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REVIEW

ORIGINAL ARTICLES

CASE REPORTS

Turkish Federation of Breast Diseases Societies

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

Société Internationale de Sénologie

Senologic International Society

Global Federation of Breast Healthcare Societies

SIS is the official supporter of the European Journal of Breast Health

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European Journal of Breast Health

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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.

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

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

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

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

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

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

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European Journal of Breast Health

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Review

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Health-Related Quality of Life in Women With Breast Cancer Undergoing Treatment With Hormonal Therapy – A Review Study

Lamya Alnaim

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ABSTRACT

This review aimed to analyze the significance and impact of health-related quality of life (QoL) in women with breast cancer undergoing treatment with hormonal therapy. This study developed a comprehensive, structured, systematic search strategy to identify literature related to health and QoL in breast cancer patients undergoing treatment with hormonal therapy. The search was conducted for published literature indexed in PubMed (Medline), Cancer Lit, CINAHL, Google Scholar, and Web of Science between 2010 and 2020. Patients associated with the study of QoL reported some difficulties in terms of depression, anxiety, chronic fatigue, sleep problems, pain, sexual dysfunction and sleep disorders. Endocrine-related symptoms did not fluctuate between interventions and remained unchanged in all groups. The evaluation of FACT-G scores (physical well-being subscale) showed statistically significant differences among participants receiving anastrozole versus tamoxifen and exemestane. It can be concluded that the QoL of postmenopausal women with breast cancer is affected by the long-term use of adjuvant endocrine therapy, with difference reported associated with the different therapies. However, further efforts are required to improve QoL instruments and the quantitative evaluation of QoL data for patients receiving adjuvant ET.

Keywords: Breast cancer; hormonal therapy; quality of life; women

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Key Points

- Postmenopausal women's quality of life (QoL) is affected by the long-term usage of adjuvant endocrine therapy.
- Clinicians and metastatic cancer patients need to make informed and shared decision.
- QoL of breast cancer patients improved through several simple and effective interventions.

Introduction

Breast cancer (BC) is the most frequently diagnosed and leading cause of mortality among women globally, with an average of 1.7 million newly diagnosed cases and 521,900 deaths annually, accounting for 25% of the cancer cases and 15% deaths due to cancer among women (1). Approximately 70% of all BCs are hormone-sensitive and likely respond to endocrine treatment (2). The success of endocrine therapies, modern chemotherapy, and targeted therapy indicates an increased number of metastatic BC patients receiving multiple lines of treatment. However, the cure for BC depends on complementary therapies and lifestyle changes alongside standard medical treatments to control symptoms of BC. Two of the most important objectives to improve treatment efficiency include survival prolongation and improvement in health-related quality of life (HRQoL) (3).

Over time, the diagnosis and treatment of BC has improved significantly. In addition to survival, another approach enhances the quality of life (QoL) as a significant clinical outcome. HRQoL is considered an essential endpoint in cancer clinical trials. HRQoL, a multidimensional concept, refers to a patient's subjective view of how their condition and treatment affect physical, psychological, and social components of everyday life (4, 5). Subsequently, in randomized control trials (RCTs), the evaluation of HRQoL while evaluating new treatments for BC patients is important. There is a diversity of QoL instruments used in clinical trials to capture different dimensions of QoL in metastatic BC trials, with the use of "European organization for research and treatment of life questionnaire C30 – EORTC QLQ C30", "EORTC BC

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module – EORTC QLQ BR23", MENQOL, FACT/FACIT or SF-36 used frequently. These questionnaires evaluate physical conditions and functioning domains and patient-reported evaluations of their health and QoL in cancer trials (6).

Agents that target particular molecular abnormalities seen in BC cells have the potential to improve clinical outcomes. This is demonstrated by the efficacy of trastuzumab and lapatinib in treating human epidermal growth factor receptor 2 (HER2)-overexpressing BC and everolimus coupled with endocrine treatment for hormone receptor-positive metastatic BC (7). Adjuvant therapy for BC involves using systemic treatment to eliminate any microscopic tumor cells that might remain in the body. It is given after primary therapy to increase the chance of long-term disease-free survival. These therapies include chemotherapy, endocrine therapy, the targeted drug Trastuzumab, radiation therapy, or a combination of treatments. Decisions associated with the treatments are based on the stage and type of cancer, the presence of hormonal and HER2/neu receptors, and the patient's health and preferences.

Advances in BC treatment have been made as the disease's frequency has increased. As a result, systematic assessment of survival outcomes in patients receiving anticancer therapy should include disease-free survival and overall survival (8). When it is taken as prescribed, hormonal therapy decreases the risk of BC recurrence by 40% and the mortality by a third (9). However, in spite of its clinical efficacy for preventing recurrence, a number of cancer survivors do not take the hormonal therapy as prescribed. About 50% of the women take less than 80% of the prescribed dosage (10) and almost 50% of women stop their treatment by the fifth year of the prescription (11). This leads to an increase in the recurrence and mortality of BC (12). Therefore, persistence and adherence to hormonal therapy is considered as a key determinant of disease-free survival. Adherence is described as the degree to which a person's behavior corresponds with the agreed treatment recommendations in the context of dose, frequency and timing. Persistence is defined as the duration of treatment from initiation to discontinuation (13).

Currently, research has started to explore the factors that affect adherence and persistence behavior and has identified socio-demographic, psychological and clinical aspects as the potential risk factors (14, 15). In a current review of barriers and facilitators of hormonal therapy adherence and persistence, a number of factors were identified as possible intervention targets, due to their effect on patients' persistence and adherence behavior. One of them was categorized as side effects of hormonal therapy and incorporated cognitive, gynecological, musculoskeletal and fatigue related symptoms. Also, a number of studies have found that patients experience hormonal therapy side-effects, such as joint pain, hot flushes, night sweats and fatigue, which affect adherence and rates of treatment discontinuation (14, 16, 17), potentially because the side effects of treatment outweighs the perceived benefits (18).

So, unlike socio-demographic and clinical aspects that are not easily changed, side effects are suggested intervention targets because effective management has the potential to increase long-term hormonal therapy adherence and reduce the rates of treatment discontinuation. However, the contribution of specific side effects to hormonal therapy non-adherence and non-persistence is not well understood, making the development and prioritization of targeted intervention strategies challenging. A number of studies prefer to use close-ended questionnaire to report side effects profile where the presence or absence of side effects are reported as a "yes" or "no" variable (19-21).

However, QoL has become a vital outcome metric in BC clinical investigations and survival research because disease detection and treatment have substantially improved (22, 23). There is currently a range of information on the issue, but it is challenging to identify robust evidence of optimal management in practice due to contradictory conclusions. Therefore, this review study was conducted to examine and synthesize the current data on HRQoL in BC patients. Accepting and implementing robust practices and methodologies in metastatic BC clinical trials is essential to assess patients' indications, side effects, operative activities, HRQoL, and customary clinical outcomes for progression-free and complete survival. Therefore, this study aimed to analyze the significance and impact of HRQoL of women with BC undergoing treatment with hormonal therapy.

Materials and Methods

This study developed a comprehensive, structured, and systematic search strategy to identify literature about HRQoL in BC patients undergoing treatment with hormonal therapy. The search was conducted for published literature indexed in PubMed (Medline), Cancer Lit, CINAHL, Google Scholar, and Web of Science from 2010 to 2020.

This study included patients with BC and BC patients on hormonal therapy. The study used a comprehensive evidence map search strategy of systematic reviews as described by Lunny et al. (24) The medium of language for the search was English. Search algorithms used in the databases included the following terms: "Breast cancer" or "quality of life of breast cancer patients", "hormonal therapy", "breast metastasis", "health-related quality of life", "breast carcinoma", "endocrine therapy", "antihormone therapy", "hormonal therapy", "treatment", and "therapy". In this review, the BC patient population here refers to patients having treatment eligibility during the disease course; all full articles with QoL as a significant outcome in BC patients were included. The exclusion criteria included all other languages except for English, animal studies, and articles without full text. The articles were screened as per the guidelines provided by "Preferred Reporting Items for Systemic Reviews and Meta-Analyses" (PRISMA) and the AMSTAR checklist (Figure 1) to examine the quality of publication for the included articles. Initially, 1,878 articles were screened from multiple databases. Eight articles were included in the review after the removal of either duplicate or irrelevant articles. The data were synthesized using descriptive tables, including authors' names, year of publication, sample size, age, significant findings assessing the QoL, and QoL instruments.

Results

The study initially identified 1,878 articles from multiple databases, and after the removal of duplicate articles, eight of them were included in the study for 2010 to 2020. Table 1 demonstrates the essential information and characteristics of the included studies. Out of eight shortlisted studies, seven reported clinical trials and HRQoL as their secondary result. Overall, main characteristics (mean age and QoL instruments) of the included studies were almost identical to the median follow-up time of 18 months for average research.

Three studies compared the administration of hormonal therapy versus another hormonal therapy in BC patients (12-14). Three studies used N-SAS BC 04, N-SAS BC 03, and MA-17R RCTs. In a study by Takei et al. (25) comparisons of two aromatase inhibitors (AIs) with tamoxifen and overall QoL scores rose after the initiation of treatment. In the first year, improved QoL was achieved in the tamoxifen group compared to in the aromatase inhibitors sub-group. The endocrine-related symptoms did not fluctuate between interventions and remained unchanged in all the groups. This study also used FACT-G scores to evaluate QoL globally among participants receiving anastrozole versus tamoxifen and exemestane. A statistically significant difference was observed across the groups. After treatment initiation in the tamoxifen group, FACT-G scores increased. The change of score for the tamoxifen group was four, representing no significant change over time. In this study, the N-SAS BC 04 included three arms, including two AIs and a tamoxifen group and FACT-B scores remained raised in the tamoxifen group compared to the AI group for one year. Another study by Ohsumi et al. (26) compared AIs with tamoxifen. Results showed improved total FACT-G scores in the tamoxifen group and stable scores over time; however, scores in the AI group decreased but not significantly. In addition to this, the FACT-B scores remained unchanged. The third included study was reported by Goss et al. (27) and they carried out a five-year research on AIs alone. They found that compared to letrozole plus, AIs when compared using MENQOL, had no significant impact over a time period. In all three of these studies, QOL was assessed as a secondary endpoint.

Another study by Beck et al. (28) presented the BOLERO-2 trial with two arms, arm one consisting of everolimus and exemestane and the other arm consisting of exemestane only. The results showed that better QoL was observed in the everolimus group compared to the exemestane monotherapy group, despite higher adverse events reported. Another study by Hojan et al. (29) used EORTC, QLQ-C30, and EORTC QLQ BR23 questionnaires as QoL instruments in premenopausal BC patients after using endocrine therapy that negatively affected the impact of QoL in patients. The study emphasized incorporating physical exercise to reduce endocrine therapy side effects and improve HRQoL.

Two studies by Verma et al. (30) and Harbeck et al. (31) assessed the HRQoL in premenopausal (HR+/HER-) BC patients with the use of ribociclib with letrozole in the phase III MONALEESA-2 trial in 668 patients. The study by Taira et al. (32) used phase 3 MONALEESA-7 trial to study the ribociclib and endocrine therapy combination leading to improved HRQoL in patients on RIB+ET combination. Patient-reported outcomes (PROs) were assessed using (EORTC QLQ-C30), and the BC-specific (EORTC QLQ-BR23) questionnaires, and results demonstrated consistent HRQoL scores at baseline. A better AUC curve was also observed in the ribociclib arm. The impact on HRQoL during neo-adjuvant endocrine treatment with letrozole in 497 patients with a mean age of 63 was not found significant.

Discussion and Conclusion

The results of this literature review study describe the impact on HRQoL in BC patients on endocrine treatment as well as the side effects of hormonal therapy. In a detailed review of the literature from 2010 to 2020, eight articles were shortlisted, including seven RCTs, and one was a feasibility study. For evaluation of HRQoL, the EORTC QLQ-C30, EORTC QLQ BR23, EQ-5D-5L, SF-36, MENQOL, FACT-B, FACT-ES, CES-D, and FACT- G based questionnaires for the assessment of QoL were used, respectively.

Measurements of HRQoL are usually carried out with carefully designed and validated instruments, such as questionnaires or semi-structured interviews. Reliability, validity, and responsiveness are prerequisites for an ideal PRO questionnaire (33). EORTC QLQ C30 is a 30-item questionnaire that consists of five (social, emotional, physical, cognitive, and role) functional scales followed by three symptom scales (nausea/vomiting, fatigue, and pain) and a global health status scale. Similarly, the EORTC QLQ BR23 companion module to EORTC

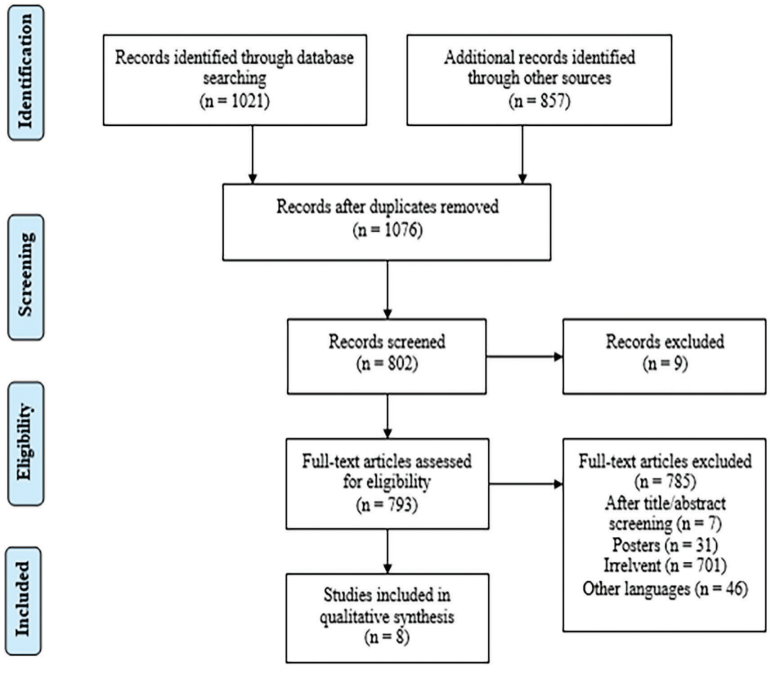

 Figure 1. PRISMA flow diagram representing the study's inclusion/exclusion criteria

Table 1. Basic information and characteristics of included studies

Study	Region	Trial name	Arms	Mean age (y)	Treatment duration (y)	QoL endpoint	QoL instruments	QoL study/ trial samples (N/N)	Main QOL findings	Clinical significance of QOL study findings	Timing of QOL measures
Takei et al. (25)	Japan	N-SAS BC 04	Arms	NA	5	Secondary	FACT-B, FACT-ES, CES-D, FACT-G	166/NR	FACT-G, FACT-G, and the FACT-ES total scores were statistically significantly better in the tamoxifen group than in the anastrozole group (p = 0.042, 0.038, and 0.005, respectively) on physical well-being subscale. Total FACT-G scores were reduced in the ANA group during one year and continued until two years; however, tamoxifen group scores were generally steady.	Yes	BL, 3 and 12 mo.
Ohsumi et al. (26)	Japan	N-SAS BC 03	TAM vs. EXE vs. ANA	63	5	Secondary	FACT-B, FACT-ES, CES-D, FACT- G	694/NR	After treatment initiation, raised FACT-G and BCS scores were recorded in the tamoxifen group. FACT-B scores increased after treatment began and remained significantly higher in the tamoxifen group than in the exemestane or anastrozole groups for one year (p = 0.045). ES scores were largely unchanged in all three treatment groups, and there was no significant difference between any groups (p = 0.36). In all patients assigned to exemestane or tamoxifen, FACT-B scores increased after treatment began and remained significantly higher in the tamoxifen group than in the exemestane group for one year (p = 0.047)	Yes	BL, 3 mo, 1 and 2 y
Goss et al. (27)	Canada, USA	MA-17R	1–4 y TAM → ANA vs. TAM	65.1	10	Secondary	SF-36, MENQOL	1630/1918	No statistically significant between-group differences were observed in the SF-36 summary scores on any of the four MENQOL symptom subscales	Yes	BL and 12, 24, 36, 48, and 60 mo
Beck et al. (28)		BOLERO-2	5 y AI + 5 y LET vs. 5 y AI + PL	62	1	secondary	EORTC QLQ C30	100/37	BOLERO-2 trial used two arms, the advantage of EVE to EXE detected in patient's subsections whose disease progressed during or after (neo) adjuvant NSAI therapy was steady with that observed in the overall population. Furthermore, the considerable advancement in PFS in this subset was achieved while sustaining HRQoL.	Yes	

Table 1. Continued

Study	Region	Trial name	Arms	Mean age (y)	Treatment duration (y)	QoL endpoint	QoL instruments	QoL study/ trial samples (N/N)	Main QOL findings	Clinical significance of QOL study findings	Timing of QOL measures
Hojan et al. (29)	Poland	feasibility study	EVE + EXE vs. EXE	41	3	Secondary	EORTC, QLQ-C30, EORTC QLQ BR23	41	ET negatively impacts premenopausal breast cancer patients' body composition, physique, and QoL. This feasibility study shows that physical activity may improve QoL and reduce adverse effects of ET on body composition and body physique, indicating appropriateness for further investigation on the use of exercise programs in premenopausal breast cancer patients to improve therapy outcomes.	Yes	
Verma et al. (30)		MONALEESA-2	GOS + TAM	62	1	Secondary	EORTC QLQ-C30, EORTC QLQ BR23	668	HRQoL was consistently maintained from baseline in postmenopausal women with HR+, HER2– advanced breast cancer receiving ribociclib plus letrozole and was similar to that observed in the placebo plus letrozole arm. Together with the improved clinical efficacy and manageable safety profile, these PRO results provide additional support for the benefit of ribociclib plus letrozole in this patient population.	Yes	
Harbeck et al. (31)		MONALEESA-7	RIB? LET vs. LET	40-49	1	Secondary	EORTC QLQ-C30, EQ-5D-5L	335/337	HRQoL was maintained longer in patients who received ribociclib + ET versus placebo + ET. Combined with previously reported improvements in PFS and OS, these data support a strong clinical benefit-to-risk ratio with ribociclib-based treatment in pre-and premenopausal patients with HR+/HER2– ABC.	Yes	
Taira et al. (32)		NEOS	RIB + ET	63	3	Secondary		497	Neoadjuvant endocrine therapy with LET had no impact on global HRQoL but influenced endocrine-related symptoms such as hot flush.	Yes	

GOS: goserelin; TAM: tamoxifen; EVE: everolimus; EXE: exemestane; LET: letrozole; AI: aromatase inhibitors; ANA: anastrozole; PL: placebo; QOL: quality of life; RIB: ribociclib; ET: endocrine therapy

QLQ C30 is BC-specific. It comprises four functional parameters (future perspective, body image, sexual functioning, and sexual enjoyment) followed by four symptom parameters (systemic therapy, arm, breast, and hair loss) (34-36).

The present study used the phase 3 MONALEESA-7 trial to study the ribociclib and endocrine therapy combination, leading to improved HRQoL in patients on RIB+ET combination.

Similarly, another study was conducted by van Nes et al. (37) to assess the QoL in the Tamoxifen, Exemestane Adjuvant Multinational (TEAM) Trial following its comparison with the adverse effects given in the central database. Dutch postmenopausal early BC patients participated in the QoL side study and completed questionnaires at 1 (T1) and 2 (T2) years after the start of ET. Questionnaires comprised the EORTC QLQ-C30 and BR23, supplemented with FACT-ES. Five hundred and forty-three patients completed questionnaires at T1 and 454 patients (84%) at T2. Overall, QoL and most functioning scales improved over time. The only clinically relevant and statistically significant difference between treatments was related to insomnia, as exemestane-treated patients reported more insomnia (38). Patients associated with the study of QoL felt some difficulties in terms of depression, anxiety, chronic fatigue, sleep problems, pain, sexual dysfunction and sleep disorders. At the same time, more adverse events were observed in patients in Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial database. Not to overlook the advantages of hormonal therapy in decreasing the risk of recurrence of BC and mortality rate, it has been found that a number of cancer survivors do not take the prescribed hormonal therapy and it has been reported in one of the studies (10) that almost 80% of women take less than 80% of the prescribed dosage and 50% stop their treatment by the fifth year of the prescription (11) thus leading to an increase in the recurrence and mortality of BC (12). This is why persistence and adherence to the treatment of hormonal therapy is considered as some of the key determinants of disease-free survival (13).

