and there should be further studies to identify the roles of the pathway and *SIRT1-FoxO* genes in gynecological cancers.

In our study, the gene identified as the hub gene and closely related to DNA damage and repair mechanism is the damage specific *DNA binding protein 1 (DDB1)* gene. It has been shown that alterations in this gene expression have been related to ovarian and breast cancers (47). Rather than DDB1 alone, mostly DDB1-DDB2 (damage-specific DNA-binding protein 2) complex as a new tumor suppressor has been associated to ovarian cancers (48). On the other hand, DDB2 overexpression has been related to breast cancers (49). The roles in cervical and endometrial cancers remains an open area to be elucidated.

H2BC6 gene has been considered as a cancer biomarker in prostate cancer by NIH Early Detection Research Network (50). Further studies should also be done for breast and gynecological cancers.

Cancer cells are related to the expression of oncogenes and tumor suppressor gene products and the balance between them. When growth factors that cause tumors are not destroyed in the ubiquitin-proteasome system, tumor formation is triggered (51). In our study, the ubiquitin-mediated proteolysis pathway is one of the pathways enriched with our hub genes such as *USP7* and *UBEO2* genes. USP7 (ubiquitin specific peptidase 7) gene has been shown to be involved in ubiquitination process of proteins during the posttranslational protein modifications process and suppression of the overexpression of this gene has led to breast cancer regression in breast cancer cell lines (52). It has been shown that it can be a prognostic factor for ovarian and cervical cancer (53). Furthermore, *UBE2O* gene has also be linked to various cancers such as breast and ovarian cancers summarized in a comprehensive review (54).

Lastly, in our study, cellular senescence has been enriched by our hub genes such as *CDC16* gene. Even though cellular senescence mechanism can be used in cancer regression via cell cycle arrest in cancer cells, there can be a possibility that cells affected by therapy-induced senescence can stay dormant and can enter again in cell cycle process (55). In this regard, according to our opinion, targeting and

inhibiting cell cycle related genes can effectively induce irreversible cellular senescence and it can be a possible prevention for the dormant cells which may re-enter the cell cycle process from the senescent state.

In our study, primarily, *RECQL4* and *FAM13C* genes were found to be similarly expressed in breast cancer and gynaecological cancers. Secondly, as a result of Drug.MATADOR analysis with hub genes, we have determined these gene/drug interactions such as NBN (targeted by Hydroxyurea), EP300 (targeted by Acetylcarnitine), and MAPK14 (targeted by Salicylate and Dibutyryl cyclic AMP).

The *NBN* gene is a gene that encodes the nibrin protein, also known as "Cell Cycle Regulatory Protein P95" and is a component of the MRE11-RAD50-NBN (MRN) complex. *NBN* gene plays an important role in DNA double-strand break repair mechanisms (56). Mutations or expression differences in the *NBN* gene may play a role in cancer processes as they may lead to deficiencies in DNA damage repair mechanisms. Variants of the *NBN* gene have so far been studied among women's cancers using breast cancer patient samples. For example, it has been shown using data from 116 patients that NBN variants may be important as diagnosis markers to be used in tests to detect hereditary breast cancer cases (57). It has also been determined that amplification of the *NBN* gene increased cisplatin and polymerase inhibitors (PARPi) resistance in breast and ovarian cancers (58). In another recent study, various analysis and experiments were conducted to determine whether the NBN gene could be a pan-cancer susceptibility gene. It was shown that pathogenic variants of the *NBN* gene increased the risk of cancer due to disruptions in the DNA damage response in breast, endometrial, ovarian and cervical cancers, respectively, as in many cancers (59). In our study, the *NBN* gene was associated with homologous recombination and especially cellular senescence.

In our study, as a result of drug component prediction analysis, hydroxyurea (hydroxycarbamide) was associated with the *NBN* gene. Hydroxyurea is an anticancer and antineoplastic agent and is known as a DNA replication inhibitor (60). According to Drugbank data, where drug research and clinical use are currently shared with the scientific world, it is frequently used in patients with chronic myelogenous leukaemia and head and neck primary squamous cell carcinoma. It is also a drug used clinically in sickle cell anaemia (https://go.drugbank.com/drugs/DB01005).

The *E1A binding protein P300* (*EP300*) gene encodes the P300 protein. P300 protein plays a role in gene expression by increasing the transcriptional activity of genes by interacting with transcription factors and serving as histone acetyltransferase, allowing histone proteins to be separated from genes during DNA replication (61). In a recently published study, it has been shown that the nucleosome assembly protein 1 like 1 (NAP1L1) protein, which is active through the DEAD-box helicase 5 (DDX5) promoter and acetylated by the EP300 protein, played a role in the progression of endometrial cancers (62). It has been shown that cervical cancer cells secrete lactic acid while performing the aerobic glycolysis mechanism (63, 64). Yang et al. (65) have identified the *EP300* gene among the genes associated with histone lactation modification via the GEPIA2 webtool by using cervical cancer patients' data (65). In addition, in a study trying to determine the effectiveness of poly- (ADP ribose) PARPi therapy on ovarian cancer cells, researchers showed that the *EP300* gene has an important role in this process (66). According to the results of the study, it was found that the histone acetyltransferase mechanism, which was inhibited as a result of the *EP300* gene, developed PARPi-resistance in patient samples (66). In studies conducted on triple negative breast cancer cell lines, it was observed that the *EP300* gene had an oncogenic effect, and with the suppression of the gene, a decrease in the metastatic capacity of the cells, a change in cancer stem cell phenotype, and a regression in the growth of tumour cells were observed (67). In another study, it was determined that the loss of heterozygosity percentages of the *EP300* gene in breast and ovarian cancer cell lines and primary cancer cells were 36% and 49%, respectively (68).

In our study, the drug component associated with the *EP300* gene and predicted to interact with it is acetylcarnitine. Acetylcarnitine is the acetylated form of the amino acid L-carnitine, which is involved in mitochondrial fatty acid metabolism (69). With this structure, Acetylcarnitine is used clinically in the treatment of peripheral nerve lesions, psychiatric diseases such as depression, dementia and neuropathies, according to Drugbank data. Furthermore, according to Drugbank data, Acetylcarnitine is also an agent used in clinical trials for the treatment of diseases such as migraines, type 2 diabetes mellitus chronic hepatitis C, progressive supranuclear palsy. (https://go.drugbank.com/drugs/DB08842).

Mitogen activated protein kinases (MAPKs) play a crucial role in balancing the responses between outside and inside the cell in the homeostasis processes of the cell. *MAPK14* gene is also known as *p38*α gene (https://www.genecards.org/cgi-bin/carddisp.pl?gene=MAPK14). Inhibition of MAPK14 (p38α) has been shown to develop anti-tumoral effects against Taxanes due to increased DNA damage in breast cancer cells in patients and murine models (70, 71). In the study conducted by Katopodis et al. (72) the role of MAPKs in women's cancers (OV, UCEC, CESC, BRCA, and UCS) was investigated, and the study focused on the expression and methylation levels of MAPK11 (p38β) as a result of bioinformatic analysis. In addition, another study has emphasized that the drug called Ralimetinib (LY2228820), known as an inhibitor of p38α (MAPK14) and p38β (MAPK11), is an agent that can target a group of cancer types, including metastatic breast cancers and ovarian cancers (73). In a study conducted in 2023, the role of the p38α signalling pathway in cancer processes was investigated, and according to proteomic analysis, it was shown that the MAPK14 (p38α) protein was important in RNA metabolism, regulated cell adhesion in breast cancer cells, and was effective in DNA replication. Breast cancer cells were used as a role model in this study (74).

Salicylates are known as salts or esters of salicylic acids, and they are frequently used for their analgesic effects. Furthermore, they are also providing anti-inflammatory and antipyretic impact (https://go.drugbank.com/categories/DBCAT000579). For example, aspirin (acetyl salicylate), used as a nonsteroidal anti-inflammatory drug, is a drug often used in people at risk of myocardial infarction (75, 76). However, it has been investigated for a while whether it can be effective in a group of cancer types, including breast and ovarian cancers (77, 78) According to the results of these studies, it has been stated that it can be used effectively in breast cancer patients among women's cancers.

The drug component shown to target the *MAPK14* gene in our study is dibutyryl cyclo-adenosine monophosphate, whose generic name is Bucladesine. Bucladesine, a cyclic nucleotide derivative, acts as an endogenous cAMP and phosphodiesterase inhibitor in the cell. It can be used as a topical product for wound healing for skin ulcers or as a cardioprotective agent (https://drugs.ncats.io/drug/63X7MBT2LQ). According to Drugbank data, there is no study showing whether Bucladesine, which is still in the experimental and research phase, is an effective agent in women's cancers (https://go.drugbank.com/drugs/DB13242#BE0000240).

The drugs mentioned in the discussion section of our article and associated with the hub genes determined in our study are not drugs used in the clinic for the treatment of breast cancer or gynecological cancers. In fact, they are not routinely used drugs in cancer treatment. In this respect, our study offers the opportunity to identify the target genes of drugs used in the treatment of different diseases in the clinic with the drug repurposing approach, which can be used in gene-targeted therapies in the treatment of breast cancer and gynecological cancers. Furthermore, before the trial of these agents on behalf of their cytotoxic effects on cell lines, future molecular dynamics simulations should be done to validate the docked structures to claim that drugs are suitable for the active regions of the target proteins. As a future perspective, total RNA and DNA samples obtained from projects including patient samples and cell lines that include validation of the obtained data should be used for further analysis by using more comprehensive and modern RNA-Seq, whole exome/transcriptome sequencing data.

Ethics

Ethics Committee Approval: Publicly available data sets were utilized. Therefore, no approval from the ethics committee was required.

Informed Consent: Publicly available data sets were utilized. Therefore, patient consent was not required.

Footnotes

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Case Report

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Rosai-Dorfman Disease Presenting With FDG-Avid Breast Masses and Axillary Lymph Nodes on PET-CT in a Patient With Recent Diagnosis of Endometrial Carcinoma: A Diagnostic Dilemma

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ABSTRACT

Rosai-Dorfman disease (RDD) is a self-limited, idiopathic, non-neoplastic disorder characterized by the proliferation of phagocytic histiocytes, which can mimic malignant lymphoproliferative disease. Cases of RDD most commonly present as bilateral painless cervical lymphadenopathy, with lesser involvement of the axilla, inguinal, and mediastinal lymph nodes. We present the case of a 62-year-old woman with a history of endometrial serous carcinoma who underwent evaluation at a dedicated breast imaging department after positron emission tomography/computed tomography (PET/CT) revealed breast masses and axillary nodes with increased uptake of fluorodeoxyglucose (FDG). Upon clinical examination, she had bilateral palpable lumps in both breasts and axillae. Subsequent dedicated breast imaging with bilateral diagnostic mammography with tomosynthesis and bilateral complete breast ultrasound were suspicious for malignancy detecting bilateral breast masses and axillary lymphadenopathy corresponding to the FDG-avid findings on PET/CT. Ultrasound-guided core needle biopsies, however, revealed a diagnosis of RDD. This case highlights the unique characteristics of RDD with an atypical clinical presentation suspicious for breast cancer both clinically and radiologically.

Keywords: Endometrial carcinoma; primary breast cancer; axillary lymphadenopathy; mammogram; core needle biopsy

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Key Points

- Despite the benign nature of Rosai Dorfman disease (RDD), its clinical presentation can mimic features of malignancy, necessitating thorough diagnostic evaluation. The diagnostic dilemma of our case was intensified by the patient's recent gynecologic cancer, requiring careful oncologic evaluation.
- Diagnosis of RDD relies heavily on histopathology, highlighting features such as sinus infiltration and emperipolesis with key immunohistochemical markers including S-100 and CD68, which aid in distinguishing RDD from other conditions.
- RDD may present as suspicious findings on breast imaging or other imaging modalities, highlighting the need for timely diagnostic evaluation and provider awareness.

Case Presentation

A 62-year-old female without a personal or family history of breast cancer, but recently diagnosed with endometrial serous carcinoma, presented to the dedicated breast imaging clinic for evaluation after staging computed tomography (CT) of the chest revealed concerning findings in the uterus, breast, left abdominal wall and right colon. CT chest showed bilateral axillary lymphadenopathy (LAD) and breast nodules, the largest of which was in the medial right breast up to 2.5 cm (Figure 1). Positron emission tomography (PET)/CT scan subsequently detected bilateral, fluorodeoxyglucose (FDG)-avid, axillary lymph nodes and breast masses, most suspicious within the medial right breast (Figure 2), further corresponding to suspicious masses reported on the prior CT chest. Thus, concern for primary breast malignancy, metastatic disease and lymphoma were all considered in the differential diagnosis.

During diagnostic workup at the breast imaging clinic, she presented with palpable areas of concern in both breasts and axillae. She underwent bilateral diagnostic digital mammography with tomosynthesis which

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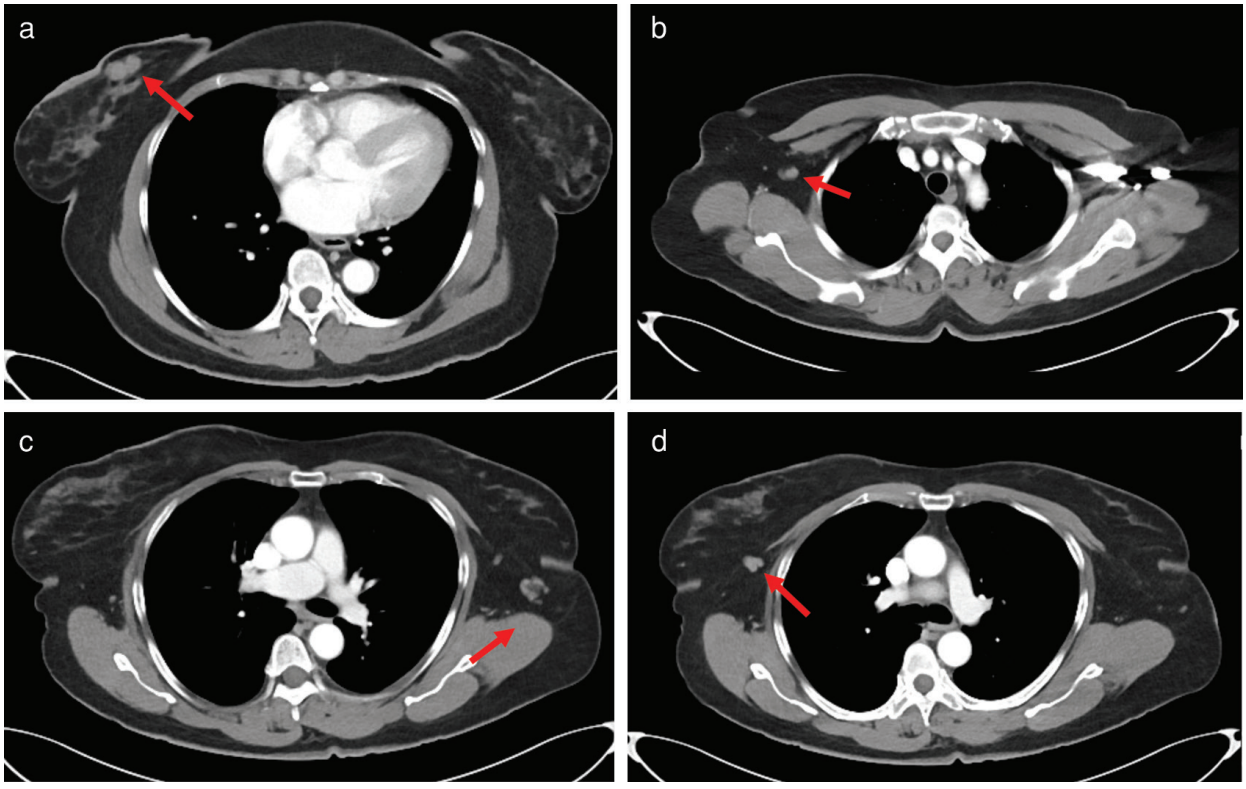

Figure 1. 62-year-old female with recently diagnosed endometrial carcinoma. Staging imaging via CT Chest showing prominent 2.5 cm right breast mass (a), and evidence of bilateral axillary LAD (b). Right axillary node with little fatty hilum and thickened cortex of 0.9 cm (c and d). Additional enlarged nodes of the left axilla, 1.6 cm x 1.5 cm, and right axilla, 1.2 cm x 1.1 cm

CT: Computed tomography; LAD: Lymphadenopathy

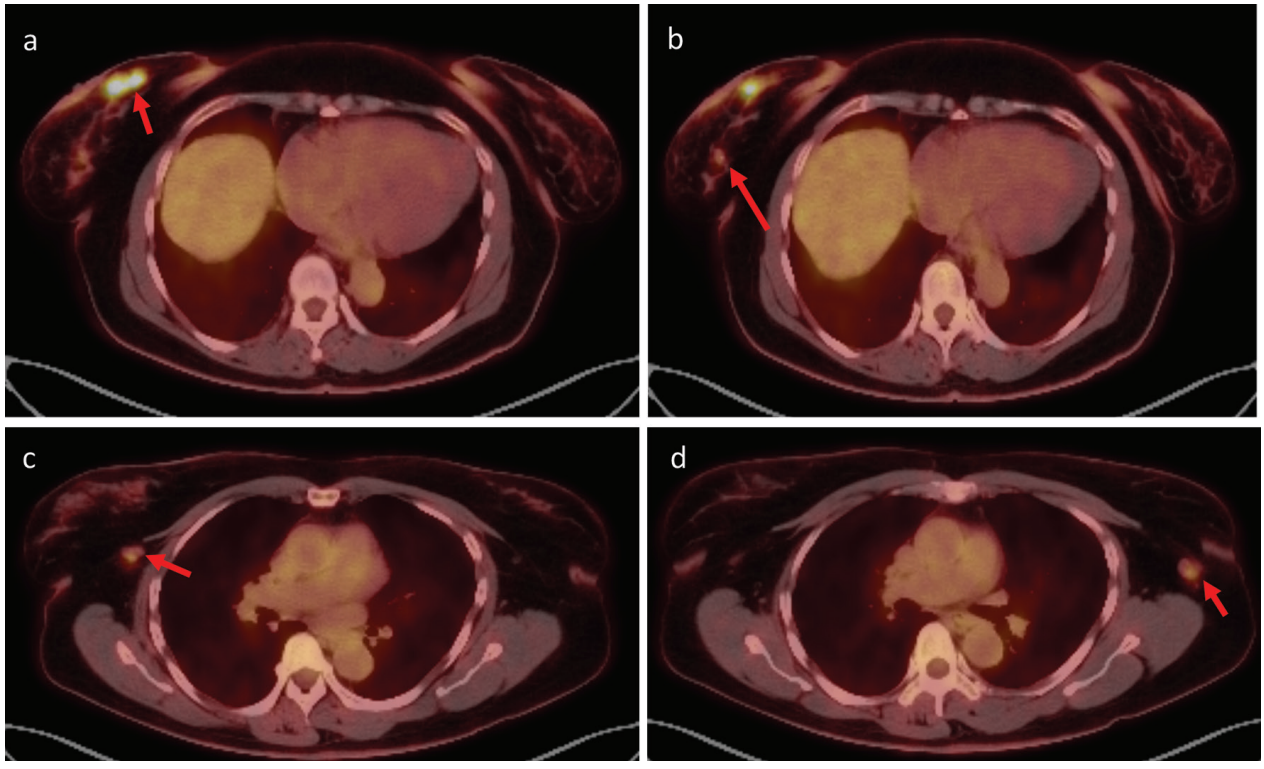

Figure 2. PET/CT showing FDG avid right breast masses SUV 9.5 medially and 7.6 laterally (a and b). Additional views with (c) right FDG avid axillary lymph node with background FDG activity and (d) left axillary node with SUV 2.4

PET/CT: Positron emission tomography/computed tomography; SUV: Standardized uptake value; FDG: Fluorodeoxyglucose

showed scattered areas of fibroglandular breast tissue and bilateral similar-appearing, partially obscured, equal density masses, including a dominant 3.3 cm mass in the right lower inner quadrant at 3-4 o'clock, containing a biopsy marker from a prior reportedly benign biopsy site performed many years ago (Figure 3). Mammography was relevant for a 1.7 cm obscured equal density mass in the right outer breast at 9 o'clock which also contained a biopsy marker at an additional reportedly benign biopsy site. There was an additional 1.8 cm obscured mass with coarse calcifications in the left inner breast at approximately 9 o'clock favoring a benign, involuting fibroadenoma, prominent axillary lymph node, and persistent asymmetry reported in the left outer breast at 3 o'clock (Figure 4). No previous screening or diagnostic images were available for comparison at the time of diagnostic evaluation. Given the areas of palpable concern and mammographic findings within the both breasts and axillae, bilateral breast ultrasound (US) was obtained. US showed multiple breast masses, with the most suspicious including a 3.2 x 1.3 x 1.3 cm oval heterogeneous mass with microlobulated margins and internal vascularity on Doppler ultrasound in the right breast at 3-4 o'clock, 2 cm from the nipple, which corresponded to the mammographic mass with adjacent biopsy marker in the right lower inner quadrant. (Figure 5). There was also an additional 1.0 x 0.7 x 0.9 cm irregular, heterogeneous mass in the left breast at 3 o'clock, 4 cm from nipple (Figure 5). On evaluation of bilateral axillae, an abnormal right lymph node was visualized with up to 0.5 cm of cortical thickening, as well as an abnormal left axillary lymph node with a cortical thickness of 0.7 cm in the mid left axilla (Figure 6). Despite the patient's account of a remote, benign biopsy result corresponding to the right breast mass at 3-4 o'clock, biopsy was indicated given the internal vascularity and FDG avidity. A Breast Imaging Reporting and Data System (BI-RADS)-4 classification was assigned to her breast imaging. Additional core needle biopsy of the abnormal right lymph node was indicated given the corresponding FDG avidity and cortical thickness. Respective biopsies were performed, and post-biopsy imaging confirmed adequate placement of biopsy markers.