It is important to remember that this evaluation of reviews has certain limitations. The key criticism is that it is impossible to generalize the results because only eight evaluations with varying agendas were examined. It is important to remember that this review is a bibliometric analysis of review articles and represents what has been accomplished over the previous decade in reviewing the QoL in BC patients. It appears that additional targeted and in-depth studies are needed. It is believed that this review might show repetition and disparities, and places that require further effort. For example, no particular reviews on the QoL in BC survivors were found, although the studies included both BC patients and survivors. Perhaps a further and intense investigation is needed to address independently considering differences in QoL between newly diagnosed patients, long-term survivors who have completed their treatments, and patients receiving different treatments. BC survival is a highly significant and relevant issue that demands more attention. Finally, it is possible that some of the publications were overlooked entirely as the method in this study was confined to using minimum key phrases to search for relevant articles.

The current review reports that the QoL in BC patients has improved dramatically in recent years, due to various basic but effective therapies, such as hormonal therapy. The current study found, however, that symptoms generated by different treatment methods are still underestimated and require more careful consideration. The study concluded that the QoL of postmenopausal women is affected by the long-term use of adjuvant endocrine therapy. However, further efforts are required to complement QoL instruments and the QoL data reporting quantitative evaluation of QoL for patients receiving adjuvant ET and, consequently, enable clinicians and metastatic cancer patients to make an informed and shared decision. The QoL of BC patients has been improved significantly through several simple and effective interventions.

Nonetheless, symptoms due to various treatment modalities are still under observation. Clinical outcomes in severe patients can be enhanced by incorporating interventions aimed at improving HRQoL, especially in patients receiving endocrine or hormonal therapy. More research on social support strategies in Asian settings is required to uncover effective ways to enhance patients' HRQoL.

Informed Consent: Not necessary.

Peer-review: Externally peer-reviewed.

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Original Article

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Is Electrocardiogram Helpful in Predicting a Rise in Troponin I as a Marker of Anthracycline Cardiotoxicity?

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ABSTRACT

Objective: Screening patients on anthracycline-based chemotherapy regimens for the development of cardiotoxicity can be resource intensive. We therefore studied various traditional electrocardiogram (ECG) parameters to correlate and possibly predict the development of elevated Troponin I as a surrogate marker of anthracycline-induced cardiotoxicity.

Materials and Methods: This was a single-centre prospective cohort study done between January 2014 to January 2016. Baseline ECG was compared with ECG performed after chemotherapy and different parameters were compared. Patients were divided into Troponin I positive and negative groups based on the test performed at the end of chemotherapy, using a cut-off of 0.06 ng/dL.

Results: Of the 160 patients studied, 131 (81.9%) were Troponin I negative (TnI-) and 29 (18.1%) were positive (TnI+). Breast cancer accounted for 79% of all cancers in this study. Many ECG parameters were compared between the TnI- and TnI+ groups. Of them, TP segment and TP/QT showed a significant decrease in the TnI+ group. The mean (95% confidence interval) TP in the TnI- group was 162.9 ms (145.4, 180.4) and in TnI+ groups was 117.9 ms (89, 146.8) (p = 0.03). Corresponding values for TP/QT were 0.47 (0.42, 0.51) and 0.35 (0.27, 0.42) (p = 0.02). These changes were not significant in multivariate analysis and likely reflected the different mean heart rates (HR) in both the groups, as suggested by partial correlation which was run with HR as a confounder.

Conclusion: ECG parameters, such as QTcH, TP and TP/QT do not helpful predicting Troponin I elevations in patients on anthracycline-based chemotherapy. Further studies based on hard endpoints, for example, clinical systolic dysfunction occurring at one year, would give better information on their utility.

Keywords: Anthracyclines; cardiotoxic agents; chemotherapy; ECG; Troponin I

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Key Points

- Little is known regarding the electrocardiogram (ECG) correlates and their role in predicting elevations in Troponin I among patients on anthracyclines.
- This study was an attempt to triage this group of patients who would require closer monitoring and detailed evaluation using advanced imaging modalities.
- Further studies based on more robust endpoints, for example the development of systolic dysfunction, would be needed to clearly understand a role for ECG in this setting.

Introduction

Anthracyclines have been the mainstay in the treatment of many malignancies, especially breast cancer, lymphomas, sarcomas and various childhood malignancies. Anthracycline-induced cardiotoxicity has been well documented at doses exceeding 550 mg/m^2 leading to recommendations not to exceed therapeutic doses above 400–450 mg/m^2 (1, 2). Reducing the cumulative doses brings down the incidence of cardiotoxicity, but the risk persists. The current incidence of clinical heart failure due to anthracycline cardiotoxicity is 1–5%, and asymptomatic cardiac dysfunction is 5–20% (3, 4). The risk increases with mediastinal radiation, advanced age (>65 years), younger age (<4 years), female sex, hypertension, diabetes, peripheral vascular disease, emphysema, bolus dose regimen and pre-existing coronary artery disease (3, 5). However, it still remains impossible to predict if a patient would develop cardiotoxicity with anthracyclines or not.

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The usefulness of Troponin I as a biomarker of cardiotoxicity has been extensively researched in a metanalysis (6). This study analysed Troponin I, Troponin T, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP). Of these, only Troponin I, measured at the end of chemotherapy, showed a significant and strong association with future development of cardiotoxicity with 85% positive predictive value and 99% negative predictive value for the development of clinical heart failure at one year. However, the use of Troponin to predict the development of cardiotoxicity merely predicts the inevitable as Troponin itself is a marker of myocardial necrosis (7). Treatment with enalapril and carvedilol has proven to be beneficial in modifying the disease course of cardiotoxicity in high-risk patients identified based on Troponin I (8). A different predictor of cardiotoxicity, based on an electrocardiogram (ECG), would go a long way to better triage such patients.

ECG could help in predicting cardiotoxicity even before irreversible damage to cardiac myocytes has occurred. Studies done on patients receiving myeloablative chemotherapy have shown that corrected QT interval (QTc) was a predictor of cardiac dysfunction (9). The novel concept of ischemic constellation (10) rather than cascade further supports the fact that ECG could act as a useful tool to predate irreversible myocardial injury. This concept would also hold for myocardial injury due to oxidative stress, as seen during chemotherapy (7). Moreover, there is a paucity of data regarding the diastolic correlates of ECG, such as TP segment and PQ interval, among patients undergoing anthracycline-based chemotherapy, which may show changes corresponding to echocardiography-derived parameters of diastolic dysfunction (11).

An interesting study done to assess the diagnostic accuracy of *TP / (PQ x Age)*, referred to as Decg, showed that a value <0.033 correlated well with the presence of diastolic dysfunction of any grade (11). This parameter (Decg) was validated in the same study and showed a sensitivity and specificity of 83% and 92%, respectively, and a positive and negative predictive value of 92% and 83%. When a combined approach was used in this study incorporating indexed left atrial end-systolic volume (LAESV) with a cut off-of >34 mL/m^2, the sensitivity and specificity only changed marginally to 90% and 92%. At the same time, the positive and negative predictive values were 95% and 86%, respectively. More importantly, the ECG counterpart of increased atrial contribution seen in patients with diastolic dysfunction, that is the PQ interval, predated the actual morphological changes in atria, characterized by left atrial (LA) enlargement denoted by Indexed LAESV. Hence, it would be intuitive to evaluate the discriminatory capacity of this variable in predicting troponin elevation in this group in patients undergoing cardiotoxic chemotherapy.

Cost-effectiveness studies performed on cancer survivors (12-14) suggest that, although newer imaging modalities like global longitudinal strain and speckle tracking, have greater sensitivity in picking up subtle changes in cardiac function, it may not be suitable for mass implementation and may be limited by interobserver variability and operator experience. Therefore there is a need to investigate cheaper, more objective and readily available modalities to help identify patients who would require closer monitoring for the development of chemotherapy-induced cardiotoxicity. The aim of this study was to identify ECG predictors of positive Troponin in patients undergoing anthracycline-based chemotherapy.

Materials and Methods

Study Population

This was a single-centre, prospective, cohort study conducted at Government Medical College Hospital, Kozhikode, Kerala, India, during two years period from January 2014 to January 2016. The study was approved by the Institutional Ethics Committee, reg no: ECR/395/Inst./KL/2013 having approval number GMCKKD/RP 2016/IEC/76. The trial was overseen by the head of the department of cardiology.

All patients who were >18 years of age, with malignancy and were planned to be given a doxorubicin-based chemotherapy regimen, were screened for eligibility. Those who had an ejection fraction of <55%, moderate to severe valvular heart disease based on the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (15) were excluded from the study. The presence of diabetes and hypertension was ascertained based on history. Previous myocardial infarction (MI) was defined as a documented acute coronary syndrome in the past or ECG evidence of pathological Q waves (16). Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Measurement of ECG Parameters

ECG was recorded using the EdanUSA SE-1200 (EdanUSA, San Diego, CA, USA) machine and was scanned to a computer as an image file (.jpeg) at 600 dpi. The various measurements taken were: QT interval; RR interval; TP segment; and PQ interval (Figure 1). These were measured using the Cardio Calipers v3.3 software (Iconico Inc., Philadelphia, PA, USA). Heart rate (HR) was calculated from

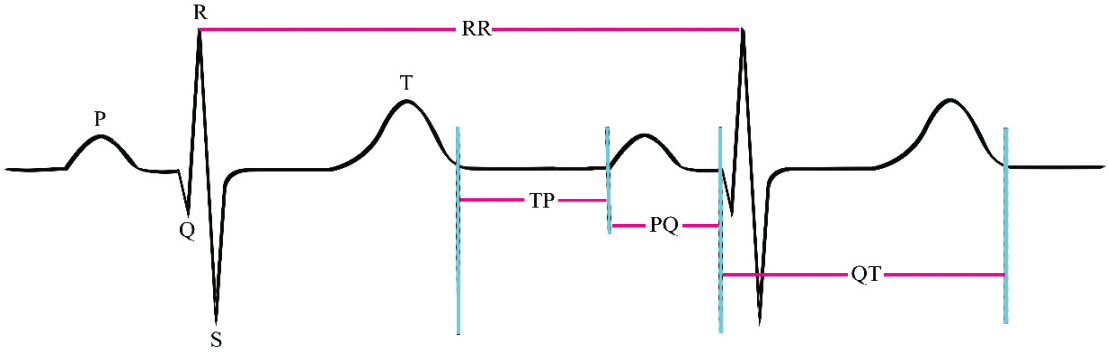

Figure 1. Various measurements of ECG segments and intervals used in this study

ECG: electrocardiogram

the RR interval, measured in milliseconds, by the formula 60,000 ÷ RR. For QT measurement, the lead showing the longest QT was taken. In patients with bundle branch blocks, the QT interval is overestimated due to the widening of the QRS complex and not due to the abnormalities of repolarization. Besides, the formulas used for corrected QT interval calculation are not standardized for use in patients with bundle branch blocks (17). Hence, patients with such ECG abnormalities were excluded from the study to prevent non-uniformity in the study population. QTc was calculated using the Hodges formula (QTcH) (18). Lead II was used to measure TP and PQ as P waves are best delineated in this lead (19). Patients with atrioventricular dissociation will show a beat-to-beat variation in the TP and PQ intervals and therefore were excluded from the study. Decg was measured using the formula *TP / (PQ x Age)*, where TP is the duration of the TP segment measured in milliseconds, PQ is the duration of the PQ interval measured in milliseconds, and age is given in years (11).

Troponin I Assay

Troponin I (TnI) was measured on a Beckman Coulter machine using the Access AccuTnI 3 assay. Based on the validation studies for this assay, the manufacturer claimed 99th percentile of the upper reference level was 0.04 ng/mL. At this cut-off, the total imprecision was <14%. A value of ≥0.06 ng/mL had an imprecision of <10% and was used in this study to define a positive test (20), as previously described (6).

Data Collection

Patients or the public were not directly involved in the design of the study or the collection of data. The patients were asked to report to us at specified intervals, and the institution itself did data collection. Once the patient fulfilled the criteria for enrolment, baseline demographic data collection, and risk factors assessment were done. A baseline ECG was taken, after which the patients were instructed to begin chemotherapy. At the end of their final cycle of chemotherapy, ECG was repeated, and blood samples were collected to test for Troponin I. The study population was then divided into two groups based on their Troponin I results. They were considered Troponin I positive (TnI+) or Troponin I negative (TnI-) based on a cut-off of 0.06 ng/mL. The ECG measurements obtained were then compared between the two groups, as were the change in parameters from baseline to post-chemotherapy.

Chemotherapy Regimens

Two chemotherapy regimens used for breast cancer at our centre during the study were the AC regimen consisting of doxorubicin and cyclophosphamide, and the FAC regimen consisting of 5-fluoro uracil, doxorubicin, and cyclophosphamide. The AC regimen used doxorubicin at a dose of 60 mg/m^2 for four cycles, giving a cumulative dose of 240 mg/m^2. In comparison, the FAC regimen used doxorubicin at a dose of 50 mg/m^2 for six cycles, giving a cumulative dose of 300 mg/m^2. In Non-Hodgkin's lymphoma, doxorubicin was used at a dose of 50 mg/m^2 for six cycles, giving a cumulative dose of 300 mg/m^2. The corresponding dosing regimen for sarcomas and malignant fibrous histiocytomas used doxorubicin at a dose of 75 mg/m^2 for six cycles, giving a cumulative dose of 450 mg/m^2.

Statistical Analysis

Statistical analysis was performed using SPSS, version 26.0 (IBM Inc., Chicago, IL, USA). All variables were evaluated separately in TnI- and TnI+ groups. Categorical variables are presented as frequencies in each group, and their inter-group differences were assessed using the chi-square test or Fisher's Exact test depending on the variable. The normality of data was confirmed using skewness and kurtosis, as well as histograms and Normal Q-Q plots. Continuous variables are presented as mean with their 95% confidence intervals (CI) given in parenthesis. The difference in means of continuous variables between groups was compared using the independent samples t-test. For assessing the difference scores of ECG parameters from baseline to post-chemotherapy, paired t-test was used. For those variables showing statistically significant differences, multivariate analysis using binary logistic regression was done. A cut-off ≤0.05 was used for alpha error. Linear regression was run using Troponin I as a continuous dependent variable and all statistically significant post-chemotherapy variables to predict positive Troponin I, based on the cut-off of ≥0.06 ng/mL. Pearson's correlation was run on Troponin I values with significant post-chemotherapy variables followed by Pearson's partial correlation to eliminate confounders.

Results

A total of 240 patients who were referred to the cardiology department for pre-chemotherapy fitness were screened and found to be eligible. Of them, 32 patients were excluded, and another 48 patients were lost to follow-up. Hence, a total of 160 patients completed the study and were used for this analysis. There were 29 patients (18.1%) who were TnI+ and 131 patients (81.9%) were TnI- (Figure 2). Baseline characteristics (Table 1) were comparable between the two groups. The mean age in both groups was similar, 52.8 (50.7, 54.8) years in the TnI- group and 51.5 (47.4, 55.5) years in the TnI+ group (*p*

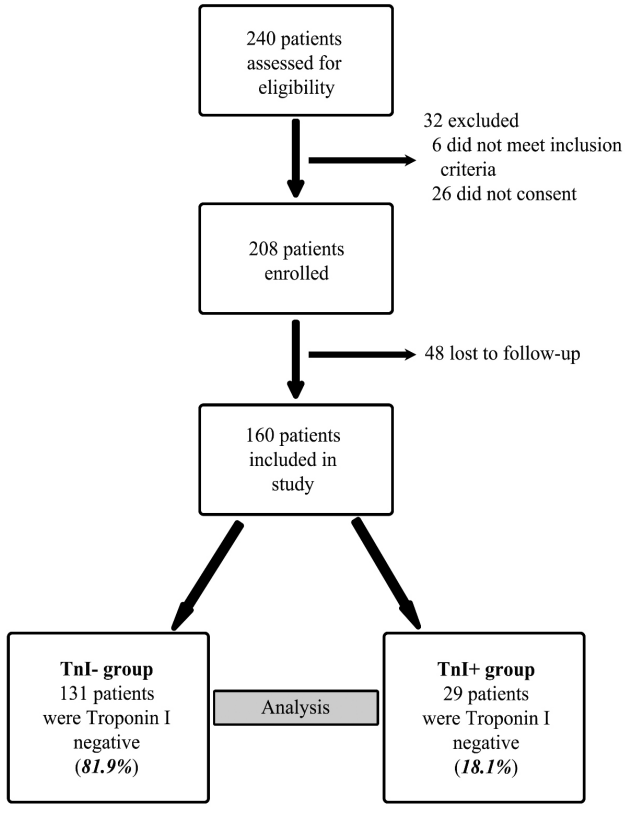

Figure 2. CONSORT diagram

= 0.59). Breast cancer accounted for more than three-quarters of all cancers in both groups, and as expected, females predominated the study population accounting for 86.3% of TnI- group and 93.1% of TnI+ group. Other malignancies in the remainder included bladder cancer, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, sarcoma, and stomach cancer. The risk factors considered were hypertension, diabetes, and previous myocardial infarction, and none of these showed a difference between groups. Baseline ECG parameters were also comparable between groups (Table 2).

Post-chemotherapy ECG showed a statistically significant difference in three variables between groups (Table 3). These were HR, TP, and TP/QT, which had a significant difference between means. Other parameters (QT, QTcH, PQ, and PQ/QT) were not different between groups. The mean HR in the TnI- group was 97.2 beats per minute (bpm) (94.3, 100) beats and in the TnI+ group this was 106.4 bpm (99.8, 113.1) (p<0.01). The mean TP segment in the TnI- group was 162.9 milliseconds (ms)(145.4, 180.4) and in the TnI+ group was 117.9 ms (89, 146.8) (p = 0.03) and the TP/QT in the respective groups were 0.47 (0.42, 0.51) and 0.35 (0.27, 0.42) (p = 0.02).Change in the baseline values of ECG parameters after chemotherapy were assessed using the paired samples t-test. All parameters, except for HR and PQ/QT, showed a statistically significant change from baseline (Table 4). The mean difference in QT in the TnI- group was 11.5 ms (5.7, 17.2; p<0.01), HR was - 9.2 bpm (-11.8, -6.7, p<0.01), TP was 41.5 ms (26.4, 56.7, p<0.01), TP/QT was 0.1 (0.06, 0.14, p<0.01) and PQ was 6.6 (0.9, 12.2, p = 0.02). In the TnI+ group, the mean HR difference was -12.9 bpm (-18.9, -6.8, p<0.01), QTcH was -14.2 ms (-25.3, -3.1, p<0.01), TP was 52.4 ms (19.5, 85.4, p<0.01) and TP/QT was 0.14 (0.05, 0.23, p<0.01). QT, PQ, and PQ/QT did not show a significant change in the mean. Difference scores of all the ECG parameters were also calculated and compared between groups to see if this change in parameters was significant. To calculate the difference-scores, post-chemotherapy scores were subtracted from the baseline scores and independent samples t-test was performed. It did not show

Table 1. Comparison of baseline categorical variables between Troponin I negative and positive groups

Variable	Subgroups	% in Troponin Negative	% in Troponin Positive	*p*-value
Gender	Male	13.7	6.9	0.53
	Female	86.3	93.1	
Malignancy	Bladder	0.8	0	0.7
	Breast	78.6	82.8	
	Hodgkin's lymphoma	2.3	0	
	Non-Hodgkin's lymphoma	5.3	10.3	
	Sarcoma	4.6	6.9	
	Stomach	6.9	0	
	Others	0.8	0	
Hypertension	Yes	30.5	27.7	0.75
	No	69.5	72.4	
Diabetes	Yes	16	17.2	0.53
	No	84	82.8	
Myocardial infarction	Yes	2.3	3.4	0.55
	No	97.7	96.6	

Table 2. Comparison of baseline continuous variables between Troponin I negative and positive groups

	Troponin Negative		Troponin Positive		
Parameter	Mean	95% CI	Mean	95% CI	*p*-value
Age	52.8	50.7, 54.8	51.5	47.4, 55.5	0.59
QT	352.8	347, 358.6	340.7	329.5, 351.9	0.08
HR	88	85.3, 90.6	93.6	88.2, 98.9	0.07
QTcH	401.7	398, 405.4	399.4	393, 405.8	0.60
TP	204.2	185.7, 223.2	170.3	137.4, 203.3	0.12
TP/QT	0.56	0.52, 0.61	0.49	0.40, 0.58	0.16
PQ	152.5	147.3, 157.7	143.5	133, 153.9	0.14
PQ/QT	0.44	0.42, 0.45	0.43	0.39, 0.46	0.59

CI: confidence interval; HR: heart rates

a statistically significant difference in any of the measured variables (Table 4). Multivariate analysis was performed on the ECG variables QTcH, TP, TP/QT, and PQ, and none of the variables showed a significant association with a positive troponin test.