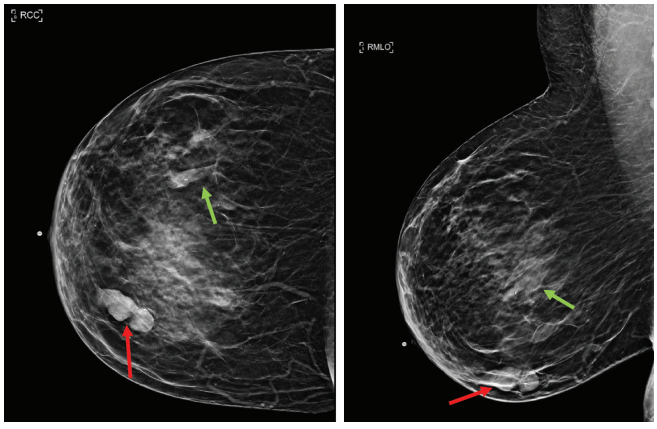

Figure 3. Bilateral diagnostic digital mammography with scattered areas of fibroglandular breast tissue. Right breast cranial-caudal (left image) and medial lateral (right image) views showing 3.3 cm oval circumscribed mass denoted by red arrow in the right lower inner quadrant at 3:00-4:00, also containing a prior biopsy marker. An additional 1.7 cm obscured equal density mass also containing a biopsy marker was noted in the right outer breast, approximately 9:00, denoted by green arrow

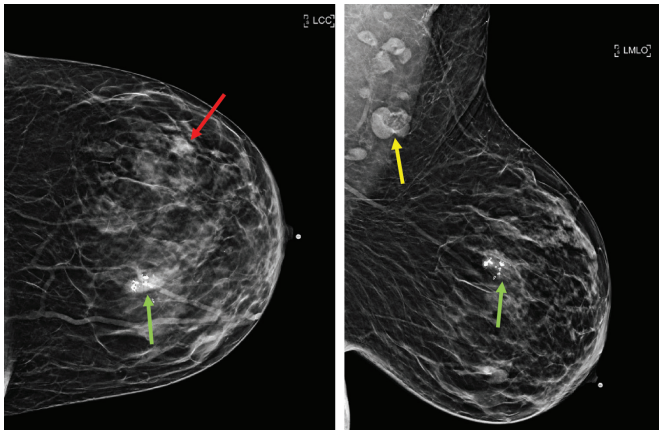

Figure 4. Bilateral diagnostic digital mammography with scattered areas of fibroglandular breast tissue. Left breast cranial-caudal (left image) and medial lateral (right image) views showing a 1.8 cm obscured mass with coarse calcifications in the left inner breast at approximately 9:00 favoring a benign, involuting fibroadenoma (green arrow). Additional persistent asymmetry in the left outer breast, best seen on craniocaudal (CC) view (red arrow), approximately 3:00, middle depth which was further evaluated with spot compression views (Figure 7 below). Prominent left axillary node appreciated on the left medial-lateral oblique (MLO) view (yellow arrow)

Ultimately, histopathological results from the biopsies performed of the right breast and right axillary node demonstrated intramammary lymph nodes with sinus histiocytosis, consistent with RDD, and a benign lymph node with paracortical hyperplasia and sinus histiocytosis. Cytology studies revealed marked paracortical expansion by patchy histiocytic proliferation with round nuclei and small nucleoli, surrounded by abundant pale cytoplasm, with emperipolesis present. There was no evidence of metastatic disease or atypia (Figure 7). Immunohistochemical studies revealed the histiocytes were positive for S-100, OCT2, cyclin D1, and BCL6, and negative for CD1a. Biopsy of the suspicious left breast mass at 3 o'clock was also performed with pathology revealing benign mammary parenchyma with dense stromal fibrosis. The results were concordant with her breast imaging. Patient consent was obtained prior to preparation of the following case and manuscript.

Discussion and Conclusion

RDD, also known as sinus histiocytosis with massive lymphadenopathy, is a benign disorder first described in 1969 (1). RDD is characterized by the non-neoplastic proliferation of activated histiocytes within tissues, often presenting as extensive peripheral lymphadenopathy (2, 3). Diagnosis is largely based on clinical history and pathology.

Cases of RDD are more common within the pediatric population with peripheral lymphadenopathy as the cornerstone of the disease syndrome. When presenting in adults, RDD has been reported to present in the second decade of life with cervical lymphadenopathy, usually bilateral and painless in about 87% of patients (4-6). The axilla, as in our case, has been found to be involved in RDD to a lesser degree, in roughly 23.7% of cases. Involvement of the inguinal (25.7%) and mediastinal (14.5%) regions have also been reported (1, 6-7). Other signs and symptoms of RDD include fever, weight loss, anemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, malaise, and night sweats (8-9). RDD has also been shown to affect various extra nodal sites in nearly half of patients with greatest prevalence within the head and neck region, specifically the paranasal sinuses and nasal cavity (4, 8, 10). Additional extra nodal cases of RDD in adults have been reported to present with cutaneous findings without LAD, most often in the form of papules, nodules, and plaques (11). Extra nodal RDD was most frequently reported in older patients

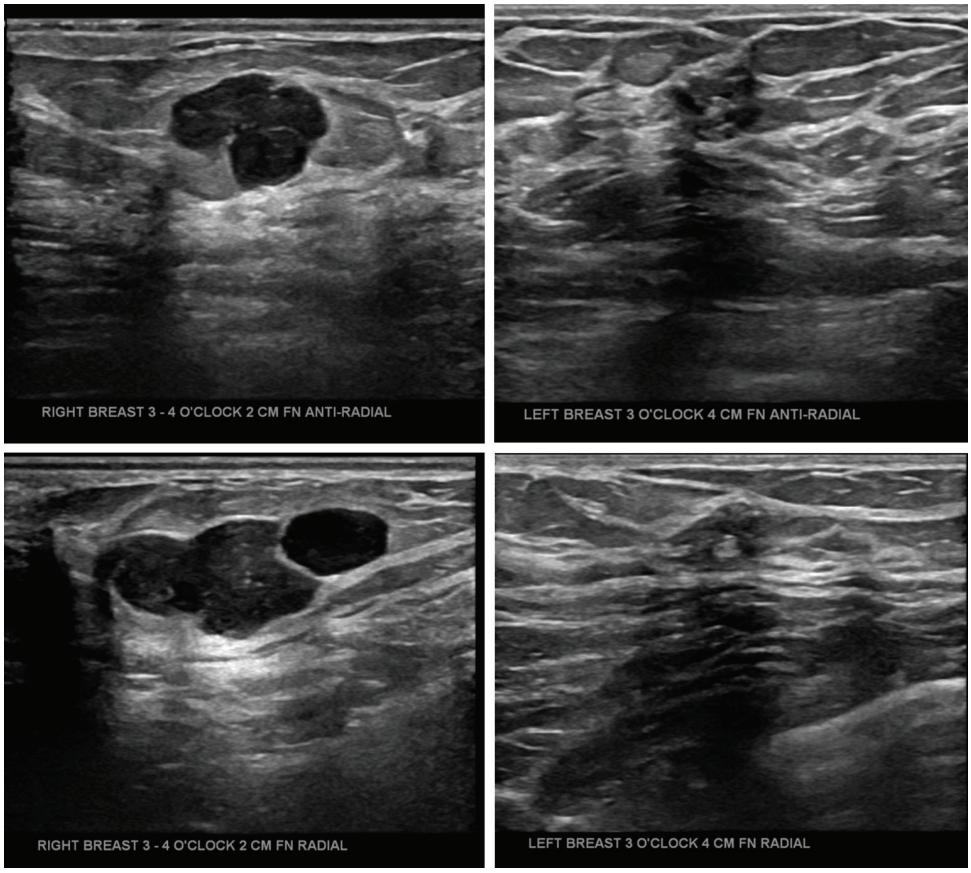

Figure 5. Bilateral complete breast ultrasound with findings of 3.2 x 1.3 x 1.3 cm oval heterogeneous mass with predominantly circumscribed however some micro lobulated margins and internal vascularity in the right breast 3-4:00, 2 cm from nipple, corresponding to the mammographic mass with adjacent biopsy marker in the right lower inner quadrant (left images) and 1.0 x 0.7 x 0.9 cm irregular, heterogeneous mass in the left breast 3:00, 4 cm from nipple, concordant with asymmetry on mammographic images. Core biopsy yielded intramammary lymph nodes with sinus histiocytosis, consistent with Rosai-Dorfman disease

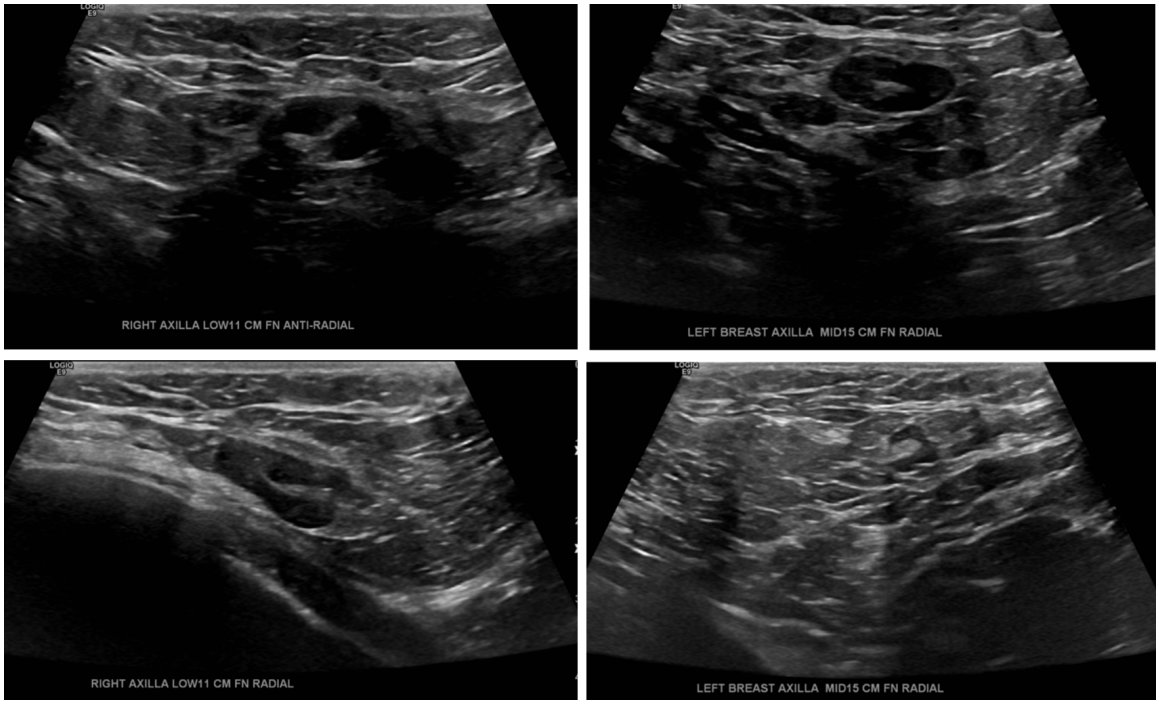

Figure 6. Bilateral complete breast ultrasound with findings of abnormal right lymph node with 0.5 cm cortical thickening in the low right axilla 11 cm from nipple (left images), and abnormal left axillary lymph node with cortical thickness of 0.7 cm and peripheral vascularity in the mid left axilla at 15 cm from nipple (right images). Core biopsy yielded a benign lymph node with paracortical hyperplasia and sinus histiocytosis