There was a linear correlation between HR, TP, TP/QT, and Troponin I values. However, when Pearson's partial correlation was run to control for HR as a confounder, the relationship of both TP and TP/QT with Troponin I ceased to be statistically significant ($p = 0.35$).

Discussion and Conclusion

This is the largest single centre data available on ECG and Troponin I elevations in patients on anthracyclines. Breast cancer was the predominant malignancy for which doxorubicin was used. Our study demonstrates that HR, TP, and TP/QT showed a significant difference in the Troponin positive group in univariate analysis, but this did not hold in multivariate analysis. Besides, the changes in TP and TP/QT were likely related to the changes in mean HR between groups. Other ECG parameters did not show any difference between groups, nor was a change from baseline significant in any of the parameters assessed.

Ever since animal models demonstrated a prolongation of QT interval with the use of anthracyclines (21), QTc assessment had attracted a lot of attention for its putative role in predicting not only arrhythmias but also heart failure. Association with heart failure was suggested by a study done in 2003 in patients undergoing myeloablative chemotherapy (9). Since then, numerous small studies (22-24) in patients on anthracyclines have documented a prolongation of QTc, but the clinical significance or the association with cardiotoxicity has not been ascertained. The present study also showed a significant change in QTcH (δQTcH) from baseline in the TnI+ group compared to the TnI- group but this difference was not statistically different between groups. Also, the mean δQTcH in the TnI+ group was -14.2 (-25.3, -3.1) msec, which is too small a change to have any practical application. This makes δQTcH a weak parameter to identify TnI+ patients.

The diastolic ECG parameters measured in this study (PQ, PQ/QT, TP and TP/QT) have never been previously studied in the context of anthracycline cardiotoxicity, to the best of our knowledge. PQ and PQ/QT did not show any difference between groups, but both TP and TP/QT showed a significant difference. There was an average drop of approximately 50 ms in the TnI+ group, which was significant ($p = 0.03$). With the development of diastolic dysfunction, the TP segment was expected to prolong but in the present study, a reduction in TP and TP/QT was observed among those with positive Troponin I. This might be because diastolic dysfunction might not have been present and direct subclinical oxidative damage could have released Troponin I into the blood. This was indeed confirmed in studies that evaluated diastolic function on echocardiography. In a study that evaluated changes in echocardiographic measurements of diastolic dysfunction like E/A ratio (which is the ratio of the velocity of mitral

Table 3. Comparison of post-chemotherapy ECG characteristics between Troponin I negative and positive groups

	Troponin Negative		Troponin Positive		p-value
Parameter	Mean	95% CI	Mean	95% CI	
QT	341.4	336.2, 346.6	332.4	322, 342.9	0.15
HR	97.2	94.3, 100	106.4	99.8, 113.1	<0.01
QTcH	405.9	401.9, 409.9	413.7	404.9, 422.4	0.11
TP	162.9	145.4, 180.4	117.9	89, 146.8	0.03
TP/QT	0.47	0.42, 0.51	0.35	0.27, 0.42	0.02
PQ	146	140.7, 151.2	144.1	134.7, 153.5	0.85
PQ/QT	0.44	0.41, 0.46	0.44	0.40, 0.47	0.72

CI: confidence interval; HR: heart rates; ECG: electrocardiogram

Table 4. Change in ECG parameters from baseline to post-chemo in Troponin negative and positive groups

	Troponin Negative			Troponin Positive			p-value for diff between groups
Parameter	Mean diff	95% CI	*p*-value	Mean diff	95% CI	*p*-value	
QT	11.5	5.7, 17.2	<0.01	8.3	-3.1, 19.6	0.15	0.64
HR	-9.2	-11.8, -6.7	<0.01	-12.9	-18.9, -6.8	<0.01	0.24
QTcH	-4.2	-9.1, 0.7	0.09	-14.2	-25.3, -3.1	<0.01	0.09
TP	41.5	26.4, 56.7	<0.01	52.4	19.5, 85.4	<0.01	0.55
TP/QT	0.1	0.06, 0.14	<0.01	0.14	0.05, 0.23	<0.01	0.34
PQ	6.6	0.9, 12.2	0.02	-0.7	-13, 11.6	0.91	0.28
PQ/QT	-0.01	-0.02, 0.02	0.98	-0.1	-0.05, 0.03	0.57	0.46

CI: confidence interval; HR: heart rates; ECG: electrocardiogram

vale opening in the early rapid filling phase vs the same in late rapid filling phase), Isovolumetric Relaxation Time (IVRT; which is the time between the closure of the aortic valve at the end of systole to the opening of the mitral valve at the beginning of diastole), and deceleration time (time from the peak of E wave to the equalization of pressures between left ventricle and left atrium before the onset of A wave) in patients undergoing chemotherapy with anthracyclines, it was not found to be associated with the future development of cardiotoxicity (25). Another small study of 51 patients showed that diastolic dysfunction on echocardiography developed during chemotherapy with a significant reduction in e' and E/e'. This change was not correlated with Troponin I or ejection fraction, and thus it had limited ability to identify patients at risk of developing cardiotoxicity (26). Such heterogeneity in studies suggest that diastolic dysfunction may not necessarily be part of the spectrum of chemotherapy-induced cardiotoxicity. This could be explained by the fact that diastolic dysfunction parameters are heavily dependent on the loading conditions of the heart, meaning, when intravascular volume is high, the load borne by the left ventricle could strain it enough to worsen the diastolic properties of the heart and vice-versa. This makes echocardiographic diastolic parameters quite unreliable and for this reason, load independent variables, such as global longitudinal strain imaging, have gained importance.

TP interval is known to be inversely correlated with HR. It is likely, in our study, that the change in the TP segment duration and TP/QT observed is merely a function of the different mean HR values in each group. Both groups showed a significant decrease in mean HR from baseline with a significant reduction of 9.2 bpm in the TnI- group and 12.9 bpm in the TnI+ group. Although there was a numerically greater reduction in HR in those with positive Troponin I, this difference was not significant. This association was conclusively proven by Pearson's partial correlation controlling for HR. This further demonstrates that TP/QT is not a reliable way to control the TP segment duration for HR.

Although a Troponin I test done at the end of chemotherapy has a high negative predictive value, it is only a marker in high-risk patients. Elevation of Troponin I does not always predict the development of clinically significant left ventricular dysfunction, with only 85% positive predictive value (6). Our study was conducted to find ways to predict the development of elevated Troponin I. Testing ECG against hard endpoints, like systolic dysfunction, over a year's follow-up would have provided more conclusive evidence regarding a correlation. An interim analysis of ECG would have helped in understanding the temporal changes occurring in these parameters and would have identified subtle changes that predate the occurrence of positive Troponin I itself.

In conclusion, none of the studied ECG parameters used in this study are useful to identify patients at risk of developing anthracycline-induced cardiotoxicity. HR, TP, and TP/QT showed a significant reduction in Troponin I positive patients on univariate analysis, but it did not prove significant in multivariate analysis. Also, the differences observed in TP and TP/QT between groups were merely a reflection of different mean HRs in the two Troponin I groups.

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee, Government Medical College, Kozhikode, Institutional Ethics Committee, Government Medical College, Kozhikode, reg no: ECR/395/Inst./KL/2013 having approval number GMCKKD/RP 2016/IEC/76.

Informed Consent: Consent was obtained from the study participants prior to inclusion.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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The Influence of Screening Mammography Cessation and Resumption on Breast Cancer Presentation and Treatment: A Multi-Hospital Health System Experience During the Early COVID-19 Pandemic

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ABSTRACT

Objective: To assess the impact of the coronavirus disease-2019 (COVID-19) pandemic screening restrictions on the diagnosis and treatment of breast cancer in a single health system.

Materials and Methods: We performed a retrospective, cohort investigation of breast cancer patients at a multi-institution health system from March 1, 2019 to December 31, 2020 with two time periods related to the pandemic: "Early phase" (March 18 – June 7) reflecting the time of the screening mammography moratorium and "Late phase" (June 8 – December 31) to reflect the time once screening mammography resumed. 2020 was compared to 2019 to exclude potential differences from temporal or seasonal changes. Variables included demographics, COVID related-deferral, cancer specific data, method of detection, type of treatment recommended and received.

Results: Fewer patients presented with a breast cancer diagnosis during Early phase 2020 when compared to any other time period. Numbers increased significantly in Late phase 2020; total numbers of patients seen in 2020 approached but did not completely reach that of 2019. When compared to other time periods, patients who presented during the moratorium on screening were younger, more likely to be black, had a higher Body Mass Index, and were more likely to have a human epidermal growth factor receptor 2 positive tumor. There was a slight increase in size of presenting tumor and node positivity, although no differences in breast or axillary surgical management were identified.

Conclusion: Despite an increase in tumor size and positive nodal status seen during the screening moratorium, surgical treatment was not negatively impacted.

Keywords: Breast cancer; COVID-19; neoadjuvant systemic therapy; surgery

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Key Points

- A slight increase in presenting tumor size and positive nodal status was identified after screening mammography was halted.
- Although endocrine therapy was offered as a temporizing measure during the lockdown, there was low uptake.
- Ultimate surgical treatment was not impacted by screening cessation.

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Introduction

Coronavirus disease-2019 (COVID-19) has affected healthcare delivery more than any other crisis in recent memory. The World Health Organization first announced concerns about a coronavirus-related pneumonia in Wuhan, China on January 5, 2020. The first documented COVID-19 positive patient in the United States occurred on January 21, 2020 (1). In Massachusetts, the first case was documented on February 1, 2020 (2). A state of emergency was declared on March 10, 2020 with cessation of all elective procedures as of March 16, 2020. Screening imaging was halted at our institution on March 18, 2020 and resumed June 8, 2020.

Routine screening mammography has resulted in earlier detection of breast cancer and a reduction in the extent of treatment. Screening has been so effective that the benefit of self breast exam (SBE) and clinical breast exam (CBE) have been called into question (3, 4). The American Cancer Society currently advises against CBE in women undergoing screening and against SBE for women of any age (5). Some studies have questioned the benefit of SBE even in regions of the world where mammography is not readily available, as discussed in a 2003 Cochrane review (6).

Screening imaging cessation would be expected to have an impact on the detection of early breast cancer and therefore result in a more advanced stage at presentation and worse outcomes (7-10). What is less clear is how COVID-19 restrictions would affect the number of patients presenting with palpable (and likely more advanced) cancers in a population accustomed to screening mammography and discouraged to perform SBE.

The goal of this study was to assess the impact these restrictions had on the diagnosis of breast cancer presentation and the therapies offered. We hypothesized that the disruption of the availability of screening imaging and "routine" CBE would result in a delay in the diagnosis of breast cancer, increased stage at presentation, and altered treatment recommendations. We also hypothesized that there would be a decrease in patients presenting with breast cancer, due both to a lack of screening and patients purposefully delaying the evaluation of palpable abnormalities due to fear of contracting COVID-19 while seeking medical care.

Materials and Methods

We conducted an Institutional Review Board (IRB)-approved retrospective, cohort study at a 720-bed tertiary care center with three regional hospitals in Western Massachusetts. We identified patients presenting with a new breast cancer diagnosis from March 1, 2019 to December 31, 2020 using the institution's IRB-approved Breast Disease Patient Repository, a secure, HIPAA compliant REDCap database, which is prospectively maintained. All patients with a new breast cancer diagnosis who presented between March 18 – December 31, 2020 were included in the study and compared to all patients with a breast cancer diagnoses who presented between March 18 – December 31, 2019. March 18th, the first day of the screening moratorium in 2020, was chosen as the start date. Exclusion criteria were those patients with breast cancer who presented outside this time frame. Supplemental information was obtained from the health system's electronic medical record.

We created two time period groups referred to as "Phases". The first time period reflected the pause in screening mammography (Early phase: March 18 – June 7, 2020) and the second time period reflected screening mammography resumption (Late phase: June 8 – December 31, 2020). We compared groups from 2020 (during COVID) to 2019 (before COVID) to assess whether any potential differences were due to COVID-19 and not to temporal or seasonal changes.

Eligible encounters were uploaded to a REDCap database, hosted by Tufts Clinical and Translational Science Institute (Grant Number UL1TR001064) for abstraction from the electronic medical record. Variables collected included patient age, gender, ethnicity, Body Mass Index (BMI), COVID deferral (treatment was treatment delayed or not), cancer specific data [specifically AJCC 8th edition clinical stage, grade, hormone receptor status and human epidermal growth factor receptor 2 (HER2) status], and method of detection (including imaging, self-detected, clinically detected). The type of treatment (surgery first *versus* neoadjuvant therapy) and the type of neoadjuvant therapy (chemotherapy *versus* endocrine therapy) that would have been recommended if the COVID pandemic had not occurred, as well as the surgical treatment of breast (lumpectomy, mastectomy, none) and surgical treatment of axilla (sentinel node biopsy, axillary dissection, completion axillary dissection, none) that patients ultimately received were also collected.

Statistical Analysis

All variables were checked for completeness and plausibility using frequencies (percentage, categorical) and means/ranges (continuous, ordinal). Descriptive statistics were calculated for baseline time periods from 2019 (prior to the COVID pandemic) and 2020 (after the onset of the COVID pandemic), including percentages for binary categorical variables, means (standard deviation) and medians (interquartile range) for continuous variables. The t-test was used for continuous variables and Fisher's Exact test for categorical variables. In order to further evaluate temporal trends within our data, we conducted stratified analysis among Early phase 2020 versus Early phase 2019, Late phase 2020 versus Early phase 2019 and Early phase 2020 versus Late phase 2020. Statistical significance was set at an alpha of 0.05. Data were analyzed using STATA 16 (StataCorp, College Station, TX, USA).

Results

We identified a total of 583 patients with breast cancer who presented between March 18, 2019 and December 31, 2020. In 2019, Early phase and Late phase consisted of 88 and 217 patients, respectively, for a total of 305 patients, whereas in 2020 Early and Late phase included 27 and 252 patients, respectively, for a total of 279 patients. Demographics, clinical characteristics, cancer specific data and treatment data for the study population are shown in Table 1. Patients who presented during Early phase 2020 were younger ($p<0.01$) and were more likely to be black ($p = 0.05$) than during the other three phases. Tumors were more likely to be HER2 positive ($p<0.01$) as seen in Figure 1. In the cohort analysis, there was no difference in tumor size ($p = 0.24$) or lymph node positivity ($p = 0.11$). Metastatic disease at presentation was equally infrequent among all phases. There was no difference in the type of breast surgery ($p = 0.95$) or axillary treatment ($p = 0.39$) that the patients ultimately received, regardless of the pandemic, as seen in Figure 2.

Sensitivity analysis was performed to compare the period of the moratorium on screening mammography (Early phase 2020) against the other phases (Tables 2-4). This confirmed the absence of a treatment difference in the surgical management of the breast and axilla that was seen in analysis of the entire cohort (Table 1), even when other differences were noted.

Table 1. Demographic, clinical, cancer specific and treatment data, n = 583

	Early phase 2019	Late phase 2019	Early phase 2020	Late phase 2020	*p*-value
n (%)	88 (15.1)	216 (37.0)	27 (4.6)	252 (43.2)	
***** Patient Characteristics**	***	***	***	***	***
Age, mean (SD)	60.0 (14.6)	61.5 (13.2)	54.8 (18.6)	64.0 (13.8)	<0.01
Race/Ethnicity, n (%)					
Caucasian	69 (78.4)	166 (76.9)	21 (77.8)	198 (78.6)	
African American	5 (5.7)	10 (4.6)	5 (18.5)	11 (4.4)	
Hispanic/Latino	7 (8.0)	19 (8.8)	0 (0.0)	18 (7.1)	
Ashkenazi	1 (1.1)	1 (0.5)	0 (0.0)	8 (3.2)	
Asian	2 (2.3)	6 (2.8)	0 (0.0)	9 (3.6)	
Not recorded/blank	4 (4.5)	10 (4.6)	1 (3.7)	2 (0.8)	
Other	0 (0.0)	4 (1.9)	0 (0.0)	6 (2.4)	0.05
***** Clinical Characteristics**	***	***	***	***	***
BMI, median (IQR)	28.1 (8.7)	29.2 (9.2)	30.6 (13.1)	28.8 (8.8)	0.24
Method of Detection, n (%)	***	***	***	***	***
None	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.8)	
Imaging	63 (71.6)	142 (65.4)	0 (0.0)	187 (74.5)	
Self-detected	25 (28.4)	65 (30.0)	27 (100.0)	56 (22.3)	
Clinically detected	0 (0.0)	9 (4.1)	0 (0.0)	6 (2.4)	<0.01
*****Cancer Specific Data**					
Type of Cancer, n (%)					
Invasive carcinoma NOS or Invasive carcinoma with Ductal and lobular features	0 (0.0)	6 (2.8)	0 (0.0)	7 (2.8)	
IDC-invasive ductal carcinoma	63 (71.6)	149 (69.0)	23 (85.2)	168 (66.7)	
ILC-invasive lobular carcinoma	9 (10.2)	16 (7.4)	1 (3.7)	20 (7.9)	
DCIS-ductal carcinoma *in situ*	16 (18.2)	32 (14.8)	3 (11.1)	46 (18.2)	
Other	0 (0.0)	13 (6.0)	0 (0.0)	11 (4.4)	0.31
Endocrine therapy taken as part of the COVID deferral, n (%)	0 (0.0)	0 (0.0)	6 (22.2)	0 (0.0)	<0.01
ER Positive, n (%)	68 (84.0)	175 (83.7)	21 (80.8)	196 (85.6)	0.90
PR Positive, n (%)	58 (71.6)	153 (73.2)	18 (69.2)	162 (71.1)	0.95
HER2 Positive, n (%)	8 (9.9)	25 (11.9)	9 (39.1)	18 (8.2)	<0.01
Grade 1, n (%)	25 (31.3)	71 (34.6)	6 (26.1)	73 (33.5)	
Grade 2, n (%)	38 (47.5)	81 (39.5)	8 (34.8)	92 (42.4)	
Grade 3, n (%)	17 (21.3)	53 (25.9)	9 (39.1)	53 (24.3)	0.06
Clinical T-stage, mean (SD)	1.1 (0.8)	1.2 (0.8)	1.5 (1.1)	1.2 (0.9)	0.24
Clinical N-stage, mean (SD)	0.1 (0.3)	0.1 (0.3)	0.2 (0.6)	0.1 (0.3)	0.11
Distant metastases present, n (%)	2 (2.3)	3 (1.4)	1 (3.7)	6 (2.4)	0.80
***** Treatment Data**	***	***	***	***	***
Initial treatment recommendation (if not in the COVID pandemic in 2020), n (%)					
Surgery first	73 (83.0)	179 (82.5)	17 (63.0)	209 (83.3)	
Neoadjuvant therapy	15 (17.0)	38 (17.5)	10 (37.0)	42 (16.7)	0.07
Type of Neoadjuvant therapy recommended (if not in the COVID pandemic in 2020), n (%)					
Chemotherapy	14 (93.3)	33 (84.6)	9 (90.0)	35 (81.4)	
Endocrine therapy	1 (6.7)	6 (15.4)	1 (10.0)	8 (18.6)	0.69
Ultimate surgical treatment of breast, n (%)					
Lumpectomy	57 (79.2)	147 (81.2)	13 (81.3)	171 (82.2)	
Mastectomy	15 (20.8)	34 (18.8)	3 (18.8)	37 (17.8)	0.95
Ultimate surgical treatment of axilla, n (%)					
Sentinel node biopsy	51 (69.9)	110 (60.4)	11 (64.7)	127 (60.8)	
Axillary dissection	1 (1.4)	3 (1.6)	1 (5.9)	5 (2.4)	
None	21 (28.8)	69 (37.9)	5 (29.4)	77 (36.8)	0.39

BMI: Body Mass Index; SD: standard deviation; IQR: interquartile range; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor; COVID: coronavirus disease; NOS: not otherwise specified

During the initial screening moratorium (Early phase 2020), only 27 patients presented with breast cancer compared to 88 patients in the same time period in 2019 (Table 2). Patients in Early phase 2020 who presented with a new diagnosis of breast cancer were noted to have a higher BMI (30.6 *versus* 28.1, $p = 0.05$).