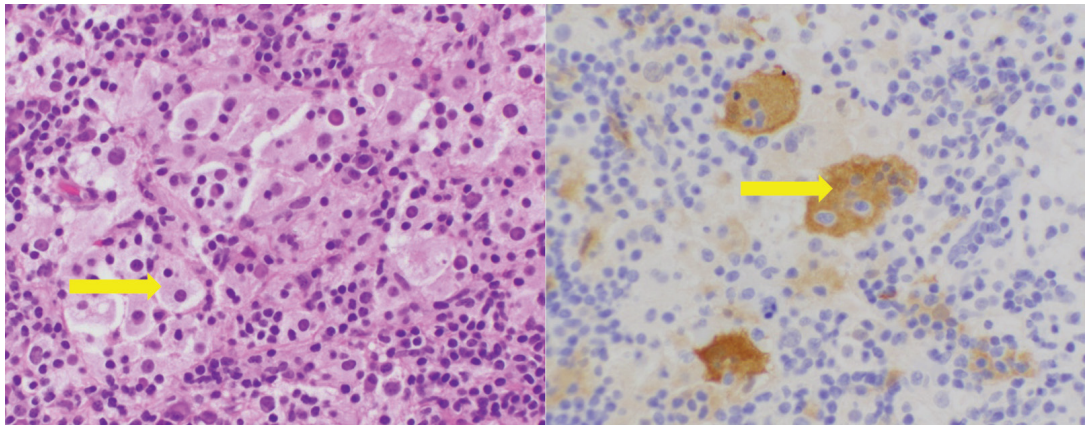

Figure 7. Photomicrographs showing representative histologic section of breast core with marked paracortical expansion and patchy histiocytic proliferation with round nuclei and small nucleoli, surrounded by abundant pale cytoplasm, emperipolesis (left image, yellow arrow, H and E, 600X). Higher power photomicrograph with both H and E (600X) and S100 immunostaining shows diffuse, strong cytoplasmic positivity within histiocytes (right image, yellow arrow)

(1, 5, 8). Rare extra-nodal presentations of RDD are still documented, including cases involving the CNS and breast, exemplifying the vast clinical presentations of RDD.

The histiocytosis of RDD may be sporadic, familial, or cutaneous. Sporadic cases are the most prevalent and may be secondary to neoplasia, seen with hematologic malignancies, or autoimmune related such as with systemic lupus erythematosus or human immunodeficiency virus (3, 12). The etiology of RDD is widely debated, and has also been attributed to an exacerbated immune response to viruses such as Epstein-Barr virus, human herpes virus 6, cytomegalovirus, and parvovirus B19, (8, 13, 14). Histopathologic hallmarks of RDD include sinus infiltration, emperipolesis or pale histiocytic cells containing engulfed lymphocytes, and immunohistochemical features such as positive staining for S-100, alpha1-anti-chymotrypsin, CD68, and staining negative for CD1a (4, 5, 8, 10). While emperipolesis is commonly seen histologically in RDD, it is not pathognomonic nor a requirement for diagnosis. In a study by Hoffman et al. (15), 22 cases of RDD of the breast were analyzed for comparison of histopathologic characteristics with 19/22 showing numerous plasma cells and prominent sclerosis in majority of cases, and 22/22 displaying emperipolesis (15, 16). Histopathology in our case demonstrated emperipolesis with positive staining of S-100 and CD68, and negative staining for CD1a.

Imaging findings of RDD are confounding and often complicate the broad differential diagnoses. Such differentials may include lymphoma, malignant histiocytosis, tuberculosis, noninfectious granulomatosis, and others. CT, magnetic resonance imaging (MRI), PET/CT, and radionucleotide bone scans have been used in diagnostic work-up and surveillance of patients with documented RDD. The lymphadenopathy present in RDD can be well identified using ultrasound, CT, MRI, and PET/CT, as also seen in the presented case. CT findings in patients with RDD may reveal enhancing isolated or disseminated lymphadenopathy. RDD lesions on MRI have been reported to be isointense on T1-weighted images and iso- to hypo-intense on T2-weighted images (18-20). Lymphadenopathy in RDD on ultrasound studies have been reported to mimic malignant appearing nodes, underscoring the importance of histopathologic evaluation (21). On PET/CT, lesions of RDD have been reported to demonstrate increased gallium uptake and increased metabolism of FDG (19). The avidity and high standardized uptake value of 9.5 of the right breast mass in our case further demonstrates this.

RDD of the breast is rare, with only a few cases reported in the literature (22-25). Similar to that of our patient, documented cases often presented with unilateral or bilateral breast masses. Green et al. (22) described seven documented cases of RDD within the breast included disease findings confined to one breast itself, involvement of one breast and ipsilateral axillary nodes, or both breasts with disseminated systemic disease, and all with findings concerning for malignancy (23, 24). On dedicated breast imaging, findings of RDD cases have been classified as suspicious or highly suspicious for malignancy during diagnostic work-up. On mammography specifically, cases of RDD have been reported to present as a high-density, irregular or lobulated mass with circumscribed or ill-defined margins, multiple masses, or even small diffuse breast nodules (23, 24). On breast ultrasound, cases of RDD have been reported to appear with a hypoechoic mass with indistinct or angulated margins with increased vascularity on Doppler (23, 24). A study by Wang et al. (25), noted that breast masses in RDD were categorized as BI-RADS-4 or 5 during workup for all evaluated patients, similar to the degree of suspicion elicited by our case. On targeted breast US, the palpable right breast mass found to be RDD in our case showed an oval heterogeneous mass with microlobulated margins and internal vascularity, further emphasizing the concerning nature to which RDD has been documented in previous cases, both clinically and radiologically.

RDD follows an unpredictable, and often slowly progressive, clinical course with most patients not requiring treatment. Spontaneous remission has been noted in approximately 20–40% of patients after several years, with others showing a chronic pattern of exacerbations and remissions (26, 27). Nodal cases and those of cutaneous disease are more commonly self-limited compared to those with multifocal and extra-nodal RDD (2, 26). A study conducted of 238 cases of RDD revealed mortality due to direct complications, infections, or amyloidosis, in only about 7% of patients (2, 26). Ultimately, a limited number of RDD cases have been documented and studied, creating a challenge when examining effective treatment modalities. Treatments with corticosteroids, surgical resection, systemic chemotherapy, and radiotherapy have been studied without consistent clinical evidence favoring one modality. Symptomatic patients without significant morbidity will most often undergo treatment with steroids as first-line therapy with unpredictable response (28). Given the rarity of the disease and the absence of a definitive therapeutic pathway, treatment is tailored to individual clinical circumstances.

In conclusion, RDD presents a unique diagnostic challenge due to its diverse clinical manifestations and imaging characteristics that can often mimic malignancy. The present case underscores the importance of a thorough evaluation, particularly in patients undergoing oncologic assessments or with concerning history of malignancy. Although benign and sometimes self-limiting, awareness of the diverse clinical presentation of RDD is important for accurate diagnosis, management and to enhance patient care and clinical outcomes.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

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Case Report

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Pyoderma Gangrenosum: A Nightmare for Breast Surgery-Two Case Reports

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ABSTRACT

Pyoderma gangrenosum (PG) is a rare, chronic, neutrophilic dermatosis characterized by painful ulcers that are often misdiagnosed as wound infections. We report two cases of postsurgical PG following breast surgery: A 46-year-old woman with a non-healing ulcer after a breast biopsy and a 37-year-old woman with wound dehiscence after bilateral reduction mammoplasty. Both cases were initially managed with repeated debridements, antibiotics, and wound care without improvement. The diagnosis of PG was made based on the increase in wound size and irregularity. Treatment with oral doxycycline and topical tacrolimus led to favorable healing within four months. Breast surgical tehniques, which aim to achieve aesthetic results using intraglandular flaps, have become an important part of clinical practice in breast surgery. Early diagnosis and appropriate management are crucial in postsurgical PG to avoid misdiagnosis and ineffective treatments that cause patient disfigurement.

Keywords: Pyoderma gangrenosum; breast surgery, reduction mammoplasty, doxycycline, tacrolimus

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Key Points

- Postsurgical pyoderma gangrenosum is a rare, chronic neutrophilic dermatosis often misdiagnosed as a wound infection.
- Early diagnosis and appropriate treatment management are crucial to prevent patient aesthetic deformity.
- The diagnosis of pyoderma gangrenosum was made based on the erythematous, irregular borders, and increase in wound size and irregularity.
- The wound bed should be kept moist, and maceration of the surrounding skin should be prevented and not traumatized in patients.
- The combination of oral doxycycline and topical tacrolimus is a good treatment option, especially in patients with limited disease.

Introduction

Breast cancer is the most commonly diagnosed cancer type in women worldwide and the second most common cause of cancer deaths (1). The increasing frequency of breast cancer has brought screening programs and biopsies to the forefront to catch the disease early. With the understanding of cancer biology and the development of treatment algorithms, surgical treatment has evolved from mastectomies to breast-conserving surgeries and currently to oncoplastic breast surgery techniques (2). Oncoplastic techniques for biopsy, which aim to achieve aesthetic results using intraglandular flaps while preserving oncological principles, have become an important part of clinical practice in breast surgery clinics.

Pyoderma gangrenosum (PG) is a rare, chronic, neutrophilic dermatosis characterized by painful ulcers. The disorder may be associated with various diseases, such as inflammatory bowel disease, hematological and rheumatological disorders, immune system dysfunction, and malignancies. Diagnosis is established by excluding other causes of ulceration. Although immunosuppressive agents are the primary treatment options, new therapeutic approaches are also under investigation (3).

Postoperative and peristomal PG is encountered in the clinic after surgery in general surgical practice (4). Postoperative PG is detected in the clinic with wound dehiscence or ulceration following the development of painful erythema in the surgical field and is often confused in the differential diagnosis with surgical site infection, necrotizing breast infection or dermatitis (5-7). Secondary infections are encountered when PG lesions are not managed well and are diagnosed in a delayed manner.

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In this study, we report two cases of PG in breast surgery patients and discuss the treatment outcomes of oral doxycycline and topical tacrolimus.

Case Presentations

The first case was a 46-year-old woman who presented with a non-healing ulcer on her left breast that had persisted for three months after a breast biopsy. The patient had a history of rheumatoid arthritis, and prior to referral to our center, her ulcerated lesion had worsened due to repeated debridements and surgical interventions (Figures 1A, 1B, appearance at presentation 1C). She had undergone previous surgical debridements, received topical antibiotics, and various wound care applications, none of which led to improvement. The tissue culture demonstrated *Escherichia coli* growth.