All tumors were self-detected (100%) during Early phase 2020, compared with 28% (n = 25) in the same time period the year prior.

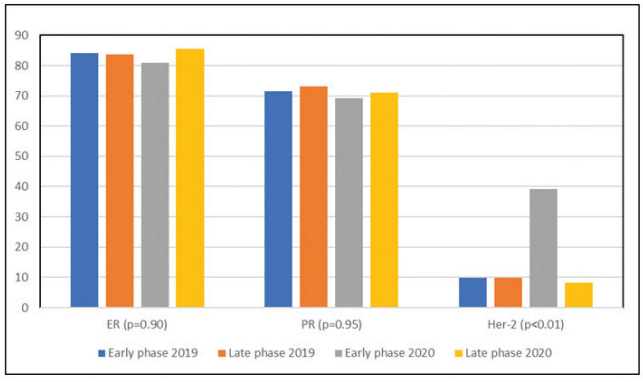


Figure 1. Percent of patients with ER, PR and HER2 positivity by COVID pandemic phase

HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor

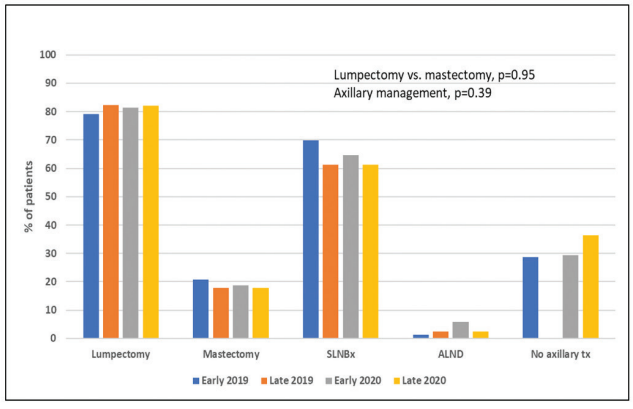
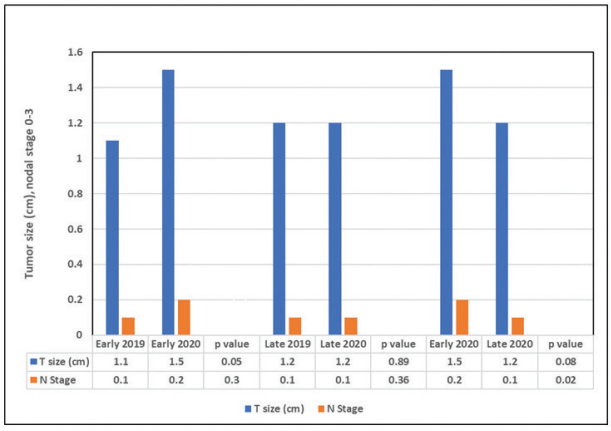


Figure 2. Surgical treatment by study phase



	Early 2019	Early 2020	p value	Late 2019	Late 2020	p value	Early 2020	Late 2020	p value
T size (cm)	1.1	1.5	0.05	1.2	1.2	0.89	1.5	1.2	0.08
N Stage	0.1	0.2	0.3	0.1	0.1	0.36	0.2	0.1	0.02

Figure 3. Tumor size and nodal status by study phase

There was no difference in tumor type, grade or receptor status when compared to the tumors diagnosed the previous year, but a slightly larger tumor size was observed among the new diagnoses during the pandemic (average T-stage of 1.5 *versus* 1.1, $p = 0.05$, Table 2 and Figure 3) although analysis of the entire cohort included in the study did not show significance ($p = 0.24$, Table 1).

During Early phase 2020, patients were more likely to be treated with neoadjuvant therapy (37.0 *versus* 17.0%, $p = 0.03$). There was no difference between the type of neoadjuvant treatment that was chosen (endocrine versus chemotherapy, $p = 0.67$). Only 6 out of 21 patients (21.4%) who were ER positive agreed to take endocrine therapy during the deferral period. There was no difference in surgical treatment of the breast or the axilla when surgery was eventually performed (Table 2).

Screening mammography resumed in the latter part of 2020 and was compared to the same time period the previous year (Late phase 2019 to 2020, Table 3). Patients diagnosed with breast cancer in the second half of 2020 were older than those diagnosed the year before (64 *versus* 61.5 years, $p = 0.04$). All other clinical characteristics, T- and N- stage and treatment types were similar.

When Early phase 2020 was compared to Late phase 2020 (Table 4), patients who presented with breast cancer in the first part of the year were younger (54.8 *versus* 64 years, $p<0.01$). HER2 positivity was higher in Early phase 2020 (11.5 *versus* 8.2%, $p = 0.02$) but there were no differences in grade or hormone receptor status between groups. The average N stage was higher when compared to after resumption of screening (0.2 *versus* 0.1, $p = 0.02$) but this did not increase use of axillary node dissection ($p = 0.39$). Neoadjuvant therapy was recommended in 37.0% of cases during the Early phase 2020 compared with 17.0% during the Late phase 2020 ($p = 0.01$).

Discussion and Conclusion

The abrupt cessation of screening imaging and elective procedures immediately caused concern about worse cancer outcomes. Within one week of the lockdown, a strategy was developed locally to address management of new cancer patients by optimizing use of endocrine therapy where possible until the COVID-19 Pandemic Breast Cancer Consortium recommendations were released (11). Other guidelines were generated over the next several months that supported similar strategies (12-14).

During the Early phase 2020, which represents our time of strict COVID lockdown, we observed a decrease in the number of patients with a new breast cancer diagnosis. As expected, all newly diagnosed cancers were self-detected with a statistically significant difference in mean tumor size. It is not surprising that more of these self-palpated cancers were HER2 positive which is indicative of a more aggressive subtype. We hypothesize that patients, upon learning about the pause of routine screening, were more likely than before to perform a self-examination and, as a result, were noticing these tumors. Once routine screening resumed, however, no significant difference in tumor size was seen between patients whose cancers were detected by imaging compared to self-examination.

Neoadjuvant therapy was recommended more often in the first phase, as surgeries including for oncologic reasons were halted at this time. The impact of delay to surgical treatment in breast cancer patients has been studied in large datasets and is predicted to result in worse all-cause mortality (15, 16). The effects of the pandemic-related

treatment delays on survival and recurrence in patients who chose to decline neoadjuvant endocrine therapy, as was our experience, will have to be further evaluated in the future. In Late phase 2020, it was determined that breast surgery could occur safely (17, 18). Oncologic teams resumed pre-pandemic protocols which allowed most patients to have surgery as a first treatment.

Similar to our local experience, screening mammography rates nationally increased and remain elevated once moratoriums were removed despite the persistence of COVID, although underserved populations are less likely to resume screening or more likely to cancel and not reschedule (19-21). We planned for the resumption of screening almost as soon as the moratorium started, due to recognition of the importance of planning and messaging (22, 23).

Table 2. Comparison of patient and breast cancer characteristics Early phase 2019 to Early phase 2020

	Phase 1 2019	Phase 1 2020	*p*-value
n (%)	88 (76.5)	27 (23.5)	
Age, mean (SD)	60.0 (14.6)	54.8 (18.6)	0.13
BMI, median (IQR)	28.1 (8.7)	30.6 (13.1)	0.05
***** Method of Detection**	*******	*******	*******
Method of detection, n (%)			
None	0 (0.0)	0 (0.0)	
Imaging	63 (71.6)	0 (0.0)	
Self-detected	25 (28.4)	27 (100.0)	
Clinically detected	0 (0.0)	0 (0.0)	<0.01
***** Cancer Specific Data**			
Grade, n (%)			
Grade 1	25 (31.3)	6 (26.1)	
Grade 2	38 (47.5)	8 (34.8)	0.22
Grade 3	17 (21.3)	9 (39.1)	
Tumor Specific Data			
ER positive status, n (%)	68 (84.0)	21 (80.8)	0.71
PR positive status, n (%)	58 (71.6)	18 (69.2)	0.82
HER2 positivity, n (%)	8 (9.9)	3 (11.5)	0.35
Stage			
Clinical T-stage, mean (SD)	1.1 (0.8)	1.5 (1.1)	0.05
Clinical N-stage, mean (SD)	0.1 (0.3)	0.2 (0.6)	0.30
Distant metastases present, n (%)	2 (2.3)	1 (3.7)	0.68
***** Treatment Data**	*******	*******	*******
Initial treatment recommendation, n (%)			
Surgery first	73 (83.0)	17 (63.0)	
Neoadjuvant therapy	15 (17.0)	10 (37.0)	0.03
Type of neoadjuvant therapy, n (%)			
Chemotherapy	14 (93.3)	9 (90.0)	
Endocrine therapy	1 (6.7)	1 (10.0)	0.76
Ultimate surgical treatment of breast, n (%)			
Lumpectomy	57 (79.2)	13 (81.3)	
Mastectomy	15 (20.8)	3 (18.8)	0.85
Ultimate surgical treatment of axilla, n (%)			
Sentinel node biopsy	51 (69.9)	11 (64.7)	
Axillary dissection	1 (1.4)	1 (5.9)	
None	21 (28.8)	5 (29.4)	0.52

BMI: Body Mass Index; SD: standard deviation; IQR: interquartile range; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor

Nearly the same number of mammograms were performed in 2020 as in 2019 using extended hours and weekend schedules to accommodate social distancing guidelines and the backlog patients. Our institution diagnosed 279 patients with breast cancer during the pandemic in 2020, 92% of the number of patients diagnosed in 2019 and less of a decrease than we had feared.

Once screening imaging or routine clinical examination is not available, patients become reliant on self-examination for cancer detection. During the Early phase 2020, the time of strict COVID lockdown, the number of patients presenting with a new cancer diagnosis decreased as all newly diagnosed cancers were self-detected. A small, statistically significant difference was seen in mean tumor size, but this did not impact ultimate surgical treatment. No significant difference in tumor

Table 3. Comparison of patient and breast cancer characteristics: Late phase 2019 *versus* Late phase 2020

	Phase 2 2019	**Phase 2 2020**	***p*-value**
n (%)	216 (46.2)	252 (53.8)	
Age, mean (SD)	61.5 (13.2)	64.0 (13.1)	0.04
BMI, median (IQR)	29.2 (9.2)	28.2 (8.7)	0.49
***** Method of Detection**	*******	*******	*******
None	1 (0.5)	2 (0.8)	
Imaging	141 (65.3)	188 (74.6)	
Self-detected	65 (30.1)	56 (22.2)	
Clinically detected	9 (4.2)	6 (2.4)	0.13
***** Cancer Specific Data**	*******	*******	*******
Grade, n (%)			
Grade 1	71 (34.6)	73 (33.5)	
Grade 2	81 (39.5)	92 (42.2)	
Grade 3	53 (25.9)	53 (24.3)	0.85
Tumor Specific Data			
ER positive status, n (%)	175 (83.7)	196 (85.6)	0.59
PR positive status, n (%)	153 (73.2)	162 (71.1)	0.62
HER2 positivity, n (%)	25 (11.9)	18 (8.2)	0.32
Stage			
Clinical T-stage, mean (SD)	1.2 (0.8)	1.2 (0.9)	0.89
Clinical N-stage, mean (SD)	0.1 (0.3)	0.1 (0.3)	0.36
Distant metastases present, n (%)	3 (1.4)	6 (2.4)	0.43
***** Treatment Data**	*******	*******	*******
Initial treatment recommendation, n (%)			
Surgery first	178 (82.4)	209 (82.9)	
Neoadjuvant therapy	38 (17.6)	43 (17.1)	0.88
Type of neoadjuvant therapy, n (%)			
Chemotherapy	32 (82.1)	36 (81.8)	
Endocrine therapy	7 (17.9)	8 (18.2)	0.98
Ultimate surgical treatment of breast, n (%)			
Lumpectomy	146 (80.7)	171 (82.2)	
Mastectomy	35 (19.3)	37 (17.8)	0.69
Ultimate surgical treatment of axilla, n (%)			
Sentinel node biopsy	111 (61.0)	128 (61.2)	
Axillary dissection	1 (0.5)	5 (2.4)	
Completion axillary dissection	2 (1.1)	0 (0.0)	
None	68 (37.4)	76 (36.4)	0.21

BMI: Body Mass Index; SD: standard deviation; IQR: interquartile range; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor

size was seen between patients whose cancers were detected by imaging compared to self-examination once imaging was performed. In Late phase 2020, care returned to normal and most patients underwent surgery first when it was found that breast surgery could occur safely (17, 18).

Tonneson et al. (24) did not see a difference in the stage of presentation when looking at patients who presented between March and August 2020. We were able to also look at patients in the six months after screening resumed to determine if there was any difference in presentation. Sensitivity analysis revealed a marginal difference in T-stage (1.5 *versus* 1.1, $p = 0.08$) and a small but statistically significant difference in N stage (0.2 *versus* 0.1, $p = 0.02$). Ultimately, we did not see a resulting difference between lumpectomy and mastectomy rates, nor was there a difference in axillary treatment (Figure 2).

Early-stage breast cancer diagnosis relies on effective screening programs, facilitates greater rates of breast conservation and allows some women to avoid radiation and axillary sentinel node biopsy as part of the Choosing Wisely campaign (25-27). A logical consequence

Table 4. Comparison of patient and breast cancer characteristics: Early phase 2020 *versus* Late phase 2020

	Phase 1 2020	Phase 2 2020	p-value
n (%)	27 (9.7)	252 (90.3)	
Age, mean (SD)	54.8 (18.6)	64.0 (13.1)	<0.01
BMI, median (IQR)	30.6 (13.1)	28.2 (8.7)	0.06
***** Method of Detection**	*******	*******	*******
Method of Detection, n (%)			
None	0 (0.0)	2 (0.8)	
Imaging	0 (0.0)	188 (74.6)	
Self-detected	27 (100.0)	56 (22.2)	
Clinically detected	0 (0.0)	6 (2.4)	<0.01
***** Cancer Specific Data**	*******	*******	*******
Grade, n (%)			
Grade 1	6 (26.1)	73 (33.5)	
Grade 2	8 (34.8)	92 (42.2)	
Grade 3	9 (39.1)	53 (24.3)	0.30
Tumor Specific Data			
ER positive status, n (%)	21 (80.8)	196 (85.6)	0.51
PR positive status, n (%)	18 (69.2)	162 (71.1)	0.85
HER2 positivity, n (%)	3 (11.5)	18 (8.2)	0.02
Stage			
Clinical T-stage, mean (SD)	1.5 (1.1)	1.2 (0.9)	0.08
Clinical N-stage, mean (SD)	0.2 (0.6)	0.1 (0.3)	0.02
Distant metastases present, n (%)	1 (3.7)	6 (2.4)	0.68
***** Treatment Data**	*******	*******	*******
Initial treatment recommendation, n (%)			
Surgery first	17 (63.0)	209 (82.9)	
Neoadjuvant therapy	10 (37.0)	43 (17.1)	0.01
Type of neoadjuvant therapy, n (%)			
Chemotherapy	9 (90.0)	36 (81.8)	
Endocrine therapy	1 (10.0)	8 (18.2)	0.53
Ultimate surgical treatment of breast, n (%)			
Lumpectomy	13 (81.3)	171 (82.2)	
Mastectomy	3 (18.8)	37 (17.8)	0.92
Ultimate surgical treatment of axilla, n (%)			
Sentinel node biopsy	11 (64.7)	128 (61.2)	
Axillary dissection	1 (5.9)	5 (2.4)	
None	5 (29.4)	76 (36.4)	0.62

BMI: Body Mass Index; SD: standard deviation; IQR: interquartile range; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor

of delayed screening during the pandemic would be a subsequent increase in mastectomy rates in the setting of higher numbers of palpable advanced stage cancers, for which breast conservation is not an option. Although other studies have shown an impact on surgery (28, 29), we did not observe that impact.

It should be noted, however, that the findings of this study do not negate or refute the established data on the mortality reduction seen with established screening mammography protocols. Our data reflects short-term mammography cessation of three months and supports the need for quick resumption of screening to prevent longer delays in cancer detection. Even a short period of screening stoppage can result in a longer delay to presentation due to patient hesitance. Studies that look at longer interruptions in screening showed significantly worse alterations in both stage and surgical treatment (30). Concerns about the need for a proactive approach by radiology to ensure timely screening resumption are well documented (31).

This study reflects a single institution's experience with breast cancer and the moratorium against screening imaging during the initial phases of the COVID-19 pandemic. As a result, the single institution design limits generalizability and small numbers preclude discrete statistical analysis.

Despite these limitations, our study adds important information and raises points for discussion. It may be appropriate to revisit the recommendation to avoid self-examination, as it can be a very valuable tool to detect new breast cancer, especially when routine screening is not available. Our study contributes valuable data to evaluate the impact of short interruptions to breast cancer radiology screening on stage at diagnosis. We did not see any difference between lumpectomy and mastectomy rates or axillary management when comparing Early or Late phase by years or by yearly totals themselves. At the time of manuscript preparation, there was no published literature specifically evaluating the impact of the pandemic on breast conservation rates or axillary management with such a short interval of screening deferment; thus, this paper is additive to available information. The implications of these findings are still unclear. Distinct differences in cancer presentation during the initial pandemic phase were observed, but these did not appear to be associated with clinically significant differences in treatment. Additional long-term follow-up is necessary to determine the impact of this screening moratorium and the resulting treatment delays on breast cancer recurrence and survival.

In conclusion, patients who presented with breast cancer during the COVID-19 pandemic in the absence of screening mammography were more likely to be younger, have a higher BMI, present with HER2 positive cancers, be node positive, and receive neoadjuvant treatment most commonly with endocrine therapy. Despite these differences, ultimate surgical management was not impacted by pandemic-related screening cessation.

Ethics Committee Approval: No ethical approval was obtained because this study did not involve a prospective evaluation, did not involve laboratory animals and only involved non-invasive procedures (e.g. faecal samples, voided urine etc).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.M., D.J.; Conception: H.M., A.K.F., D.J.; Design: H.M., D.J., A.P.C.; Data Collection: H.M., D.J., S.N.; Analysis or Interpretation: J.C., H.M., D.J., S.N., A.P.C.; Literature Search: H.M., S.N., D.J.; Writing: H.M., D.J., J.C., S.N.

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Original Article

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Salvage Mastectomy Is not the Treatment of Choice for Aggressive Subtypes of Ipsilateral Breast Cancer Recurrence: A Single-Institution Retrospective Study

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ABSTRACT

Objective: Patients with triple-negative (TN) or human epidermal growth factor 2 (HER2)-enriched ipsilateral breast cancer recurrence (IBCR) seem to be excluded from a second breast-conserving surgery (BCS) under the assumption that salvage mastectomy would provide better oncological outcomes. The objective of this study was to describe the clinical features of these patients, to compare the two surgical alternatives (salvage mastectomy *versus* second BCS) in terms of oncological results, and to identify independent factors influencing prognosis and surgical treatment.

Materials and Methods: We retrospectively reviewed all the consecutive patients with histologically confirmed TN or HER2-enriched IBCR. Disease-free survival (DFS), distant disease-free survival (DDFS), overall survival (OS), and breast cancer-specific survival (BCSS) were analyzed and compared between the two groups.