The second case involved a 37-year-old woman with a surgical wound persisting for two months after bilateral reduction mammoplasty. Post-surgery, wound dehiscence in the right breast and a preliminary diagnosis of a surgical site infection were considered. The necrotic area was managed with repeated debridements. The patient was followed up on an outpatient basis, according to chronic wound follow-up principles. Due to an increase in wound size and tissue defect enlargement, pyoderma gangrenosum (PG) was suspected, and a dermatology consultation was obtained (Figure 2). A minimal opening on the incision line in the left breast was managed with wet and dry dressings, and the area healed spontaneously without debridement. A well-defined ulcer, approximately 10x12 cm in size, was observed under the left breast. A skin sample from the lesion edge showed focal erosion, non-specific chronic inflammation in the upper-middle and deep dermis, and a marked increase in fibroblastic activity (Figure 3). The wound culture grew *Staphylococcus aureus*.

The physical examinations of both patients were normal except for the surgical incisions, with no lymphadenopathy or organomegaly detected. Neither the patients nor their family members had a history of inflammatory bowel disease or hematological diseases. Laboratory tests, including complete blood count with differentials, liver, kidney, and thyroid function tests, erythrocyte sedimentation rate, C-reactive protein levels, rheumatoid factor, and serum protein electrophoresis, were all within normal limits. No abnormalities were observed on chest X-rays. Tests for anti-nuclear, anti-cryoglobulin, and antiphospholipid antibodies were negative.

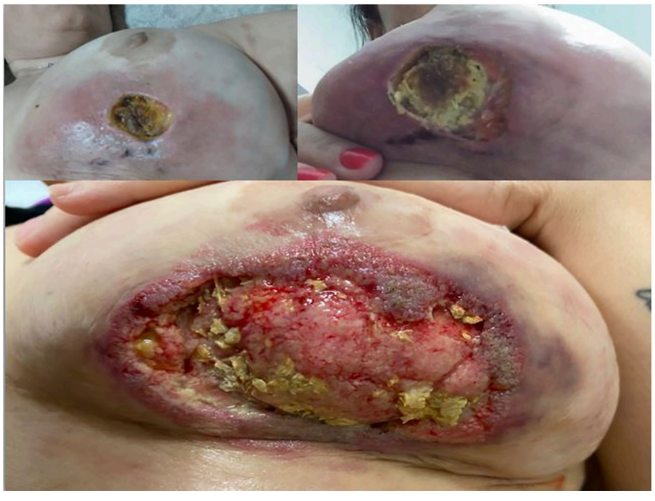

Figure 1. (Figure 1A, 1B, view at presentation-1C) The incision debrided before the patient presented to our center. (Figure 1C) shows the appearance at the time of presentation

Previous surgical pathologies were benign. Based on clinicopathological correlations, both cases were diagnosed as PG (Figure 4). The patients were administered 200 mg/day of doxycycline orally and topical 0.1% tacrolimus ointment twice daily. Epithelialization appeared in the lesions of both patients within the first two weeks.

Wound dressings were carefully changed after the diagnosis of PG without debriding and traumatizing the wound area. The wound bed was washed with saline or antiseptic solutions. Enzymatic debridement gels were used for necrotic areas and to moisturize the wound bed. When signs of infection regressed in the tissue defects of the patients, the frequency of dressing changes was initially reduced to every other day. When granulation was achieved in the wound bed and there was no suspicion of infection, bioactive wound dressings were used for rapid closure of the tissue defect and epithelialization. The frequency of dressing changes was then reduced to every 3-4 days to minimize the possibility of trauma. A collagen laminin-based dermal matrix (Dermalix®) containing resveratrol-loaded microparticles was used to fill the tissue defects and further promote granulation (8) (Figure 5).

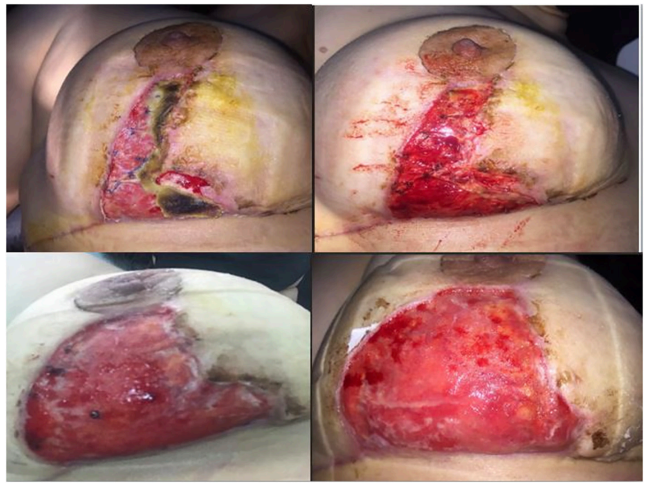

Figure 2. The appearance of the incision line after debridements until the diagnosis of pyoderma gangrenosum was made

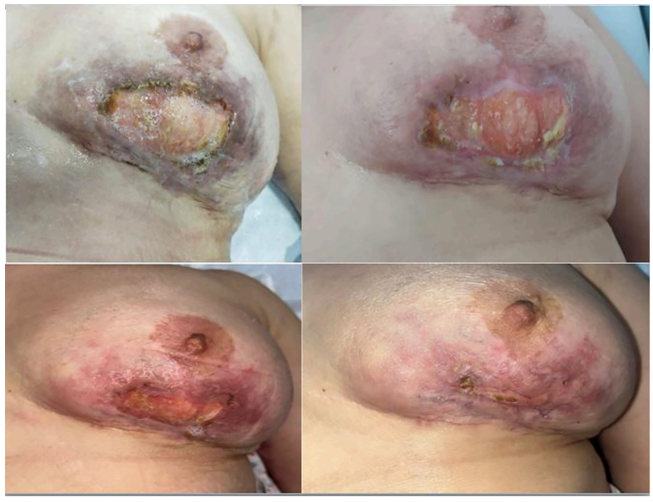

Figure 3. Treatment stages and healing process progressing to epithelisation

Complete recovery was achieved after six and two months of therapies, respectively (Figure 6), and the therapies were stopped. The patients did not experience any drug-related side effects. There were no recurrences or new lesions during the 12-month follow-up period. Written informed consent was obtained from both patients.

Discussion and Conclusion

Breast biopsy surgery and reduction mammoplasty using glandular flaps are performed to achieve cosmetically satisfactory results (9). Since the pouches in the resected area are closed after breast surgery, wound complications, such as seroma, infection, and wound dehiscence, occur at low rates (10). After reduction mammoplasty, incision gaps and suture line ischemia may occur, especially in cases where the inferior pedicle technique is used. The development of PG should be considered in patients who develop a suspected resistant wound infection after breast surgery, undergo debridement of the incision line and necrotic areas, and if the wound bed enlarges and atypical limited ulcers develop. PG development should be suspected in postoperative cases with inflamed and painful ulcers. The development of PG leads to catastrophic cosmetic results, especially in patients with implants and oncoplastic surgical techniques (7, 11, 12). Another important issue is the delay of adjuvant chemotherapy in cancer patients due to prolonged wound problems with late diagnosis of PG in oncological patients.

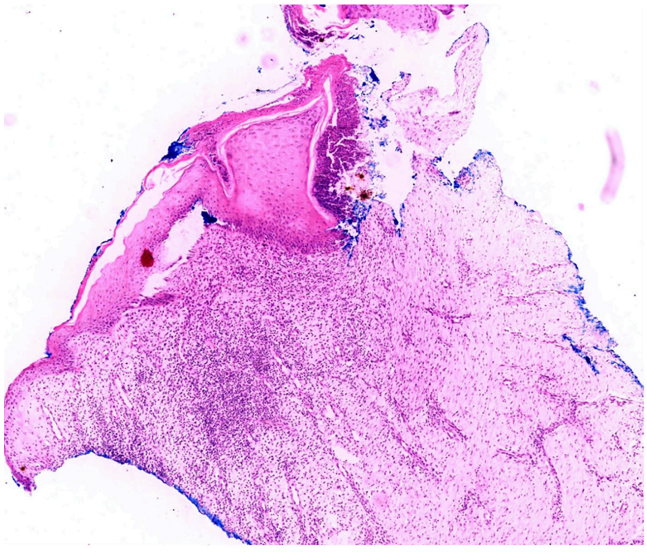

Figure 4. Histopathological examination of the ulcer edge of patient; focal erosion, non-specific chronic inflammation in the upper-middle and deep dermis, marked increase in fibroblastic activity (X10, H&E)

H&E: Hematoxylin and eosin

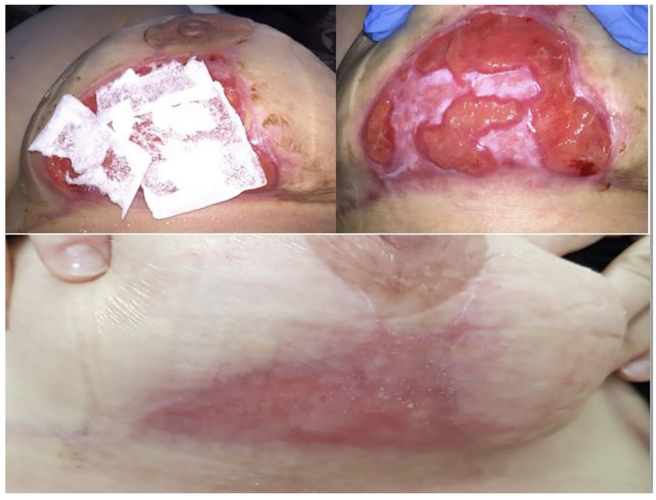

Figure 5. Stages of treatment, use of bioactive wound dressing and healing process progressing to epithelisation

The first rule of approach to all chronic wounds that develop after surgery, regardless of etiology, is to debride the wound bed to prevent the formation of a possible resistant infection and biofilm layer (13). This curettage and debridement, which removes necrotic, ischemic tissues, eliminates possible biofilm layers, and stimulates granulation tissue in the wound bed, is contraindicated in PG patients (13, 14). It leads to the triggering of a disease similar to the pathergy test used in the diagnosis of PG. Postoperative infection, dermatitis, and foreign body reactions due to sutures should be considered in the differential diagnosis of PG, although they occur less frequently.

The wound should not be traumatized in patients who develop PG after surgery. It is useful to wash the wound bed with antiseptic solutions and physiological saline (14). Enzymatic and autolytic debridement gels should be used for necrotic tissues in the wound bed and slough tissues that pose a risk for possible biofilm layer formation (14, 15). The wound bed should be kept moist, and maceration of the surrounding skin should be prevented. Wound dressings may be beneficial in wound healing. In the diagnosis of PG cases after surgery, it is important to measure and photograph the wound dimensions, which is one of the principles of chronic wound care treatment. Lack of reduction in size between two dressings or irregular limited increase in size should suggest the diagnosis of PG, not infection. Late diagnosis and lack of disease management skills may lead to catastrophic consequences for PG (16).

PG may manifest as a classical ulcerative form or atypical bullous, vegetative, or pustular variants (17). While systemic immunosuppressive agents are the preferred treatment for most cases of PG, local therapies, including topical and intralesional corticosteroids, topical sodium

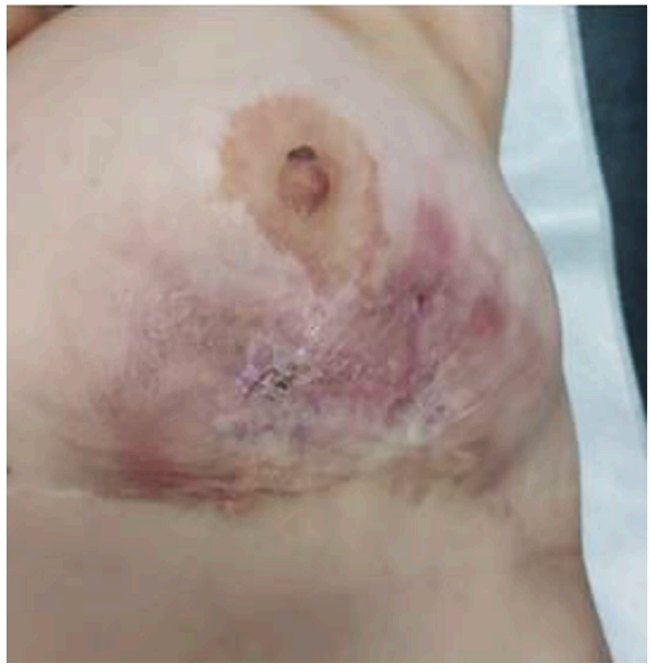

Figure 6. The stage where epithelisation is achieved and treatment is terminated

cromoglycate, benzoyl peroxide, hyperbaric oxygen therapy, skin grafts, and radiotherapy, are the most frequent options for a localized form (18). In severe cases, systemic immunosuppressive agents, such as systemic corticosteroids, dapsone, tumor necrosis factor-alpha (TNF-α) inhibitors, and cyclosporine are used (19). These treatment algorithms should be determined based on the severity of the disease and the level of treatment resistance.

Doxycycline is a tetracycline antibiotic that reduces proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and TNF-α. Due to its anti-inflammatory properties and good safety profile, doxycycline is widely used in dermatology for various skin disorders, such as acne rosacea, bullous pemphigoid, and perforating dermatoses (20). Moreover, there are reports of successful outcomes in patients with PG treated with doxycycline. A retrospective study conducted in France compared the treatment results of 42 PG patients. Twenty-three patients were treated with 200 mg/day of doxycycline, either as monotherapy or in combination with topical steroids or topical tacrolimus, 15 patients were treated with systemic steroids, either as monotherapy or in combination, and four patients were treated with other treatment methods (colchicine, dapsone, or topical steroids only). The response rates to doxycycline and systemic corticosteroid treatment in PG were found to be comparable, with a lower recurrence rate in the doxycycline group (21).

Tacrolimus is an immunomodulator that inhibits T-lymphocyte activation by suppressing the expression of IL-2 genes (22). Tacrolimus also inhibits gene transcription for IL-3, IL-4, interferon-α, TNF-α, and granulocyte-macrophage colony-stimulating factor. A further action of tacrolimus is to block degranulation of mast cells, neutrophils, basophils, and cytotoxic T-cells. However, the specific mechanism by which tacrolimus improves PG remains unclear. Since central neutrophilic and peripheral lymphocytic infiltrates characterize PG, tacrolimus may act through inhibiting the accumulation and activation of lymphocytes and neutrophils in PG (23). The effect of topical tacrolimus was compared with topical corticosteroids in a study of 24 patients with peristomal PG (24). Eleven patients were treated with 0.3% topical tacrolimus monotherapy, and thirteen patients were treated with topical 0.05% clobetasol propionate. The treatment response and healing time were superior in the topical tacrolimus group compared to the topical steroid group. Seven patients in the tacrolimus group healed in an average of 5.1 weeks, while five patients in the clobetasol propionate group healed in an average of 6.5 weeks. Topical tacrolimus was more effective in patients with ulcer diameters greater than 2 cm. While topical tacrolimus does not cause skin atrophy, unlike topical steroids, it may lead to sensations of burning, itching, and may also predispose to the reactivation of the herpes simplex virus. The absence of these side effects in our patients increased the compliance with use.

PG development after breast surgery is very rare. When PG develops after breast surgeries, it can pose significant challenges for clinicians. Early diagnosis of PG can be achieved, particularly in cases with erythematous, irregular borders and an increase in size despite adhering to wound care principles.

The combination of oral doxycycline and topical tacrolimus is a good treatment option for PG, especially in patients with limited disease, due to their treatment efficacy and safety profile compared to immunosuppressive agents. However, prospective studies involving larger patient groups and longer follow-up periods are needed.

Ethics

Informed Consent: Written informed consent was obtained from both patients.

Footnotes

Authorship Contributions: Surgical and Medical Practices: G.A., K.B.Y.; Concept: M.D., K.B.Y.; Design: G.A., K.B.Y.; Data Collection and/or Processing: G.A., M.D.; Analysis or Interpretation: M.D., K.B.Y.; Literature Search: G.A., M.D., K.B.Y.; Writing: G.A., K.B.Y.

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Case Report

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From Plasmacytoma to Rib Tuberculosis: The Case of A Breast Mass With An Unexpected Diagnosis

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ABSTRACT

Tuberculosis (TB) of the rib is an uncommon manifestation of extrapulmonary TB that can pose significant diagnostic challenges, especially when presenting as a breast mass. We report the case of a 74-year-old woman who presented with a left breast lump, initially suspected to be a plasmacytoma due to its imaging characteristics and clinical history. The mass was surgically excised, and histopathological analysis revealed granulomatous inflammation with caseous necrosis, suggesting TB. TB-polymerase chain reaction confirmed the diagnosis, despite negative Ziehl-Neelsen staining. The patient was treated with anti-tubercular therapy for twelve months, resulting in a favorable clinical outcome. This case highlights the importance of considering rib TB in the differential diagnosis of breast masses, particularly in endemic areas, and underscores the role of comprehensive diagnostic evaluations for timely and effective treatment.

Keywords: Breast disease; plasmocytoma; surgery, tuberculosis

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Key Points

- Tuberculosis must be considered as a differential diagnosis of breast masses, especially in endemic areas.
- The diagnosis can be challenging.
- Tuberculosis remains a major cause of death and morbidity while being easily treatable.

Introduction

Tuberculosis (TB) remains a major health issue worldwide. The causative agent is the acid-fast bacillus *Mycobacterium tuberculosis.* In 2022, the Global Tuberculosis Report estimated that 10.6 million people developed TB (1). Tunisia is no exception in terms of TB infection being a country with intermediate endemicity, with a recorded incidence of 29 per 100,000 inhabitants in 2017 (2). Following screening campaigns and the National Tuberculosis Control Program implemented since 1978, the incidence has stabilized, particularly for the pulmonary form which constitutes 62% of all TB cases.

M. tuberculosis most commonly affects the lungs, followed by lymph nodes (18 per 100 000 in 2017 in Tunisia) (2), pleura, bones, joints, and the genito-urinary system. It may rarely cause miliary TB and meningitis TB (3). Extrapulmonary TB has been reported to constitute 15–20% of all TB cases (4). Musculoskeletal TB is a very uncommon form of extrapulmonary TB, constituting 1–5% of all cases, with spinal TB, also known as Pott's spine, being the most common (3, 4). Rib involvement is rare, accounting for 0-5% of musculoskeletal TB and 0.1% of total TB cases, with fewer than 50% of the patients having active pulmonary TB (3, 5).

Cold abscesses of the chest wall and rib caries pose a diagnostic challenge, even for astute clinicians, due to their insidious and varied presentations (6). In addition, rib osteomyelitis (OM) can have various etiologies besides TB, including chronic non-specific OM, rib involvement following empyema necessitatis, eosinophilic granuloma, syphilis, and both malignant and benign tumors. Among these tumors, multiple myeloma can be a cause of rib OM (7).

The diagnosis of TB can often be missed because of the rarity of TB as a cause of symptomatic breast disease and efforts are directed at the more common causes, such as carcinomas or other benign lesions (8).

Herein, we report the case of an elderly female patient, who presented with a large breast mass, with imaging initially suggesting a plasmacytoma of the rib, but was subsequently diagnosed with rib tuberculosis after surgical resection.

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Case Presentation

A 74-year-old woman presented with a left breast lump discovered during self-examination four months prior to her admission. She has no family history of breast carcinoma. The patient did not experience any pain, swelling, or nipple discharge. She did not report weight loss or night sweats. At first, the lump was disregarded by the patient and she only sought consultation after noticing an increase in size. Physical examination revealed a soft, non-tender, well defined mass, approximatively 5x6x3 cm, in the outer quadrants of the left breast. The mass was adherent to the pectoralis muscle. There was no skin or nipple retraction, nor signs of inflammation. No axillary or supraclavicular lymph nodes were palpable, and the examination of the contralateral breast was normal. The patient was afebrile and pulmonary auscultation showed no abnormalities. The mammography of the left breast showed in both mediolateral oblique (MLO) view and craniocaudal view, an opaque, oval-shaped mass, measuring approximatively 6 cm in its largest dimension. The image was heterogeneous with calcifications and slightly irregular contours, appearing to be deep and in contact with the left pectoral muscle (Figure 1a, b). The ultrasound (US) revealed a 57x28 mm tissue mass, located at the anterior arc of the fifth rib. The mass was hypoechoic and heterogeneous with peripheral calcification. Infiltration of the pectoral muscle was noted with associated edema of the overlying tissue, suggestive of focal mastitis (Figure 2).

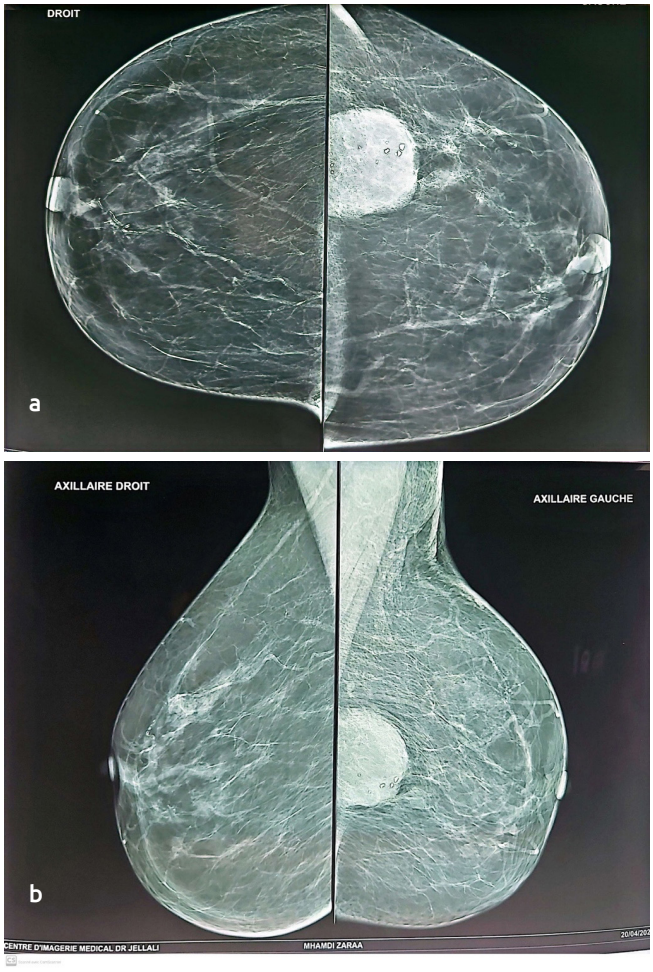

Figure 1. Mammography showing a deep opaque, oval-shaped mass with contact with the pectoral muscle **(a)** Craniocaudal projection, **(b)** Mediolateral Oblique projection

These findings suggested a possible plasmacytoma of the rib and the left breast was classified as ACR BI-RADS 0.