Results: Eighty-five patients were affected by TN or HER2-enriched IBCR. The majority of patients (72.9%) were treated with salvage mastectomy. There was no significant difference in terms of DFS between patients receiving a second BCS or mastectomy (p = 0.596). However, patients undergoing a second BCS had significantly better DDFS, OS and BCSS compared to mastectomy (p = 0.009; p = 0.002; p = 0.001, respectively). Tumor dimension <16 mm was found to significantly increase the probability of receiving a second BCS and positively affects recurrence and survival outcomes. Salvage mastectomy represents an independent poor prognostic factor for OS and BCSS.

Conclusion: Salvage mastectomy is not always necessary and it does not seem to increase survival compared to a second BCS. In patients with small aggressive subtypes of IBCR, a second conservative approach can still be evaluated and offered, presenting acceptable loco-regional control and survival.

Keywords: Breast cancer; triple-negative breast cancer; HER2; recurrence; breast-conserving surgery

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Key Points

- Up to 10% of women with breast cancer (BC) treated with breast-conserving surgery (BCS) and subsequent radiation can experience ipsilateral breast cancer recurrence (IBCR), within 10 years.
- Triple-negative and human epidermal growth factor 2-enriched BC subtypes have a higher risk of IBCR. The aggressive nature of these subtypes may appear to exclude such patients from receiving a second BCS, based on the notion that salvage mastectomy would result in improved oncological results.
- Tumor dimension <16 mm was found to significantly increase the probability of receiving a second BCS for aggressive subtypes of IBCR.
- In patients with aggressive subtypes of IBCR, salvage mastectomy should not be considered the treatment of choice, and it does not seem to increase survival compared to a second BCS.
- A second conservative approach can still be evaluated and should be offered, when technically feasible, presenting acceptable loco-regional control and survival.

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Introduction

The developments of breast cancer (BC) treatments have reflected the growing body of knowledge about BC biology (1). Different types of BC show substantial heterogeneity in spite of a common tissue of origin (2). Extensive research has taken place for subtyping BC at a molecular and genetic level, and indeed, gene expression profiling of BC has confirmed that it does not represent a single entity but a group of biologically distinct diseases (3). Triple-negative (TN) BC accounts for 10-20% of invasive breast neoplasms (2, 4), carrying a poorer prognosis than luminal-like tumors and with heterogeneous clinical presentation, behavior, and pathology (3, 4). Human epidermal growth factor receptor 2 (HER2) is a membrane tyrosine kinase and when activated affects cell proliferation and survival (5). HER2 is overexpressed in about 15–20% of BCs, representing a major driver for tumor development, progression, and poor prognosis (6). The conventional treatment for early-stage BC is breast-conserving surgery (BCS) followed by adjuvant radiotherapy (7). Even in patients affected by aggressive phenotypes, such as TN and HER2-enriched BC, when compared to mastectomy, BCS did not produce worse oncological results (8). However, roughly 5–10% of women treated with BCS and subsequent radiation can experience ipsilateral breast cancer recurrence (IBCR), within 10 years (7, 9). Previous studies have reported a higher risk of IBCR in TN and HER2-enriched BC subtypes (8, 10-13). The aggressive nature of TN and HER2-enriched BC subtypes may appear to exclude such patients from receiving a second BCS in the event of IBCR, based on the notion that salvage mastectomy would result in improved oncological results. Salvage mastectomy, despite this, may not totally eliminate the risk of a second loco-regional recurrence, metastatic disease, or cancer–related mortality (14). Up to now, there have been no prospective randomized studies to show that salvage mastectomy is preferable to a second BCS in terms of oncological safety for patients with aggressive subtypes of IBCR. The prognostic difference between repeat conserving therapy and salvage mastectomy for IBCR has been studied extensively (15-20). Salvage mastectomy should not be considered the optimal treatment for IBCR, according to two retrospective analyses conducted at our institution, and it does not appear to improve prognosis when compared to repeat BCS (21, 22) but specific long-term oncological outcomes of patients with aggressive subtypes of IBCR have not been evaluated. The objective of this study was to describe the clinical features of patients with aggressive subtypes of IBCR, to compare the two surgical alternatives (either salvage mastectomy or second BCS) in terms of oncological results, and to identify independent factors influencing prognosis and surgical treatment.

Materials and Methods

Design of the Study and Patient Management

Between January 2008 and December 2018, we analyzed all the consecutive patients with histologically confirmed TN or HER2-enriched IBCR who were treated at the Breast Unit of IRCCS Humanitas Research Hospital (Milan, Italy). The clinical characteristics of these patients were reported and the two treatment methods (second BCS or salvage mastectomy) were examined and compared. The following exclusion criteria were used: luminal-like IBCR; new ipsilateral primary tumor; disease-free interval (DFI) ≤6 months; and follow-up <36 months. The indication for re-irradiation was given based on particular clinical and pathological risk factors; patients did not receive routine adjuvant radiotherapy. Patients undergoing re-irradiation received either a hypofractionated radiation dose regimen of 40.5 Gy on the whole breast and 48 Gy on the tumor bed in 15 fractions overall or conventionally–fractionated whole breast irradiation of 50 Gy in 25 fractions with a tumor bed boost of 10 Gy in 5 fractions. Each patient gave informed consent for the operation and collection of clinical data.

Definitions

There are two types of IBCR. True recurrence is defined as the reappearance of malignant cells that were not eliminated by the initial BCS or adjuvant radiation, whereas, a new ipsilateral primary tumor is defined as a *de novo* malignancy originating from mammary epithelial cells of the remaining breast tissue (23). Although there are no conventional classification guidelines, we categorized IBCR as either true recurrence or a new primary based on biology, histology, and tumor site (21, 22). If the biology and histology of an IBCR matched that of the primary BC and it was within 3 cm of the primary tumor bed or in the surgical scar, it was considered true recurrence. If the IBCR had a change in biology or histology, or changed from infiltrating carcinoma to carcinoma *in situ*, or was more than 3 cm from the previous BC site, it was considered a new primary. TN BC was defined as absence of estrogen and progesterone receptors and negativity for HER2. HER2 status was assessed by immunohistochemistry and defined as negative if the score was 0/1+, equivocal if the score was 2+, or positive if the score was 3+. Equivocal cases were further assessed by fluorescent *in situ* hybridization. HER2-enriched and TN BCs were defined as aggressive subtypes. All the patients with IBCR who were analyzed were affected by aggressive subtypes of true recurrences.

DFI was defined as the time between the first BCS for primary BC and the onset of IBCR. Disease-free survival (DFS) was defined as the period from the date of IBCR surgery (either salvage mastectomy or second BCS) until the date of any tumor development including loco-regional recurrence or distant metastasis. Distant disease-free survival (DDFS) was defined as the duration between the date of IBCR surgery and the date of distant metastasis identification. Overall survival (OS) was defined as the time interval from IBCR treatment to death from any cause or to the date of last contact. Breast cancer-specific survival (BCSS) was calculated by choosing BC as the cause of death and recording the follow-up time after censoring deaths from other causes.

Statistical Analysis

Patients were chosen from our prospectively maintained institutional database and retrospectively analyzed. Categorical variables were compared using the chi-square test or Fisher's Exact test, as appropriate. The recurrence and survival curves were generated using the Kaplan–Meier method. The log-rank test was performed to compare the oncological outcomes of the two treatment groups (salvage mastectomy *versus* second BCS) considering demographic and tumor features. Last follow-up was updated up to February 16, 2022. Follow-up was ≥36 months in all patients with aggressive subtypes of IBCR and no patient was lost to follow-up. A logistic regression model was used in the multivariate analysis to find independent predictors of surgical therapy for aggressive subtypes of IBCR. Any variable associated with the result at the univariate analysis was included in the multivariate analysis (inclusion cut-off value $p<0.05$). Using the Cox proportional hazards model, a multivariate analysis was performed to identify independent factors influencing the prognosis of patients with aggressive subtypes of IBCR. Statistical significance was set at $p<0.05$. IBM SPSS, version 25.0 was used for data analyses and figures (IBM Inc., Armonk, NY, USA).

Results

Characteristics of Patients

A total of 309 patients with IBCR underwent surgical treatment at our institution. Of these, 85 patients were affected by aggressive biological subtypes of IBCR. Overall, 56 (65.9%) and 29 (34.1%) patients had TN and HER2-enriched IBCR, respectively, after a median DFI of 44 months (range, 8–160 months). The median age was 60 years (range, 32–87 years), and 48 (56.5%) patients were post-menopausal. One patient was affected by *BRCA1*-associated TN IBCR. The median diameter of IBCR was 16 mm (range, 3–46 mm). The majority of patients (72.9%) with aggressive subtypes of IBCR were treated with salvage mastectomy. Twenty-three (27.1%) patients underwent a second BCS and of these, 9 (39.1%) patients underwent re-irradiation. Regarding adjuvant treatment, 49 (57.7%) and 14 (16.5%) patients underwent post-operative chemotherapy and Trastuzumab, respectively. Table 1 details demographic, tumor, and post-operative characteristics of patients with aggressive subtypes of IBCR.

Oncological Outcomes and Independent Factors for Treatment and Prognosis

The median follow-up was 77 months (range, 36–224 months). At the time of the last follow-up, 32 patients (/85, 37.7%) had re-recurrence. In the BCS group, 7 (/23, 30.4%) and 3 patients (/23, 13.0%) had loco-regional recurrence and distant metastases, respectively. In the mastectomy group, 22 (/62, 35.5%) patients developed distant recurrence and of these, 13 patients developed metastatic disease associated with loco-regional recurrence. In the BCS group, all patients with loco-regional recurrence were surgically treated with mastectomy. In the mastectomy group, all patients who developed distant metastases were treated with chemotherapy and in addition 5 patients underwent excision of isolated skin metastasis. Overall, 25 patients (/85, 29.4%) died; 6 (/23, 26.1%) and 19 patients (/62, 30.7%) in the BCS and mastectomy groups, respectively. The 1-, 3-, and 5-year DFS rates were 95.8%, 69.1%, 43.2% and 78.4%, 63.3%, 49.4% in patients receiving a second BCS or salvage mastectomy, respectively. The 1-, 3-, and 5-year DDFS rates were 95.8%, 95.8%, 88.5% and 78.4%, 63.3%, 49.4% in patients receiving a second BCS or salvage mastectomy, respectively. The 1-, 3-, and 5-year OS rates were 95.8%, 87.5%, 87.5% and 93.5%, 76.6%, 55.7% in patients receiving a second BCS or salvage mastectomy, respectively. The 1-, 3-, and 5-year BCSS rates were 95.8%, 95.8%, 95.8% and 96.7%, 79.1%, 57.5% in patients receiving a second BCS or salvage mastectomy, respectively. There was no significant difference in terms of DFS between patients with aggressive subtypes of IBCR receiving a second BCS or salvage mastectomy ($p = 0.596$). However, patients with aggressive subtypes of IBCR undergoing a second BCS had significantly better DDFS, OS, and BCSS compared to salvage mastectomy ($p = 0.009$, $p = 0.002$, and $p = 0.001$, respectively). Figures 1-4 show the Kaplan–Meier recurrence and survival curves of patients with aggressive subtypes of IBCR. Comparison of oncological outcomes is summarized in Table 2. Table 3 details and compares demographic and tumor characteristics of patients with aggressive subtypes of IBCR, according to the surgical method used (second BCS *versus* salvage mastectomy). At univariate analysis, histotype, dimension, Ki67, and vascular invasion were significantly different between the two groups ($p = 0.021$, $p = 0.001$, $p = 0.040$, and $p = 0.022$, respectively). However, in multivariate analysis, only one independent predictive factor of treatment for patients with aggressive subtypes of IBCR was identified. Tumor dimension <16 mm [78.3% *versus* 38.7%, odds ratio (OR) = 3.602, 95% confidence interval (CI) = 1.534–8.459, $p = 0.003$] was found to significantly increase the probability of receiving a second BCS for aggressive

Table 1. Characteristics of 85 patients with aggressive biological subtypes of ipsilateral breast cancer recurrence

Characteristics	Number (%)/Median (range)
Patients	
Age (years)	60.0 (32.2–87.4)
Post-menopausal	48 (56.5%)
BRCA1-mutation carrier	1 (1.1%)
Tumor	
Histotype	
- Ductal	79 (92.9%)
- Lobular	6 (7.1%)
Grading	
- 1	4 (4.7%)
- 2	17 (20.0%)
- 3	64 (75.3%)
Stage	
- pT1a	4 (4.7%)
- pT1b	15 (17.7%)
- pT1c	49 (57.7%)
- pT2	16 (18.8%)
- pT3-4	1 (1.1%)
- Nx	36 (42.4%)
- pN0	44 (51.8%)
- pN1	3 (3.5%)
- pN2	2 (2.3%)
Dimension (mm)	16 (3–46)
Biological subtypes	
- HER2-enriched	29 (34.1%)
- Triple negative	56 (65.9%)
Ki67 (%)	45 (7-90)
Vascular invasion	22 (25.9%)
Treatment	
- BCS	23 (27.1%)
- Mastectomy	62 (72.9%)
- Neo-adjuvant chemotherapy	3 (3.5%)
- Radiotherapy	9 (10.6%)
- Endocrine therapy	4 (4.7%)
- Adjuvant chemotherapy	49 (57.7%)
- Trastuzumab	14 (16.5%)

BCS: breast-conserving surgery; HER2: HER2 evaluated either on immunohistochemistry or on *in situ* hybridization; according to the ASCO CAP guidelines; HER2: human epidermal growth factor receptor 2

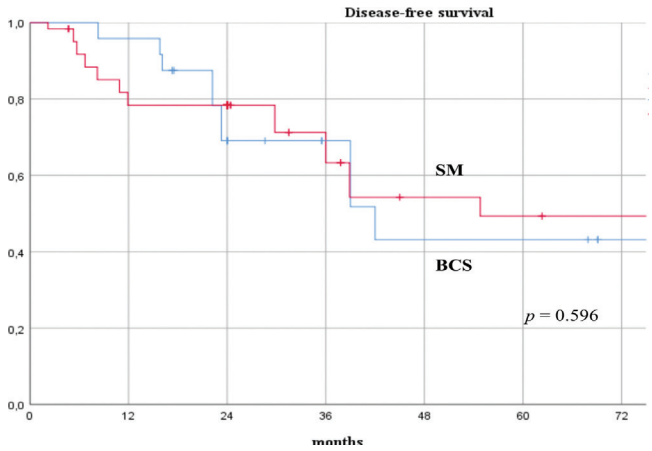

Figure 1. Disease-free survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

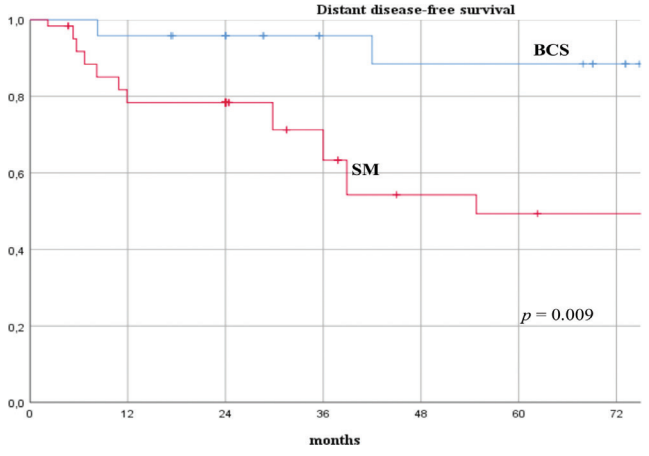

Figure 2. Distant disease-free survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

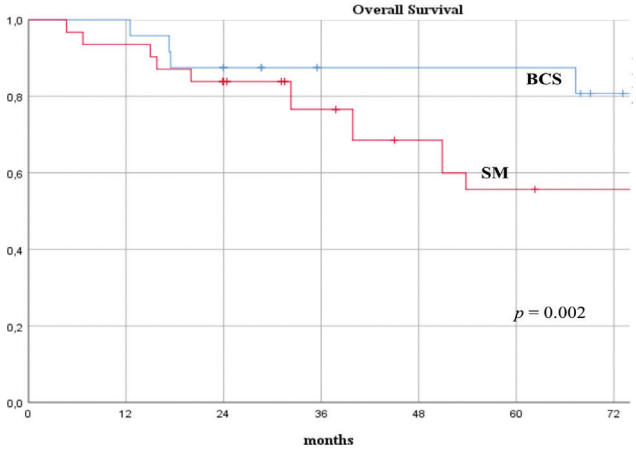

Figure 3. Overall survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

subtypes of IBCR. Additionally, dimension of the recurrent tumor <16 mm, DFI ≥44 months, and absence of vascular invasion were found to significantly increase both recurrence and survival outcomes. On the contrary, salvage mastectomy was significantly associated with a decreased OS and BCSS (p = 0.002 and p = 0.002, respectively). The univariate and multivariate analyses are summarized in Tables 3 and 4.

Table 2. Oncological outcomes after second breast cancer surgery (breast-conserving surgery versus mastectomy) of patients with aggressive biological subtypes of ipsilateral recurrence

Outcomes	BCS	Mastectomy	*p*-value
DFS rate			
- 1-year	95.8%	78.4%	
- 3-year	69.1%	63.3%	0.596
- 5-year	43.2%	49.4%	
DDFS rate			
- 1-year	95.8%	78.4%	
- 3-year	95.8%	63.3%	0.009[a]
- 5-year	88.5%	49.4%	
OS rate			
- 1-year	95.8%	93.5%	
- 3-year	87.5%	76.6%	0.002[a]
- 5-year	87.5%	55.7%	
BCSS rate			
- 1-year	95.8%	96.7%	
- 3-year	95.8%	79.1%	0.001[a]
- 5-year	95.8%	57.5%	

BCS: breast-conserving surgery; DFS: disease-free survival; DDFS: distant disease-free survival; OS: overall survival; BCSS: breast cancer-specific survival; [a]: statistically significant

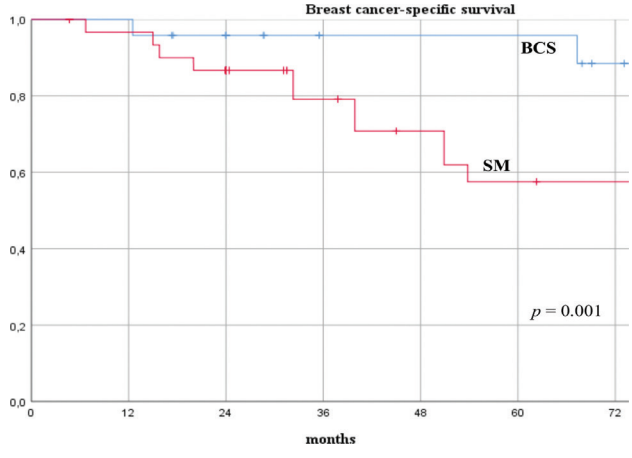

Figure 4. Breast cancer-specific survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

Discussion and Conclusion

To begin with, a higher risk of IBCR in HER2-enriched and TN biological subtypes has been reported. Therefore, the surgical management of this category of aggressive recurrence remains a matter of debate. In the review performed by Wang et al. (8), the authors analyzed the results of 15,312 BC patients and reported that the TN biological subtype presented an increased risk of both IBCR and distant metastasis compared with non-TN subtypes (OR = 1.88, 95% CI = 1.58–2.22; OR = 2.12, 95% CI = 1.72–2.62, respectively). Corso et al. (10) reported that TN and HER2-enriched breast neoplasms were significantly associated with an increased risk of IBCR (p = 0.008 and p = 0.020, respectively). Lowery et al. (12) analyzed a total of 12,592 patients and reported that luminal-like tumors had a lower risk of IBCR than both TN (OR = 0.38, 95% CI = 0.23–0.61) and HER2-

Table 3 Comparison of clinicopathological characteristics of patients with aggressive biological subtypes of ipsilateral breast cancer recurrence undergoing either breast-conserving surgery or mastectomy

Characteristics	BCS (No. 23) Tot. (%)/ median (range)	Mastectomy (No. 62) Tot. (%)/ median (range)	Univariate analysis	Multivariate analysis
			p-value	*p*-value OR (95% CI)
Demographic				
Age (years)	57.1 (38.3–87.4)	61.1 (32.2–86.3)		
- <60	13 (56.5%)	29 (46.8%)	0.223	-
- ≥60	10 (43.5%)	33 (53.2%)	-	
Menopausal status				
- Pre-menopausal	5 (21.7%)	32 (51.6%)	0.749	-
- Post-menopausal	18 (78.3%)	30 (48.4%)	-	
DFI (months)	46.4 (16.1–126.8)	41.5 (7.9–160.7)		
- <44	9 (39.1%)	32 (51.6%)	0.323	-
- ≥44	14 (60.9%)	30 (48.4%)	-	
Tumor				
Histotype				
- Ductal	21 (91.3%)	58 (93.6%)	0.021[a]	1.873 (0.657–5.338) 0.240
- Lobular	2 (8.7%)	4 (6.4%)	-	-
Grading				
- 1	1 (4.3%)	3 (4.8%)	0.089	-
- 2	2 (8.7%)	15 (24.2%)	-	
- 3	20 (87.0%)	44 (71.0%)	-	
Dimension (mm)	12 (4–28)	17 (3–46)		
- <16	18 (78.3%)	24 (38.7%)	0.001[a]	3.602 (1.534–8.459) 0.003[a]
- ≥16	5 (21.7%)	38 (61.3%)	-	-
Biological subtypes				
- HER2-enriched	5 (21.7%)	24 (38.7%)	0.219	-
- Triple negative	18 (78.3%)	38 (61.3%)	-	
Ki67 (%)	38 (15–80)	45 (7–90)		
- <45	15 (65.2%)	26 (41.9%)	0.040[a]	0.724 (0.238–2.208) 0.571
- ≥45	8 (34.8%)	36 (58.1%)	-	-
Vascular invasion				
- Yes	2 (8.7%)	20 (32.3%)	0.022[a]	1.763 (0.674–4.611) 0.248
- No	21 (91.3%)	42 (67.7%)	-	.