Due to the proximity to the chest-wall and the possibility of rib involvement, a thorax computed tomography (CT) was performed. The mass appeared as a hypodense, well-defined, lesion, with a bony erosion of the anterior arc of the left fifth rib with density of the surrounding soft tissues and infiltration of the left breast. A mild pleural thickening of reactive appearance, adjacent to the bony destruction, was also noted (Figure 3).

Laboratory investigations including serum electrolytes, kidney, and liver functions were performed and came back within normal limits. Given the suspected diagnosis of plasmacytoma, serum protein electrophoresis was requested to identify a monoclonal gamma peak, but came back normal.

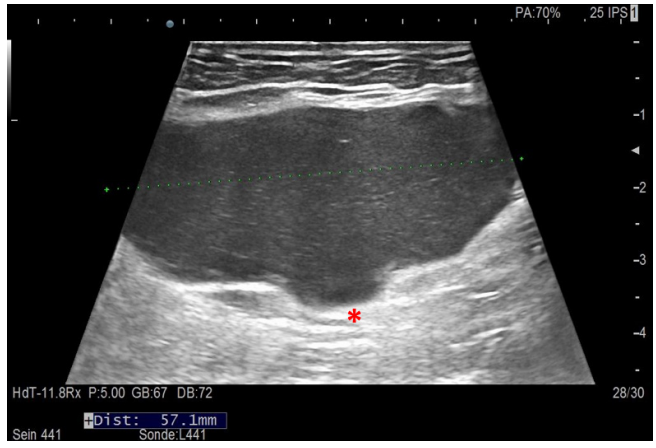

Figure 2. US of the breast showing a hypoechoic and heterogeneous mass with infiltration of the pectoral muscle (asterisk *)

US: Ultrasound

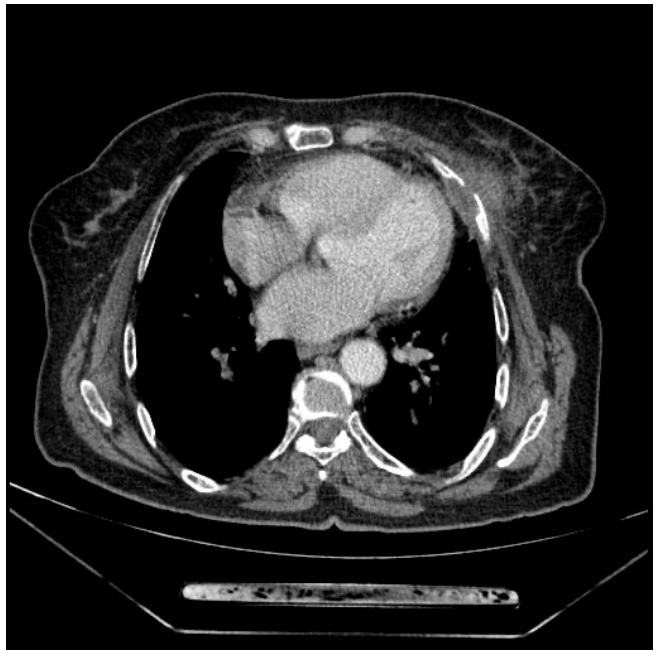

Figure 3. Axial CT section showing a hypodense lesion, with a bony erosion of the anterior arc of the left 5th rib with density of the surrounding soft tissues and infiltration of the left breast (arrow)

CT: Computed tomography

Considering the patient's age, the imaging findings, and the suggested diagnosis, a surgical excision of the mass was decided upon for curative and histopathological diagnostic purposes. The mass was separated from the mammary surrounding tissue. Due to its connection with the pectoralis muscle and the fifth rib, its excision was difficult and led to the accidental rupture of its contents, consisting of a whitish pus. Debridement was performed to remove the adherent cyst wall and any inner osteomyelitic lesions. A drain was then inserted to the site of the cyst in the breast and adequate drainage was ensured.

Gross histological exam revealed an empty and large cystic formation. Wall cyst showed hemorrhagic rearrangement. Histological exam revealed multiple and confluent granulomas made of epithelioid and numerous Langerhans cells without central necrosis (Figure 4). Theses granulomas surrounded galactophoric canals and cyst wall (Figure 5). Marked palisading of epithelioid cells was noticed on the surface of the cyst along with fibroid deposit (Figure 6). Even with negative Ziehl-Neelsen staining, the diagnosis of TB was highly likely. The diagnosis of TB was then confirmed using conventional TB-polymerase chain reaction (TB-PCR) performed on paraffin embedded tissue.

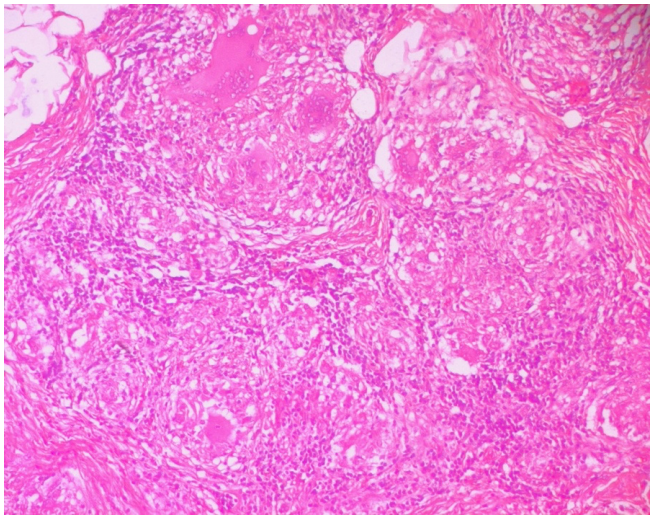

Figure 4. Microscopic exam (HEx10) showing multiple and confluent granulomas made of epithelioid and Langerhans cells

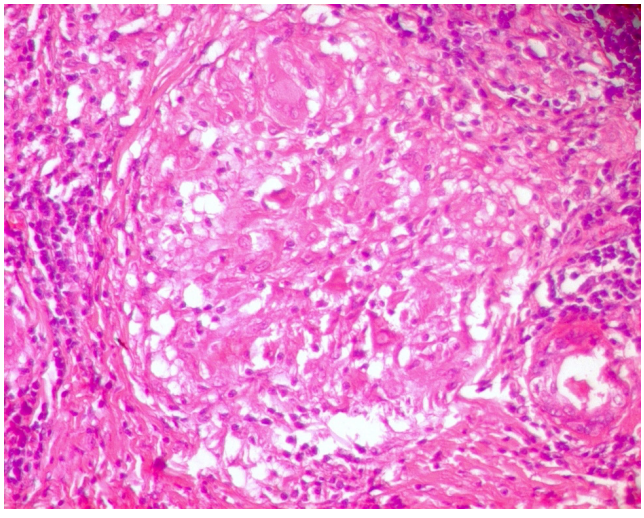

Figure 5. Microscopic exam (HEx40): Granulomas surrounding galactophoric canal (*)

Following the diagnosis, an additional Mantoux test was performed, which was negative. The patient was then prescribed oral anti-tubercular therapy (ATT), for a period of twelve months, according to the guidelines of the Tunisian National Tuberculosis Control Program. The regimen consisted of isoniazid 10 mg/kg, rifampicin 15 mg/kg, pyrazinamide 35 mg/kg and ethambutol 20 mg/kg of body weight for the initial two months, followed by a ten-month therapy with Isoniazid and rifampicin only at the same doses.

The patient's follow-up was uneventful. Written informed consent was obtained from the patient for publication of this case report.

Discussion and Conclusion

TB has been a major cause of morbidity and mortality, especially in developing countries. Although the pulmonary form is the most frequent (1), extrapulmonary TB cases are increasing, posing serious challenges to clinicians. Chest-wall TB is a rare form of extrapulmonary TB (7). Cold abscesses, which are swellings without inflammation, are the characteristic presentation of chest-wall TB (4). Although the definitions vary, chest-wall TB, cold abscesses of the chest-wall, and rib tuberculosis, are all used for the same pathological entity (4).

The pathogenesis of chest-wall TB is commonly lymphohematogenous. It can occur by reactivation of latent foci formed during hematogenous or lymphatic dissemination of primary TB (9). It is less common for the underlying lung to directly extend to the rib (10). We believe that the former route (reactivation of latent foci) is more likely, as our patient did not have a history of exposure to TB or active TB, and the chest CT did not show any pulmonary or pleural lesion suggesting TB.

The presenting symptoms of rib TB usually include a painful or non-tender chest-wall mass or chest pain. The mass can be cystic, doughy, or firm (10). Discharging sinuses can often be observed (11). TB abscesses presenting as breast masses are rare with only a few cases reported to date in the literature (8, 11, 12). This extension could occasionally pass infection to the breast causing a secondary breast tuberculosis, as reported by Wani et al. (11) in the case of a female patient with a six-years history of a breast lump and sinus discharge. We predict that this could have been the natural progression for our patient if diagnosis and management had been delayed. In the present

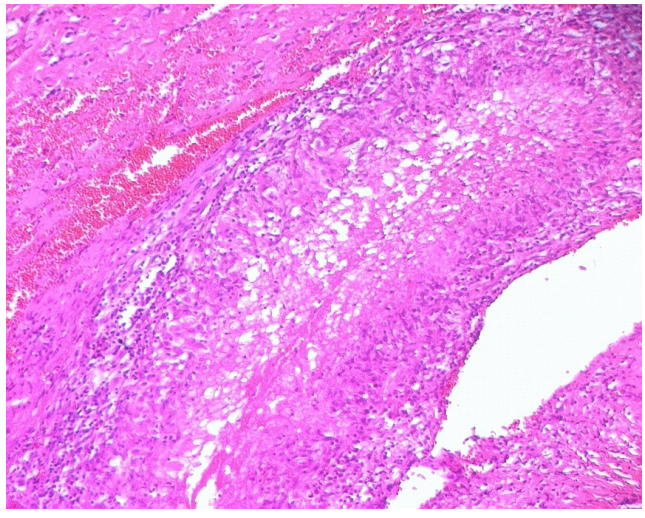

Figure 6. Microscopic exam (HEx10): Palisading of epithelioid cells around fibroid deposit on cyst wall

case, the histologic examination showed a focal mastitis associated with the rib tuberculosis.

TB of the rib presents with a combination of bone destruction and a soft tissue mass (13). Other etiologies can be responsible for bone destruction, both benign and malignant (10). In the present case, the imaging findings suggested a plasmacytoma of the rib. Despite the fact that TB is the second most common cause of rib destruction after metastases, and that we live in a TB endemic country, TB was not initially suspected. The diagnosis was further obscured by the normality of the physical examination and the clinical history of our patient. In Faure et al. (14) report, 83% of the patients had a history of TB, and there had been active pulmonary TB in 33% of their patients. However, Kuzucu et al. (4) found that none of their patients had a past history of TB or active TB. This demonstrates that chest-wall TB can occur with or without pulmonary TB.

Since rib TB is seen twice as commonly in male patients compared to female patients (10) and involves any part of the rib, the anterior chest-wall being the most common site of infection (15), chest CT is considered the imaging modality of choice (16). Indeed, it is ideal for evaluating tuberculous chest-wall lesions as it demonstrates bone erosion, the nature and extent of soft tissue collections, and accompanying intrathoracic lesions and nodes. In the present case, breast imaging was performed first, because the mass was located in the breast. US and mammography are the two main imaging modalities used to assess breast lesions. However, infiltration of the chest-wall cannot be efficiently evaluated by mammography. MLO projection is preferred when the lesion is near the chest-wall (8). US not only demonstrates internal architecture of the lesion (solid or cystic) but can effectively assess muscle and bone involvement (17), as demonstrated in the present case, which was confirmed by CT.

Final diagnosis rests on histopathological confirmation. Classical caseous necrosis with granulomatous inflammation, with or without Ziehl-Neelsen staining, is sufficient to confirm the diagnosis of rib TB (7). Specimens can be procured by fine needle aspiration and cytology (FNAC) or needle biopsy (7). However, Faure et al. (14) and Chang et al. (18) could only confirm TB after surgical excision and labeled FNAC as an inefficient tool for establishing the diagnosis. The guidelines of Chang et al. (18) have made the TB-PCR test essential for establishing a reliable and prompt diagnosis, especially when rib biopsy is not feasible (7).

There is no standardized therapeutic protocol for rib TB. Medical treatment does not differ from that of pulmonary forms, except for the duration of ATT, which is usually extended to one year. Surgical treatment is controversial; however, it has been proven to be the most effective way to treat chest-wall TB (7). In a large series of 712 cases over 11 years, surgical treatment was recommended for parietal chest-wall TB (19). It was also suggested that surgical debridement is necessary for treating TB of the ribs (20).

Despite initial assumptions, the surgical management of the present case was in accordance with practices reported in the literature, and proved to be effective, as the clinical evolution was favorable.

In summary, the present case emphasizes that the diagnosis of TB should be considered when a breast mass is undiagnosed, particularly with rib involvement, and should always come to mind, especially in endemic areas. This underscores the need for heightened clinical suspicion and comprehensive diagnostic evaluations to ensure timely and effective treatment.

Ethics

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

Footnotes

Authorship Contributions: Concept: H.A., E.G.; Design: I.B., Data Collection or Processing: H.A., S.Y.; Analysis or Interpretation: B.B., M.M.; Literature Search: H.A., B.B., S.Y., E.G.; Writing: H.A., B.B., S.Y.

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

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Editorial Summary

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Conformable Ultrasound Breast Patch - The Future of Breast Cancer Screening?

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ABSTRACT

Breast cancer is the most common cancer type among women worldwide with an average lifetime risk of 12.9%. Early detection and screening are the most important factors for improved prognosis and mammography remains the main screening tool for the average risk patients. Ultrasound (US) is used in women with elevated breast cancer risk, younger patients and patients with extremely dense breasts. Conventional US has certain limitations including operator dependence and reported low specificity. We designed a conformable US device (cUSBr-Patch) which offers large-area, deep tissue scanning and multi-angle, repeatable breast imaging. It is able to detect lesions as small as 1mm with excellent accuracy and reliability validated by *in vivo* comparison with conventional US. This is a user-friendly, innovating device designed to be used by patients with the potential to reshape our approach to breast cancer screening.

Keywords: Conformable ultrasound; elevated breast cancer risk screening; artificial intelligence, innovation in breast cancer

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Key Points

- Breast cancer screening is key to early detection.
- Breast ultrasound is a particularly helpful tool in screening and diagnostic work up of women with elevated breast cancer risk, the younger female population and patients with heterogeneously and extremely dense breasts.
- To eliminate the challenges of conventional ultrasonography, we designed a conformable ultrasound device (cUSBr-Patch) with an easily operable nature-inspired patch design, which offers large-area, deep tissue scanning and multi-angle, repeatable breast imaging.

Introduction

Breast cancer is the most common cancer type among women worldwide after skin cancers and remains the second leading cause of cancer deaths among the female population after lung cancer (1). Increasing awareness, early detection, efficient screening tools and strategies along with individualized systemic and locoregional treatments are all contributing to improved outcomes and overall prognosis. Early detection and screening are the most important factors, and mammography is considered the gold standard screening tool. Multiple studies have demonstrated reduction of breast cancer mortality and improved overall patient outcomes with implementation of mammography-based screening models (2). To overcome certain limitations of mammography, including decreased sensitivity with increased breast tissue density, supplemental screening with ultrasonography (US) and magnetic resonance imaging has been incorporated in breast cancer work up in women with elevated breast cancer risk (3-5). US is a particularly helpful tool in screening and diagnostic work up of this population and patients with heterogeneously and/or extremely dense breasts (6). Addition of a single screening US to mammography has been shown to increase sensitivity and diagnostic yield when compared to mammography alone (7, 8). The main limitations of US have been reported to be operator dependence, intra-observer and inter-observer variability and low specificity (9). The variability in size and shape of the breast is an additional challenge for conventional US since current transducers lack the ability to conform to curved body surfaces. Techniques such as automated breast ultrasound, which reduce operator-dependence by separating the moment of image acquisition from the moment of image interpretation have been developed and have successfully eliminated most of the limitations of conventional US. (10)

Another adjunct for breast cancer screening is artificial intelligence (AI) in the form of artificial neural networks (ANN), a powerful and

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useful tool with multiple applications in the field of medicine (11, 12). The use of AI in breast cancer care is evolving rapidly and the most popular potential applications are increased accuracy of diagnostic and predictive tests and reduced workload for health care providers. Retrospective and observational studies suggest at least similar if not superior cancer detection rates when comparing AI to regular radiologist assessment, even in low breast cancer prevalence cohorts (12, 13). Predictive models for breast cancer risk and mortality using ANN have been validated and shown to be more accurate compared to conventional clinical and statistical risk assessment models (14, 15). The use of ANN and deep learning algorithms expands beyond image reading with applications in pathology and lymphedema diagnosis, among others (16, 17).

To eliminate the challenges of conventional US, Dr. Dagdeviren and her team at Massachusetts Institute of Technology, Media Lab designed a conformable ultrasound device (cUSBr-Patch) with an easily operable, nature-inspired patch design, which offers large-area, deep tissue scanning and multi-angle, repeatable breast imaging (18). This nature-inspired breast patch has a honeycomb design and is composed of three main components including a soft bra as an intermediary layer, the honeycomb patch, which provides structure and guidance for the ultrasound array as an outer layer, and the tracker, which is responsible for handling and rotation of the ultrasound array. The patch and the arrays are held in place with magnets. At any given array position the tracker can rotate 360° and the views of each area are combined to form a comprehensive set of images that sufficiently covers the breast. *In vivo* comparison of the patch with a standard linear probe suggests that it can reliably identify lesions as small as 0.3 cm.

After studying the device on breast models, we studied this device on an actual patient. A female subject with a history of benign breast pathologies was imaged using the cUSBr-Patch, with results cross-validated by a conventional US linear probe. The cUSBr-Patch was applied to the left breast and scanned along multiple positions, revealing a 1 cm cyst at the 4:00 position. A smaller 0.3 cm cyst was also detected in the right breast. Cross-validation confirmed the presence of both cysts, demonstrating the cUSBr-Patch's precision in detecting even sub-centimeter lesions. The cUSBr-Patch provided similar imaging performance to the conventional US system, with a consistent field of view and stable results over time, suggesting its potential for early breast cancer detection.

This device has demonstrated great repeatability of array positioning which is a crucial component of a reliable breast screening tool. Compared to conventional US, it eliminates the operator bias and the need for an operator altogether. It has the ability to detect lesions as small as 0.1 cm and with application of the innovating rotating design at multiple array locations, it expands the lesion localizing ability beyond the standard four quadrant designated views. These technical characteristics make the cUSBr-Patch ideal for higher risk population including younger women with denser breast tissue, for which mammography has been shown to have inferior sensitivity to US (4).

As our understanding of factors influencing future breast cancer risk has expanded, breast cancer screening has also become more personalized. While yearly mammographic screening remains the gold standard for average-risk women, there exists a subgroup of patients who require more intensive screening. In addition, in certain cases, we may opt for short-interval follow-ups to monitor suspicious lesions in the breast. Normally, this process involves patients commuting back and forth to an imaging center. In addition to the commute, an US technician is necessary to capture the images and radiologist to interpret them. This device aims not only to reduce commuting between home and radiology facility but also offers long-term cost-effectiveness by removing the necessity for both an ultrasound technician and a radiologist. The user-friendly design and autonomic nature of the device offers patients at-will screening from the comfort of their home. Remote images will be collected and analyzed by a DL-based model which will limit traveling needs and expenses to only those necessary. This can be particularly useful for patients in remote areas, with poor access to healthcare or limited health awareness.

Finally, it is important to note that this device is not to be viewed as a substitute for traditional screening systems. Mammography is a well-studied modality with multiple cohorts establishing its efficacy. Conventional US is an overall inferior screening tool in patients within the typical screening age range and breast density. The cUSBr-Patch can detect small changes from baseline and select the patients who need to undergo conventional US or mammography outside of their standard timeframes which can be crucial, especially for patients with more aggressive subtypes of breast cancer. This device may be the "first guard" in detecting minor changes and abnormalities that would initiate an official and more comprehensive work up. We envision that our device will be utilized by imaging centers, hospitals and insurance companies to facilitate patients who need frequent follow-ups due to increased risk or a suspicious lesion. When our device detects any abnormalities, these patients will then be recalled to radiology facilities and breast centers for further work up and testing. Following the very promising early results, our device is now being tested in a large cohort. Pending confirmation of our preliminary findings, it could soon become commercially available as a portable, easily accessible and very cost-effective initial imaging tool for women with increased breast cancer risk or dense breast tissue.

Footnotes

Authorship Contributions: Concept: C.D., T.O.; Design: C.D., T.O.; Data Collection or Processing: C.D., T.O.; Analysis or Interpretation: T.O.; Literature Search: A.G.; Writing: A.G., T.O.

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

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