BCS: breast-conserving surgery; OR: odds ratio; CI: confidence interval; DFI: disease-free interval; HER2: human epidermal growth factor 2; HER2: HER2 evaluated either on immunohistochemistry or on *in situ* hybridization, according to the ASCO CAP guidelines, [a]: statistically significant

enriched BCs (OR = 0.34, 95% CI = 0.26–0.45) following BCS. Kim et al. (13) evaluated 2,102 consecutive BC patients who underwent BCS followed by adjuvant radiotherapy, reporting an increased risk of IBCR in the HER2-enriched subtype (OR = 12.24, 95% CI = 2.54–57.96).

Nonetheless, whereas conservative therapy is the gold standard for primary BC (7), there is no strong evidence to support the use a second BCS, as well as salvage mastectomy, as the standard of care in case of aggressive subtypes of ipsilateral recurrence. In general, the prognostic significance of surgery (either salvage mastectomy or second BCS) for IBCR is unknown, and past studies reported conflicting outcomes (17, 18). Recent studies, however, have found that patients with IBCR who were treated with a second BCS had no significantly worse outcomes than those who underwent salvage mastectomy. The meta-analysis performed by Mo et al. (15) included 2,532 patients with IBCR undergoing either salvage mastectomy or a second BCS and showed that the DFS rate after a second conserving treatment was higher than that after mastectomy (OR = 1.87, 95% CI = 1.22–2.86, p = 0.004). Wu et al. (16) reported the results of 475 patients who underwent a second BCS and 1,600 patients who underwent salvage mastectomy for IBCR. During a median follow-up of 130 months, no significant differences were observed in the OS and BCSS rates between the two treatment groups before and after a propensity score matching analysis. The latest studies seem to indicate that a second BCS is a safe and feasible alternative for patients with IBCR. Similarly, our analysis also shows the superiority of the DDFS, OS, and BCSS rates in aggressive biological subtypes of IBCR treated with a second BCS compared to salvage mastectomy.

In patients with IBCR, there is no unanimity on the feasibility and oncological safety of a second course of re-irradiation. The need for a second course of radiation often represents the reason for not offering repeat BCS to patients with IBCR. Although it is often assumed that a second course of adjuvant radiotherapy is not well tolerated by the tissues, resulting in intolerable toxicity, several authors have

Table 4. Multivariate analyses of independent factors influencing the oncological outcomes of patients with aggressive biological subtypes of ipsilateral breast cancer recurrence

Independent factors	DFS HR (95% CI)	*p*-value	DDFS HR (95% CI)	*p*-value	OS HR (95% CI)	*p*-value	BCSS HR (95% CI)	*p*-value
Patient								
Age (years)								
- <60	Reference		Reference		Reference		Reference	
- ≥60	1.800 (0.388–8.354)	0.453	1.600 (0.268–9.570)	0.606	1.231 (0.206–7.348)	0.819	0.583 (0.074–4.584)	0.608
DFI (months)								
- <44	Reference		Reference		Reference		Reference	
- ≥44	0.348 (0.146–0.830)	0.017[a]	0.212 (0.081–0.558)	0.002[a]	0.230 (0.081–0.655)	0.006[a]	0.168 (0.046–0.611)	0.006[a]
Tumor								
Dimension (mm)								
- <16	Reference		Reference		Reference		Reference	
- ≥16	8.065 (2.320–28.034)	0.001[a]	17.011 (3.853–75.099)	0.001[a]	13.881 (2.730–70.579)	0.002[a]	36.773 (4.579–295.322)	0.001[a]
Ki67 (%)								
- <45	Reference		Reference		Reference		Reference	
- ≥45	0.459 (0.165–1.272)	0.134	0.226 (0.067–0.758)	0.016[a]	0.235 (0.057–1.121)	0.070	0.221 (0.040–1.212)	0.082
Vascular invasion								
- Yes	Reference		Reference		Reference		Reference	
- No	7.320 (2.918–18.364)	0.001[a]	13.699 (4.592–40.865)	0.001[a]	9.258 (3.038–28.213)	0.001[a]	12.722 (3.231–50.094)	0.001[a]
Surgery								
- BCS	Reference		Reference		Reference		Reference	
- Mastectomy	0.494 (0.179–1.362)	0.173	0.526 (0.170–1.634)	0.267	0.246 (0.027–0.697)	0.002[a]	0.313 (0.092–0.511)	0.002[a]

DFS: disease-free survival; DDFS: distant disease-free survival; OS: overall survival; BCSS: breast cancer-specific survival; HR: hazard ratio; CI: confidence interval; DFI: disease-free interval; BCS: breast conserving surgery, [a]: statistically significant

found that re-irradiation represents a feasible and safe treatment with promising oncological outcomes. Deutsch (24) reported 5-year OS and DFS rates of 77.9% and 68.5%, respectively, in 39 patients with IBCR treated with a second BCS and a repeat course of external beam radiotherapy. The NRG Oncology/RTOG 1014 phase II clinical trial (25), evaluated the results of 58 patients with IBCR who underwent a second lumpectomy and external beam partial breast re-irradiation. After a median follow-up of 5.5 years, four patients had BC re-recurrence, with a 5-year cumulative incidence of 5% (95% CI = 1–13%). Both the DDFS and OS rates were 95% (95% CI = 85–98%). In our analysis, only nine (39.1%) patients treated with a second BCS underwent a second course of adjuvant radiotherapy. However, no significant difference in terms of DFS between patients receiving repeat BCS or mastectomy was observed.

Oncoplastic breast surgery and prosthetic reconstruction in previously irradiated breasts represent additional matters of controversy in IBCR treatment. Oncoplastic techniques do not delay adjuvant therapies but a second course of radiotherapy may lead to a higher incidence of fat necrosis, volumetric depression, and deformity (26). To reduce the complication rate, there is a frequent tendency to perform oncoplastic techniques, seeking the reconstruction of the breast cone and mobilizing the smallest possible volume of parenchyma (27). Regarding salvage mastectomy followed by prosthetic breast reconstruction, very little literature has evaluated the short-term morbidity and complication rates in previously irradiated breast but patients with IBCR have been discouraged from implant placement. Prior irradiation, according to Lee and Mun (28) increases the risk of reconstructive failure (13.9% *versus* 7.2% not irradiated), total complications (36.6% *versus* 18.8% not irradiated), capsular contracture (15.4% *versus* 4.8% not irradiated), infection (16.1% *versus* 7.9% not irradiated), and seroma (7.5% *versus* 2.9% not irradiated). According to Reish et al. (29) nipple-sparing mastectomy and immediate reconstruction in patients who had radiation is associated with a greater rate of complications and operative revisions. Chen et al. (30) found that patients who previously received radiation, had a higher risk of complications, with a reconstructive failure occurring in 50% of breasts. Given these considerations, we assume that, when technically feasible in terms of cosmetic results, a second BCS with oncoplastic breast reconstruction should be considered the preferred surgical option for aggressive subtypes of IBCR.

Study Limitations

It is important to note that this study has some limitations. To begin with, this is a single-center study subject to limitations due to its retrospective design using observational data. Secondly, the majority of patients with aggressive subtypes of IBCR treated with a second BCS did not undergo repeat radiotherapy. Therefore, the prognostic value of this adjuvant treatment could not be fully evaluated. However, this study also presents some strong points, including the classification method and inclusion criteria which were used enabled the identification of a homogeneous group of patients and no patient was lost to follow-up.

In conclusion, our outcomes corroborate the oncological results of previous studies on IBCR and provide additional evidence in support of a second conserving surgery for the treatment of aggressive biological subtypes. Salvage mastectomy is not always necessary and it does not seem to increase survival compared to a second BCS. This reinforces the concept that the prognosis of TN and HER2-enriched BC recurrence is mainly driven by the biology of the disease, rather than by the extent of surgery. In patients with small (<16 mm) aggressive subtypes of IBCR, a second conservative approach can still be evaluated and offered, presenting acceptable loco-regional control and survival.

Ethics Committee Approval: This study was approved by The Humanitas University Research Ethics Committee (approval number: H22-04-IBCR, date: 04.04.2022).

Informed Consent: Each patient provided informed consent for operation and clinical data acquisition.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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Original Article

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Comparison of Clinical, Pathological, and Prognostic Features in *BRCA* Mutant and Wild-Type Male Breast Cancer Patients

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ABSTRACT

Objective: Published studies on male breast cancer (MBC) and *BRCA* mutations are scarce and usually include, a small number of patients. The clinicopathological characteristics of *BRCA* mutant and wild-type MBC patients were compared in more than forty patients in this study.

Materials and Methods: A retrospective review of MBC patients' clinical and histopathological data was conducted. To compare the patients' characteristics, chi-square test and Fisher's Exact test were utilized. Kaplan–Meier analysis was used to examine the survival analysis.

Results: In total 43 cases were reviewed. The average duration of follow-up was 35.8 months. *BRCA* mutations were found in 11 (25.6%) of the patients. *BRCA1* mutations were found in four patients (9.3%), *BRCA2* mutations in six patients (14%), and *BRCA1* and *BRCA2* mutations in one patient (2.3%). The median age at diagnosis was 58 years old, and there was no statistically significant difference between groups (p = 0.7). Tumor location (p = 0.3), human epidermal growth factor receptor 2 overexpression (p = 0.5), estrogen receptor status (p = 0.05), progesterone receptor status (p = 0.6), tumor stage (p = 0.9), lymph node positivity (p = 0.5), tumor histology (p = 0.06), and recurrence status (p = 0.6) were similar between *BRCA*-wild type and -mutated patients. Overall survival averaged 115.6 months (range: 76.0–155.3), with no statistically significant differences between groups (p = 0.6).

Conclusion: This study investigated clinical and pathological characteristics and prognoses of *BRCA* wild and mutant-type MBC and these were similar in all groups studied.

Keywords: *BRCA* mutations; male breast cancer; pathology features; prognosis

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Key Points

- Patients with *BRCA* mutant or wild-type male breast cancer (MBC) had similar clinical features.
- Patients with *BRCA* mutant or wild-type MBC had similar pathological features.
- Patients with *BRCA* mutant or wild-type MBC had similar survival outcomes.

Introduction

Breast cancer is rarely diagnosed in men and accounts for less than 1% of cancers in men (1). Many risk factors have been identified in the development of male breast cancer (MBC), such as age, obesity, orchitis, and radiation exposure (2). About 5% of patients present with *de novo* metastatic disease (3). In terms of tumor subtypes, more than 80% are hormone-positive and less than 5% are triple-negative (4). In general, the treatment approach in MBC patients is similar to that in female breast cancer (FBC) patients. However, the prognosis in patients with MBC was found to be worse than in patients with FBC (5).

BRCA1 and *BRCA2* mutations are risk factors for the development of many cancers, including breast, ovarian, prostate, and pancreatic cancer. The *BRCA1* gene is located at position 21 of the q arm of chromosome 17, while the *BRCA2* gene is located at positions 12 and 13 of the q arm of chromosome 13 (6). *BRCA1* and *BRCA2* genes maintain the genomic stability of DNA by repairing double-strand breaks (7). The

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presence of *BRCA* mutation may lead to the development of cancer due to the disruption of DNA repair mechanisms. *BRCA1* and *BRCA2* mutations have been defined as risk factors for the development of MBC. The cumulative risk of developing breast cancer in men with a *BRCA1* mutation is around 1%, while it is around 7% in those with a *BRCA2* mutation (8). Also, in patients with MBC, *BRCA1* mutation is detected in approximately 0–5%, and *BRCA2* mutation in approximately 5–15% (9). In the literature, there are limited data on the clinicopathological features and prognosis of MBC patients based on the *BRCA* mutation status. The aim of this study was to compare the disease characteristics according to the *BRCA* mutation status in a cohort of patients with MBC.

Materials and Methods

Patients and Data Collection

The study was designed retrospectively. Ethics committee and academic board approval were obtained before the study. The local ethics committee approved this study at the Istanbul University Faculty of Medicine (approval no: 1398, date: 28.11.2019). The study was conducted according to good clinical practice guidelines. The patients were identified from the hospital data processing system and cancer genetic center database, Patients that were diagnosed and treated in the outpatient clinic of a single oncology center between 2005 and 2020 were evaluated. Patients with MBC whose *BRCA* mutation was analyzed were included in the study. Patients with insufficient statistical data were excluded from the study. Genetic, pathological, clinical, and radiological features of the patients were recorded. All treatments (surgery, chemotherapy, radiotherapy, and hormone therapy) administered to the patients during the entire follow-up period were recorded.

Estrogen receptor (ER) and progesterone receptor (PR) were examined by the immunohistochemistry (IHC) method. Patients with a score of 3+ by IHC or positive by fluorescence in situ hybridization were considered human epidermal growth factor 2 (HER2)/neu positive. *BRCA* mutation analysis was performed with next-generation sequencing and multiplex ligation-dependent probe amplification methods. The smoking histories of the patients were recorded as never, current and former. Alcohol use more than three times a week was defined as regular alcohol intake. Body Mass Index was calculated as kilograms/height in metres^2. Tumor staging was performed according to the 8th TNM Classification of malignant tumors, and molecular subtyping was performed according to the St Gallen consensus. Histopathological type, ER, PR, HER2, tumor grade, tumor stage, smoking history, and alcohol use history were compared between groups stratified by *BRCA* mutation status of the patients.

The time from diagnosis to death from all causes was defined as overall survival (OS). The living conditions of the patients were evaluated through the death notification system of the Ministry of Health. The factors affecting the survival of the patients were analyzed, and the effect of *BRCA* mutation status on OS was evaluated.

Statistical Analysis

Statistical analysis was performed with SPSS, version 25 (IBM Inc., Armonk, NY, USA). Continuous variables are shown as median value (with minimum–maximum value), and categorical variables are shown as numbers and percentages. The Kaplan–Meier method was used for survival analysis and curve. Multivariate analysis was performed with Cox regression analysis. Clinical and pathological differences between groups were evaluated using chi-square and Fisher's Exact test. Independent sample t–test was used for comparison to mean values. A p-value of <0.05 was assumed to indicate significance.

Results

Patient Characteristic

The data of 43 MBC patients were evaluated. Thirty-two (74.4%) patients had no *BRCA* mutations, and 11 (25.6%) patients had *BRCA* mutations. There were six (14%) patients with *BRCA2* mutations and four (9.3%) patients with *BRCA1* mutations. One (2.3%) patient had both *BRCA1* and *BRCA2* mutations. All patients with *BRCA* mutations had pathogenic variants. The median age was 62 in *BRCA* wild-type patients and 57 in *BRCA* mutant patients. The mean value of age between the two groups was similar (p = 0.7). *BRCA* mutant or wild-type MBC patients had similar clinical features (Table 1). Although a multifocal tumor was detected more frequently in *BRCA* mutant patients, no statistically significant difference was found (p = 0.07). When the two groups were compared in terms of pathological features, ER positivity and invasive ductal adenocarcinoma histology were found more frequently in *BRCA* wild-type patients (Table 2). The patients showed similar characteristics in terms of surgery, chemotherapy, radiotherapy, and endocrine therapy (Table 3).

Survival Outcomes and Prognosis

The patients were followed up for a median of 35 months (2.2–225). Ten (23.2%) patients had died by the time of analysis. Median OS was 115.6 (95% confidence interval, 76–155) in all patients (Figure 1). When parameters affecting OS were evaluated in univariate analysis, *BRCA* mutation status was not found to be statistically significant (p = 0.6) for OS (Figure 2). Also, age (p = 0.6), tumor stage at diagnosis (p = 0.7), tumor focality (p = 0.1), histopathological type (p = 0.1), ER status (p = 0.2), PR status (p = 0.09), and HER2 status (p = 0.5) were not statistically significant for OS. Multivariate analysis could not be performed due to the limited number of events.

Discussion and Conclusion

In this study, we compared the clinical and pathological features of MBC patients according to the presence of *BRCA* mutations. In one of the rare studies in the literature published by Ottini et al. (10) it was reported that family history of breast cancer, contralateral breast cancer, grade 3 tumor, PR negativity, and HER2 positivity was more common in patients with MBC with *BRCA2* mutation compared to *BRCA* wild type patients. Although the number of patients is limited due to being a rare tumor, we found that *BRCA* mutant and wild-type patients showed similar characteristics in our study. However, although it was not statistically significant in terms of tumor focality, histopathological subtype and ER positivity, we detected proportional differences between patient groups. MBC is a tumor that shows biological differences from FBC, and hormone receptor positivity and *BRCA2* mutation are detected more frequently (11). In addition, in a multicenter study comparing *BRCA* mutant MBC and FBC in terms of pathological features, it was found that *BRCA2* mutant MBC patients showed more aggressive features than FBC patients in terms of stage and tumor grade at the time of diagnosis, and hormone positivity was more frequent (12). Studies evaluating breast cancer characteristics according to *BRCA* mutation status were mostly conducted in patients with FBC. In a study conducted by Atchley et al. (13), when evaluated according to the *BRCA* mutation status, triple-negative and high-grade

Table 1. Clinical characteristics of the patients according to *BRCA* status

	Patients with *BRCA* wild type		Patients with *BRCA* mutant type		p
	Number	%	Number	%	
Age at diagnosis, years					
Mean age at diagnosis	58.2		59.7		0.7
Family history of breast cancer (n = 37)					
Yes	8	29.6	5	50	0.2
No	19	70.4	5	50	
Body Mass Index (n = 32)					
Obese	4	17.3	3	33.3	0.3
Non-obese	19	82.7	6	66.7	
Smoking status (n = 39)					
Current	17	58.6	5	50	0.7
Never	12	41.4	5	50	
Regular alcohol consumption (n = 37)					
Yes	7	25.9	2	20	0.5
No	20	74.1	8	80	
Tumor locations (n = 41)					
Right side	16	51.6	4	40	0.3
Left side	15	48.4	6	60	
Tumor focality (n = 39)					
Unifocal	28	100	9	81.8	0.07
Multifocal	0	0	2	12.2	
The stage at diagnosis (n = 41)					
Stage 1	8	26.7	3	27.3	0.9
Stage 2	11	36.7	5	45.4	
Stage 3	10	33.3	3	27.3	
Stage 4	1	3	0	0	

tumors were significantly more common in patients with *BRCA1* mutation in FBC. In another study, the relationship between triple-negative disease and *BRCA* mutation in FBC was evaluated with a meta-analysis, and it was found that *BRCA1* mutation was associated with triple-negative disease, larger tumor burden, and higher-grade tumor (14).

In the literature, there are very limited studies evaluating survival according to *BRCA* mutation status in MBC. In a study published by Gargiulo et al. (15), which included 17 patients with MBC with known *BRCA* mutation status, OS was found to be better in patients with *BRCA* wild type in the survival analysis performed according to *BRCA* mutation status. Seven of the patients included in this study were *BRCA* mutant, ten were *BRCA* wild type, and the *p*-value was borderline significant ($p = 0.044$). In our study, patients with *BRCA* wild type showed a better trend in terms of OS compared to *BRCA* mutant patients, but this trend was not significant. This inconsistency can be explained by the limited number of patients in both studies, and patient heterogeneity. In a meta-analysis conducted on patients with FBC according to *BRCA* mutation status, it was found that patients with a *BRCA1* mutation had a worse prognosis in terms of OS than those with *BRCA* wild type. Also, patients with *BRCA2* mutation were shown to have a worse prognosis in terms of breast cancer-specific mortality than those with *BRCA* wild type (16). In another meta-analysis, it was reported that patients with FBC with *BRCA1* mutation had a significantly worse prognosis in terms of OS but similar characteristics in terms of progression-free survival (PFS). Also, the presence of *BRCA2* mutation did not make a difference in terms of OS and PFS (17). There seems to be a need for better-designed studies showing the impact of *BRCA* mutations on the prognosis in MBC and FBC.

Study Limitations

Our study had some limitations. Due to the rarity of MBC, the number of patients in our study was limited. The patient group in the study was heterogeneous, and some data were missing.

In our study, we showed the real-life outcomes of MBC patients, and compared the clinicopathological features in *BRCA* mutant or wild-type patients. We found that patients with *BRCA* mutations or wild-type MBC had similar clinical and pathological features.

Table 2. Pathological features of the patients according to *BRCA* status

	Patients with *BRCA* wild type		Patients with *BRCA* mutant type		p
	Number	%	Number	%	
pT status (n = 39)					
pT1-pT2	33	86.8	8	61.5	0.4
pT3-pT4	5	13.2	5	38.5	
pN status (n = 38)					
Node negative	16	57.1	4	40	0.5
Node positive	12	42.9	6	60	
Histological type (n = 41)					
Invasive ductal carcinoma	27	90	7	63.6	0.06
Other types	3	10	4	36.4	
Molecular subtype (n = 41)					
Luminal A	6	19.3	3	30	0.07
Luminal B	20	64.5	4	40	
HER2 positive	5	16.2	1	10	
Bazal-like	0	0	2	20	
ER receptor (n = 41)					
Positive	31	100	8	80	0.055
Negative	0	0	2	20	
PR receptor (n = 41)					
Positive	22	71	6	60	0.6
Negative	9	29	4	40	
HER2 receptor (n = 41)					
Positive	5	16.1	1	10	0.5
Negative	26	83.9	9	90	
Grade (n = 32)					
1-2	12	46.1	3	50	0.8
3	14	53.9	3	50	

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor 2

Table 3. Treatment approaches in the patients according to *BRCA* status

	Patients with *BRCA* wild type		Patients with *BRCA* mutant type		p
	Number	%	Number	%	
Breast surgery (n = 41)					
Simple mastectomy +SNB	11	36.6	5	50	0.2
Modified radical mastectomy	19	63.4	5	50	
Radiotherapy (n = 41)					
Adjuvant-neoadjuvant	19	63.4	8	72.7	0.3
No radiotherapy	11	36.6	3	27.3	
Chemotherapy (n = 42)					
Adjuvant-neoadjuvant	21	67.7	9	81.8	0.4
No chemotherapy	10	32.3	2	18.2	
Endocrine therapy (n = 41)					
Adjuvant	26	86.6	9	81.8	0.9
No endocrine therapy	4	13.4	2	18.2	

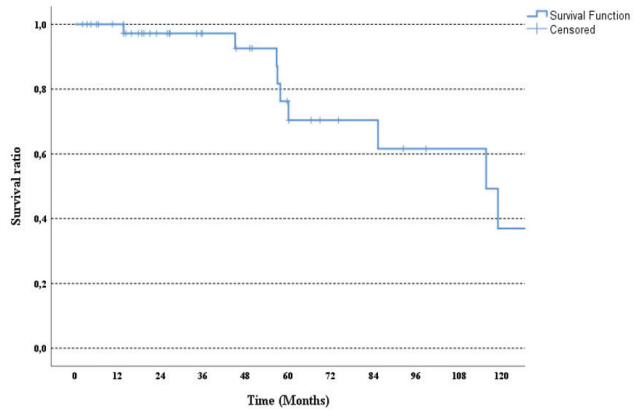

Figure 1. Kaplan–Meier curve for OS in the patients with MBC

OS: overall survival; MBC: male breast cancer

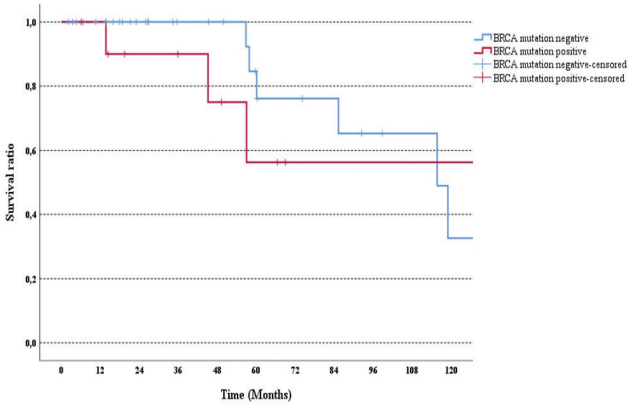

Figure 2. Kaplan–Meier curve for OS by *BRCA* mutation status in the patients with MBC

OS: overall survival; MBC: male breast cancer

This study is one of the few published studies examining the differences in MBC according to *BRCA* mutation status. In our study, some clinical and pathological factors remained at the limit in terms of statistical significance. Multicenter studies with larger patient groups are needed for verification of our findings. Furthermore, cancer development and treatment processes will be better understood with translational studies examining the relationship between *BRCA* mutation and the development of MBC.

Presentation at a meeting: This study was presented as a poster at 2020 San Antonio Breast Cancer symposium.

Ethics Committee Approval: The local ethics committee approved this study at the Istanbul University Faculty of Medicine (approval no: 1398, date: 28.11.2019).

Informed Consent: For this type of research, informed consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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Evaluation of Arab Cultural Barriers That Influence Muslim Arab Iraqi Women's Breast Cancer Screening Behavior

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ABSTRACT

Objective: Little is known about Iraqi women's practice towards breast cancer screening (BCS), breast self-examination (BSE), clinical breast examination (CBE) and mammography, and the influence of Arab culture. The aim of this study was to assess women's behavior towards BCS, and to explain the influence of specific Arab culture barriers.

Materials and Methods: This descriptive study was carried out with 1,066 women. Three structured questionnaires were used in the data collection. Descriptive statistics and multivariable logistic regression were used for data evaluation.

Results: Many Iraqi women did not practice regular BSE, CBE, and mammography. The most common reason was "not having a breast complaint". Specific Arab cultural barriers such as exposure [odds ratio (OR) = 0.545; 95% confidence interval (CI) = 0.440 to 0.674; $p<0.001$], environment (OR = 0.571; 95% CI = 0.464 to 0.703; $p<0.001$) and uneasiness barriers (OR = 0.736; 95% CI = 0.557 to 0.974; $p=0.032$) were predictors for BSE while exposure (OR = 0.553; 95% CI = 0.447 to 0.684; $p<0.001$), and environment barriers (OR = 0.585; 95% CI = 0.474 to 0.772; $p<0.001$) was predictor for CBE. Additionally, exposure (OR = 0.324; 95% CI = 0.251 to 0.419; $p<0.001$), environment (OR = 0.636; 95% CI = 0.500 to 0.809; $p<0.001$), and uneasiness barriers (OR = 0.644; 95% CI = 0.464 to 0.893; $p = 0.008$) were predictors for mammography screening of Iraqi women.

Conclusion: Arab specific cultural barriers may be one of the key obstacles to BSC uptake in Iraq. Health education, including cultural education, may have the potential to increase BCS awareness and down-staging of the disease at presentation.

Keywords: Arab culture; barriers; breast cancer screening behaviors; Muslim Arab Iraqi women

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Key Points

- Breast cancer is the most common type of cancer in Iraqi women and breast cancer screenings are very crucial for early detection.
- Cultural spesific barriers may effect women's breast cancer screening behaviors.
- Culturally specific barriers of women that might prevent breast cancer screening need to be determined by health professionals.

Introduction

Breast cancer (BC) is the most common cause of cancer-related mortality among women, particularly in low-and medium-income countries (1, 2). It is believed that high death rates in low-income countries is due to low awareness and poorer knowledge about BC and screening, insufficient diagnostic tools, and difficulties in accessing treatment (1, 3). However, early diagnosis programs are effective in increasing survival rate by early detection through screening methods, such as breast self-examination (BSE), clinical breast examination (CBE), and mammography (2).

In Iraq, the main causes of morbidity and mortality are cardiovascular diseases in the general population and BC among women (2, 4). After the destruction of the Iraqi regime in 2003, a rapid lifestyle change affected all the Iraqi population, which also affected the patterns and levels of cancer trends in Iraq. In the following years, the persistent effects of biological and chemical war have had a major negative impact, with high levels of uranium and radiation across many areas of the country. Furthermore, widespread bombing had significant impacts on infrastructure, including

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accessing medical care and increased environmental pollution. All of these negative environmental and societal impacts have increased cancer incidence. Younger women have been particularly affected, and the persistent effects of warfare have become a significant additional hazard for all women's health in Iraq in the past two decades (5, 6). Unfortunately, there are no exact statistics on BC in Iraq and only the data of GLOBOCAN is taken into consideration. In Iraq, there is a national program for early detection of BC, which was established in 2001. In the Iraqi provinces, there are mammography units in some medical centers, particular clinics, and hospitals for early detection of BC where diagnostic mammography services are provided. In 2012, a preliminary, opportunistic BC screening trial was begun at the primary referral center for cancer early detection in Bagdat Medical City Teaching Hospital. In Iraq, nationwide programs for BC screening are inadequate, especially for high-risk women. Therefore, applying opportunistic screening may markedly increase the early detection rate of BC and improve awareness of BC in Iraq. Moreover, the Iraqi National Breast Cancer Research Program recommends that Iraqi women should start screening by mammography after the age of 40 years, preceded by annual CBE together with performing monthly BSE (7).

Cultural factors may influence Muslim Arab women's decisions concerning BC and screening behavior (8-10). Positive or negative factors related to health behavior are learned by experience and shaped by the influence of culture. These behaviors may not be evaluated directly. On the other hand, behavior can be predicted by measuring the behavior of a sample of individuals' behavior, as it may be difficult to evaluate attitudes by simply observing individual behavior or by examining individual physiological responses. Thus, there are some scales for measuring behavior, beliefs, or attitudes. To our knowledge, no study has been published which investigated the influence of the Arab culture-specific barriers on women's BC screening behavior in Iraq.

The elucidation of information about BC, risk factors and screening behavior of Iraqi women will both guide the country's cancer screening programs and improve BC awareness in women which may, in turn, result in improved participation in screening programs (7). Furthermore, survival rates in Iraq are lower because of the delay in detection, leading to much poorer prognosis at presentation when BC is often incurable. Survival rates are further impacted by lack of early detection programs coupled with inadequate diagnostic and treatment facilities, low socioeconomic status, and low levels of knowledge and incorrect beliefs about BC prevention (6, 7).

Materials and Methods

Design, Setting and Sample Size

A cross-sectional study was conducted in Sulaymaniyah city in the North of Iraq during the period from 3rd February 2019 to the 3rd of February 2021. Suleymaniyah, a governorate located in the North of Iraq, Sulaymaniyah city is bordered in the east by Iran and the Iraqi provinces of Erbil, Kirkuk, Salah Al-Din, and Diyala to the North, West, and South, respectively. The Iraqi population consists of ethnic Sunni Muslim Arabs, Kurds, Shiites, and Chaldean Christians (11). The population of Iraq was 40,800,438, based on Worldometer detailing of the latest United Nations data in 2021. The total population of Suleymaniyah city is 723,170 based on Worldometer elaboration of the latest United Nations data of Iraq Population in 2021. In Iraq, women make up 20,562,885 of the total Iraqi population according to Countrymeters estimates, based on the latest United Nations data in 2021. The population of women between the ages of 20 to 70 in Sulaymaniyah city according to 2012 data is 464,259. The inclusion criteria were female gender, being between 20–70 years of age, and being able to read and write. Exclusion criteria were being ≤20 years or ≥70 years of age and having difficulty in communication. The sample size was calculated that at least 295 women, between the ages of 20 and 70, with a known population (n = 464,259). In this study, 1,066 Iraqi women were included (12).

Data Collection and Tools

Research data were collected through face-to-face interviews with women using a self-questionnaire. The questionnaire consists of three parts and total 59 items. These questionnaire parts are detailed below.

Part 1. Socio-demographic characteristics (21 items): This part was designed by the researcher according to literature (1-3, 7) for determining women's socio-demographic characteristics and BC/screening related questions including age, occupation, marital status, presence of children, economic status, age of first birth, breastfeeding status, contraceptive use, age first menstrual period, previous breast problems, heard about BC and screening, having a family history of BC, performing, or having BSE, having a CBE, having a mammogram.

Part 2. Participants breast cancer screening practices: This part was created with reference to relevant literature (1-3, 7). It included 17 items with nominal and binomial (Yes/No) answers and was divided into three sections, BSE (seven questions), CBE (five questions) and mammography (five questions).

Part 3. Arab culture-specific barriers to breast cancer questionnaire (ACSB) was used these section: Permission was obtained from the authors to utilize the scales. The Arab Culture-Specific Barriers to Breast Cancer Questionnaire (ACSB) was developed by Cohen and Azaiza in 2008 (13). The ACSB has been tested and validated with Sunni Muslims, Druze, and Christian Arab women in Israel and the Palestinian Authority. This tool is composed of 21 items and five sub-scales (exposure barriers, social barriers, religious beliefs concerning cancer, environmental barriers, and uneasiness with own body). All items have five response choices ranging from strongly agree (1 point) to strongly disagree (5 points). A low score indicates a high level of cultural obstacles related to BC screening behavior. It was reported that Cronbach's alpha for this tool ranged from 0.76 to 0.90 (13). In the present study, Cronbach's alpha ranged from 0.86 to 0.96.

Data Collection

Data collection was conducted during six months, from February to July in 2021. After explaining the study objectives and assuring confidentiality and privacy of the data, verbal and written informed consent was obtained from each woman. All documents, including surveys and consent forms were made available in English and Arabic. A researcher translated the English materials into Arabic and checked the translations for accuracy. Data were collected by the researcher in real-time interviews. Data collection lasted about 25 minutes per woman.

Statistical Analysis

Data were analyzed using SPSS, version 21 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (percentage, mean, and standard deviation) were calculated to find the distribution of the socio-demographic characteristics of the women, practices about breast

health, and Arab culture-specific BC screening barriers. A backward stepwise (conditional) regression method was used. The significance of each independent variable in the bivariate model was assessed by a Wald-type chi-square test. The statistical significance was set at $p<0.05$ for all analyses.

Ethics of Research

Approval was obtained from the ethical committee in Karabuk University with the project-wide variety (77192459-050.01.04-E.11637) on 05/03/2020. Formal administrative approval was obtained from the Sulaymaniyah Planning and Health Research Department of the General Directorate of Health with the project number (12006 on 09/12/2020), for conducting this study. All women gave written informed consent before participation. The participants were assured of anonymity and confidentiality. The participants were assured that they were not obliged to participate in the study, and they had the right to withdraw from the study at any time.

Results

There was a total of 1,066 participants. Of the participants, 619 (58.1%) did not practice BSE and 447 (41.9%) did (Table 1). Among those who practiced BSE, 303 (67.6%) were regular. The reasons given for not performing BSE were: not having a breast complaint (69.7%); fear of discovering a tumor (22.8%); not having time (4.8%); and lack of information (2.7%).

Table 1. Practice of women towards breast cancer screening (n = 1,066)

Practices and attitudes	Yes, n (%)	No, n (%)
Practicing of BSE	447 (41.9)	619 (58.1)
If yes (n = 447)		
Regular	302 (67.6)	
As I think about it	145 (32.4)	
If no, reason (n = 619)		
I'm afraid to discover a tumor.	141 (22.8)	
I do not have a breast complaint.	431 (69.7)	
I do not have the time.	30 (4.8)	
I don't have enough information.	17 (2.7)	
CBE		
Had a clinical breast examination	400 (37.5)	666 (62.5)
When (n = 400)		
In the last 2 years	291 (72.7)	
I do not remember	109 (27.3)	
If no, reason (n = 666)		
I have never heard of it.	19 (2.8)	
I am afraid of the procedure and the bad results.	124 (18.7)	
I did not find it necessary.	40 (6.0)	
I did not have any complaints.	443 (66.5)	
I was afraid of pain and discomfort.	14 (2.1)	
Ashamed	26 (3.9)	
Mammography		
Had a mammography	374 (35.1)	692 (64.9)
If yes, when (n = 374)		
In the last 2 years	286 (76.5)	
I do not remember.	88 (23.5)	
If no, reason (n = 692)		
Mammography cannot be accessed	23 (3.3)	
I am afraid of the procedure and the bad results.	116 (16.8)	
I did not find it necessary.	53 (7.7)	
I did not have any complaints.	491 (70.9)	
Ashamed	9 (1.3)	

BSE: breast self-examination; CBE: clinical breast examination

Only 400 (37.5%) of this cohort had ever had CBE and 72.7% of examinations were in the last two years. The reasons women did not have CBE were: not having breast complaints (66.5%); fear of the procedure and/or bad results (18.7%); being ashamed (3.9%); not being advised to (1.9%); and having never heard of it (0.9%).

Similarly, only 374 (35.1%) of these Iraqi women had undergone mammography, again the majority of whom had in the last two years. The reasons given for not having mammography were: Not having breast complaints (70.9%), fear of the procedure and/or bad results (16.8%); not believing it necessary (7.7%); being unable to access mammography (3.3%); and being ashamed (1.35%).

Table 2 shows the barriers and facilitators for BCS practices. In the present study, exposure barriers, environment barriers, and uneasiness barriers were significant in attitudes to BSE. When exposure [odds ratio (OR) = 0.545, confidence interval (CI) = 0.440 to 0.674], environment (OR = 0.571, CI = 0.464 to 0.703), and uneasiness barriers (OR = 0.736, CI = 0.557 to 0.974) increased, the tendency of women to perform BSE decreased. In contrast, there were no significant relationships between social and religious barriers and performance of BSE. In terms of CBE, exposure, and environment barriers were significant. When exposure (OR = 0.553, CI = 0.447 to 0.684) and environment barriers (OR = 0.585, CI = 0.474 to 0.722) increased, the odds of them using CBE decreased. For CBE, there were no significant effects found for social, religious or uneasiness barriers. Similarly, barriers related to exposure, environment, and uneasiness with own body were found to have a significant effect on the likelihood of undergoing mammography. Once again, when exposure (OR = 0.324; CI = 0.251 to 0.419), environment (OR = 0.636, CI = 0.500 to 0.809), and uneasiness barriers (OR = 0.644, CI = 0.464 to 0.893) increased, women become less likely to have a mammogram.

Discussion and Conclusion

In Iraq, BC is the main cause of cancer-related deaths among women (7). BCS is known to be effective for early BC diagnosis and survival among women. However, we believe that Iraqi national BC screening programs are inadequate and to the best of our knowledge, there are no studies about the effect of Arab culture specifically in regard to the behavior of Iraqi women and BCS.

In the present study, just over forty percent of Iraqi women performed BSE and of these more than two-thirds performed BSE regularly. In previous studies from Iraq, it was indicated that practice of BSE, both regularly or irregularly, among Iraqi women was low (14, 15). Similar rates have been reported from other Muslim countries, such as Saudi Arabia, and Qatar (16, 17). Therefore, future research should focus on strategic plans, training programs or organizational change to improve participation in BC screening, such as BSE, amongst Muslim women.

The reasons given for not performing BSE were no breast complaint, fear of cancer diagnosis, no time, and lack of information in our study. In parallel, a previous study conducted in Iraq found that the most

Table 2. Predictors of Iraqi women's breast cancer screening practices

Variables	B (S.E.)	p	Wald	OR	95% CI	-2 Log Likelihood	Cox & Snell R^2
Breast Self-Examination							
Exposure. B	0.109	**<0.001**	31.164	0.545	0.440–0.674	1007.527[a]	0.353
Social. B	0.150	0.809	0.058	1.037	0.773–1.390		
Religious. B	0.128	0.372	0.796	0.892	0.694–1.147		
Environment. B	0.106	**<0.001**	27.911	0.571	0.464–0.703		
Uneasiness. B	0.143	**0.032**	4.603	0.736	0.557–0.974		
X^2 = 95.794 df. 8 p<0.001							
Clinical Breast Examination							
Exposure. B	0.109	**<0.001**	29.613	0.553	0.447–0.684	1015.929[a]	0.342
Social. B	0.152	0.773	0.083	0.957	0.710–1.290		
Religious. B	0.127	0.442	0.591	0.907	0.706–1.164		
Environment. B	0.107	**<0.001**	24.918	0.585	0.474–0.722		
Uneasiness. B	0.145	0.086	2.941	0.780	0.587–1.036		
X^2 = 94.765 df. 8 p<0.001							
Mammography							
Exposure. B	0.131	**<0.001**	74.411	0.324	0.251–0.419	893.249[a]	0.367
Social. B	0.175	0.291	1.115	1.203	0.854–1.694		
Religious. B	0.136	0.270	1.215	1.162	0.890–1.516		
Environmental. B	0.123	**<0.001**	13.588	0.636	0.500–0.809		
Uneasiness. B	0.167	**0.008**	6.963	0.644	0.464–0.893		
X^2 = 105.536.765 df. 8 p<0.001							

B: barriers; S: standard error; OR: odds ratio; CI: confidence interval

common reasons were lack of confidence, timidity, lack of time, and fear of discovering cancer (14). Other studies from different Muslim countries indicated that the reasons were believing it not to be necessary and not knowing how to do BSE (16-18). Despite many Iraqi women practicing of BSE, women in our sample appeared to have misconceptions about BSE and therefore, wider information and education may be beneficial in changing attitudes.

We found less than forty percent of women did not have CBE, a similar rate reported from other Muslim countries (19, 20). Interestingly, the rate of women undergoing CBE in the last two years (76.5%) was higher compared to an earlier study which reported the rate of CBE examination among Iraqi women (21). Besides, the most common reason given for not undergoing CBE was not having a breast complaint, as was the case with BSE. Other studies have shown that most common reasons given for not using BCS were not having a breast complaint, followed by fear of bad results, lack of knowledge, and not believing it necessary (19, 20). Despite many Iraqi women practicing CBE, women in our sample appeared to be unaware of the importance of CBE and have misconception about CBE.

Our results indicated that many women did not undergo mammography. Two previous studies carried out by Elobaid et al. (19) and Al-Mulhim et al. (22) reported similar findings. The reasons for not having a mammography were not having a breast complaint, fear of the procedure and fear of negative results, believing it unnecessary, lack of access to mammography services, and being ashamed; similar findings reported by other studies conducted in Iraq and other Muslim countries (22-25).

We found that exposure, environment, and uneasiness barriers were predictors for Iraqi women's performing BSE. Although studies that examine the cultural factors affecting Iraqi women's BSE are scarce, in two studies conducted in Iraq, it was found that women's BSE practices were negatively affected by a lack of knowledge and awareness (15, 21). Moreover, culture may be crucial for women and societies when considering its impact on performance and perceptions of screening for early detection of BC. Previous studies indicated that uneasiness about one's own body can create barriers, such as embarrassment at looking and touching their body and not having enough privacy to examine their body were the most important barriers to not practicing BSE (10, 26). Cultural-based BSE educational programs, including exploring Islamic mandates on prevention and individual responsibility in health promotion and cultural related beliefs toward BSE, health education, BSE training, and follow-up have demonstrated that cultural-based BSE educational programs are effective in enhancing BSE self-efficacy in Muslim populations (27). Thus, health care professionals may have a key role to create awareness and to promote culturally sensitive educational programs.

In regard to CBE, exposure and environment barriers were also significant in Iraqi women undergoing these procedures. Some studies have reported that exposure barriers were the most important barriers to women not having CBE including embarrassment due to modesty regarding an exam by a male physician, refusing to expose their breasts, and need to cover their body or breasts (10, 26, 28). Furthermore, Kawar (26) indicated that environment barriers were also important, for example not understanding medical terminology, distance and accessibility of clinics, and financial issues. We found that religious and social barriers were not barriers to CBE, similar to an earlier study by Al-Attar et al. (23). Other studies have highlighted Muslim women's misconception about BCS are more important than religious and social barriers in accessing BCS (7, 23). Abdel-Aziz et al. (28) showed that the social stigma of BC turned about a failure of BC understanding, afraid of BC screening participation, especially CBE, that may lead to getting the illness and bring embarrassment to the family. However, Islam emphasizes the importance of health. Although gender and cultural norms are influential in the Muslim religion, it also emphasizes the importance of improving the health of women, and imams or female religious leaders play a critical role in this regard (10).

We also found that as exposure, environment, and uneasiness barriers increased, women were less likely to have mammography screening. Similarly, previous studies have emphasized environmental barriers, such as transportation problems, inaccessibility of the mammography facility, cost of examination, difficulty reaching the center, and insufficient health insurance, were factors affecting if women have mammography. Religious barriers were not found to be a predictor, but some studies indicated that religion is crucial in affecting if Muslim women undergo mammography (26, 29). In a study from Ghana, it was shown that Muslim females had low participation in BC screening compared to Christian females, which highlights how religious belief plays a significant role in access to services concerning breast health and the need to consider how religious and cultural habits in subpopulations may influence a female's consultation for breast health and BCS participation (30). For mammography, religious concerns may be more influential, such as encountering a male doctor. Even if something relates to an illness, religious concerns may override and the circumstances may be haram (a term used to mention to any act that is forbidden by God). However, Islamic faith is facilitative of women's health practices, such as cancer screening, rather than being an obstacle. Islam also promotes the importance of preventing illness by edicts that suggest care of the body (9). Apart from issues around religious beliefs, it is still of great importance to educate women about BC screening methods.

The strength of this study was that we used appropriate sampling method and a large sample size. The current study is the first comprehensive study which evaluate the knowledge of women and explains the influence of Arab culture-specific barriers on women's BCS behavior in Iraq. However, data were obtained from participants in Erbil, Iraq, so this cannot be generalized to other regions of Iraq or even wider afield. During the data collection period, the COVID-19 pandemic was affecting Iraq. There were difficulties communicating with people because of the virus risk. Nevertheless, we achieved data collection with an excellent response rate. The study also has several limitations that need to be mentioned. We acknowledge that this type of study, using a self-administered questionnaire, has its limitations. Additionally, women sometimes respond in a socially desirable manner when answering questions about screening behavior and cultural items, and there was no way to independently validate the accuracy of the information provided.

Our study provided an insight into Arab culture-specific barriers affecting women's BCS behavior in a region of Iraq. We identified Arab-specific cultural barriers were one of the key obstacles to BSC uptake in this cohort. In order to provide the care consistent with Iraqi women's barriers and problems related to culture, obstacles to accessing BCS should be minimized by a number of routes, including through the actions of health care professionals by providing culturally acceptable environments for participation in BCS. We sincerely hope

that this study will provide a stimulus to minimizing Iraqi women's cultural barriers to BCS by improvement and promotion of Iraqi health policy and by reducing and abolishing misconceptions or unawareness of BCS by wider and effective education of Iraqi women.

Ethics Committee Approval: Approval was obtained from the ethical committee in Karabuk University with the project-wide variety (77192459-050.01.04-E.11637) on 05/03/2020.

Informed Consent: All women gave written informed consent before participation.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.S.A., I.I.A.; Design: S.S.A., I.I.A.; Data Collection and/or Processing: S.S.A., I.I.A.; Analysis and/or Interpretation: S.S.A., I.I.A.; Literature Search: S.S.A., I.I.A.; Writing: S.S.A., I.I.A.

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Original Article

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Tissue Expression of Neutrophil Gelatinase-Associated Lipocalin and Kidney Injury Molecule-1 in Breast Cancers

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ABSTRACT

Objective: Breast cancer is the most common cancer among women worldwide. Neutrophil gelatinase-associated lipocalin (NGAL) has important roles in immunity, cell proliferation, and carcinogenesis. Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein also known as hepatitis A virus cellular receptor 1 and T-cell immunoglobulin and mucin, has restricted expression in immune cells and healthy epithelial cells, but it is up-regulated in several human cancers. The aim of this study was to determine the prognostic values of NGAL and KIM-1 expression in tumor cells and to detect the presence of NGAL-positive neutrophils (PNL) in the tumor microenvironment.

Materials and Methods: The expression of NGAL and KIM-1 protein were assessed by immunohistochemical staining in tissue specimens from 412 primary breast cancer cases.

Results: In this series, the mean age of the patients was 55.6±12.4 years. In 218 (52.9%) cases, there was NGAL expression in tumor cells. In 104 (25.2%) cases there was KIM-1 expression in tumor cells. NGAL-positive inflammatory cells were seen in tumors of 45 (10.9%) cases. There was no significant relationship between NGAL-positive PNL presence in the tumor microenvironment and other clinicopathological features. However, there was a significant association between the presence of *in situ* carcinomas and NGAL expression (p = 0.008) and KIM-1 expression (p = 0.020) in tumor cells.

Conclusion: This study has demonstrated positivity of NGAL and KIM-1 in breast cancer cells. Considering the development of anti-KIM-1 therapies, the presence of KIM-1 expression may be a new treatment option in breast cancer, especially in *in situ* component-rich tumors. These findings should be confirmed in larger series.

Keywords: Breast carcinomas; ductal carcinoma *in situ*; neutrophil gelatinase-associated lipocalin; kidney injury molecule-1; prognosis

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Key Points

- This study has demonstrated that the positivity of neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) will be effective on breast cancer, especially *in situ* component-rich ones.
- This result showed that NGAL and KIM-1 may be effective during the early carcinogenesis of breast cancer.
- Recently the new immune modulatory drug for TIM-1.
- Considering the development of anti-KIM-1 therapies, the presence of KIM-1 expression may be a new treatment option in breast cancer.

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Introduction

Breast cancer is the most common malignancy in women around the world. The development of breast carcinoma is regulated by many factors, such as hormonal effects, advanced age, alcohol consumption, obesity, dietary habits, and genetic factors (1-3). Ductal carcinoma *in situ* (DCIS) is also considered to be a precursor to invasive breast carcinoma and in which the proliferation of tumor cells is confined within the lumen of the breast ductal system (4-6). While the traditional classification of malignant breast tumors by the World Health Organization (WHO) was made based on histological features of the tumor, currently some subtypes have been described according to molecular characteristics of the tumors (1-3, 7, 8).

As a member of the lipocalin superfamily, neutrophil gelatinase-associated lipocalin (NGAL), also called lipocalin 2 or 24p3, was first isolated as a 25 kDa glycoprotein covalently bound to matrix metalloproteinase 9 (MMP9) in neutrophils. NGAL has been initially classified as an acute phase protein, which is rapidly released, mainly from neutrophils, as a response to inflammation and tissue injury (9-11). Initially, NGAL was thought to be an antibacterial factor and a component of the innate immune system and present in a large variety of cell types including hemopoietic cells. During hematopoiesis, immature ($CD34^+$) bone marrow progenitor cells, granulocyte precursors, activated monocytes, macrophages and neutrophils express NGAL. In contrast, NGAL protein expression has never been reported in lymphocytes and plasmacytes (9-13). Circulating low levels of NGAL can be detected in the urine and blood of healthy people, possibly secreted by neutrophils and renal epithelial cells. Expression of NGAL may play several physiological roles, including transporting hydrophobic molecules across cell membranes, regulating immune responses, modulating iron metabolism, and promoting epithelial to mesenchymal translations. In summary, NGAL is involved in many functions during diverse processes of growth, development, and tumorigenesis (12, 13).

Kidney injury molecule-1 (KIM-1) was first described in I996, as a mucin-like membrane glycoprotein type I, homologous to the immunoglobulin family proteins and which facilitated the intracellular penetration of the hepatitis A virus. Therefore, it was named hepatitis A virus cellular receptor 1 (HAVcr-1). Two years later, it was found to be a very sensitive and specific predictor of renal proximal tubule injury and was redesignated as KIM-1. In the 2000s, a group of proteins, belonging to the T-cell immunoglobulin and mucin (TIM) domain family, which are especially expressed in T cells functioning in the respiratory system was identified. TIM-1, one of these proteins, is homologous to KIM-1. In summary, the definitions of HAVcr-1, KIM-1 and TIM-1 (CD365) mentioned in the biological databases today describe the same protein (14-16). KIM-1 is normally expressed at a low level in the healthy kidney. However, cell-associated KIM-1 expression increases dramatically in post-ischemic kidney tissue and KIM-1 exerts an anti-inflammatory role following kidney injury (16, 17). Its expression is also up-regulated in several human cancers, most notably in renal and ovarian carcinomas, but has very restricted expression in healthy tissues, thus representing a promising target for antibody-mediated therapy. Recently, a human monoclonal IgG1 antibody specific for the extracellular domain of TIM-1 was developed. This antibody (CDX-O14) was shown to bind purified recombinant chimeric TIM-1-Fc protein and TIM-1 expressed on a variety of transformed cell lines. However, it has not been included in the routine treatment regimen to date (14-19).

Hitherto, as relevant markers for assessing the proliferative activity and tumor cell dynamics of breast carcinomas, many parameters have been suggested. However, among these parameters NGAL and KIM-1 have not been investigated extensively. In this study we aimed to explore the clinical importance NGAL and KIM-1 expressions in breast cancers.

Materials and Methods

The expression of NGAL and KIM-1 protein was investigated by immunohistochemical staining in tissue specimens from 412 primary breast cancer cases who underwent mastectomy, and excisional breast biopsy between the years 2011 and 2018, and were subsequently diagnosed as breast carcinoma in the Pathology Laboratory of İzmir Tepecik Training and Research Hospital. Patients' files were retrospectively evaluated. This study was approved by the local Ethics Committee of the Hospital. Hematoxylin-Eosin (H&E) stained, archived slides were re-evaluated, based on 2012 breast tumor classification of the WHO. For immunohistochemistry (IHC), H&E staining was used to select appropriate paraffin blocks and to identify the viable tumor areas. The paraffin block most suitable for IHC evaluation was selected, and labeled firstly on the slide, and then the block, and 2 mm thick cylindrical paraffined tissue samples were harvested from donor blocks. Then multiple blocks were prepared using mapping and addressing techniques. Then IHC was performed using diluted (1:300) monoclonal rabbit antibodies against NGAL (Novus Biologicals, Littleton, USA; NDP1- 90331) and KIM-1 (Bioss, Philadelphia, USA; HAVCRI). Histopathologists, blinded to the clinical features of the patients, examined the slides and staining patterns were classified according to the intensity of staining. NGAL positivity was defined as diffuse cytoplasmic and/or nuclear staining in both invasive and *in situ* components of tumor (Figure 1). KIM-1 positivity was defined as diffuse cytoplasmic staining in both invasive and *in situ* components of tumor (Figure 2). For both antibodies, focal staining occupying less than 1–2% of the high-power field of view or weak staining visible under a microscope was considered as NGAL or KIM-1 negativity. In addition, the presence of NGAL-positive neutrophils and/or macrophages that infiltrated the tumors was evaluated (Figure 3).

Statistical Analysis

Statistical analysis was performed using SPSS, version 25.0 (IBM Inc., Armonk, NY, USA). For comparison of quantitative data the chi-square test was used. For the comparison of non-parametric data Mann–Whitney U test were used. For comparison of the measurements

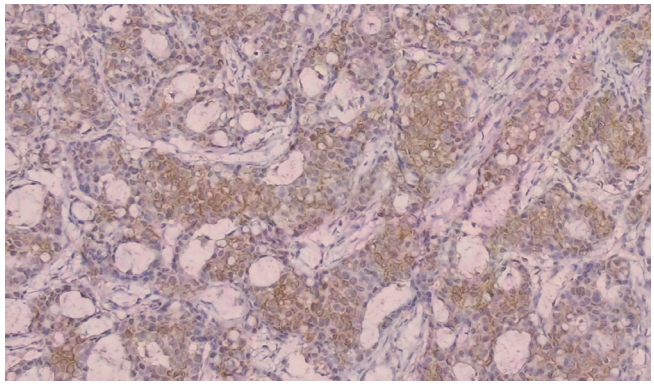

Figure 1. A case with immunohistochemically detected cytoplasmic and/or nuclear NGAL positivity in tumor cells (DAB x 200)

NGAL: neutrophil gelatinase-associated lipocalin; DAB: diaminobenzidine

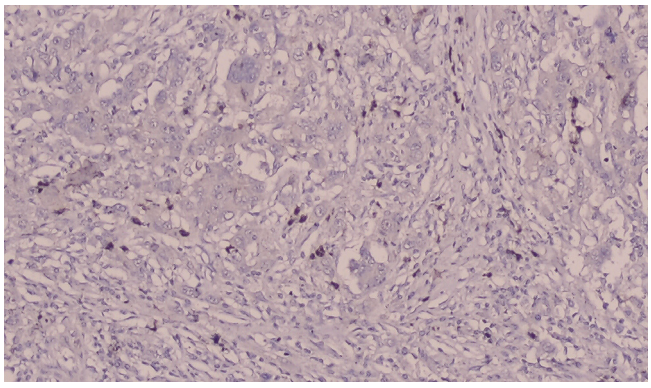

Figure 2. NGAL-positive inflammatory cells in tumor stroma (DAB x 200)

NGAL: neutrophil gelatinase-associated lipocalin; DAB: diaminobenzidine

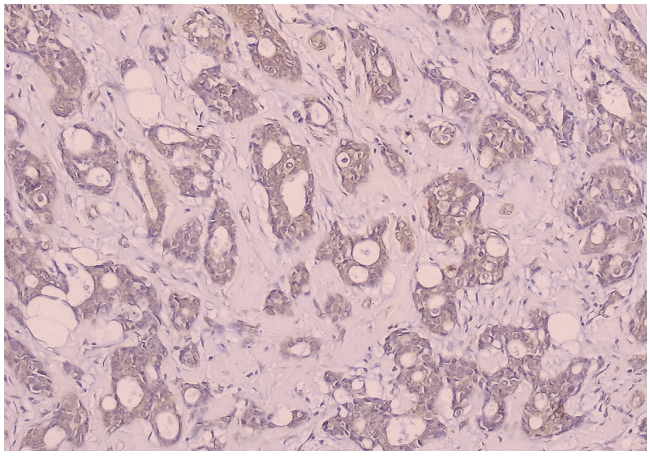

Figure 3. A case with immunohistochemically detected cytoplasmic KIM-1 positivity in tumor cells (DAB x 200)

KIM-1: kidney injury molecule-1; DAB: diaminobenzidine

in more than two groups the non-parametric Kruskal–Wallis test was utilized. Kaplan–Meier survival analysis was applied to compare the difference in survival between groups. A $p \leq 0.05$ was accepted as the level of statistical significance.

Results

In this series, the mean age of the 412 patients was 55.6±12.4 years (range: 30–85 years) at the time the samples were obtained. The mean follow-up period was 37.75±21.4 (range: 0.83–111.07) months. Three hundred and sixty-five (88.6%) patients survived, and 47 (11.4%) patients died. Tumor location was reported in 342 cases, as follows. There were 163 (47.7%) tumors in the right and 178 (52%) in the left breast. There was only one case (0.3%) with bilateral breast tumor in the series. The mean tumor diameter was 2.94±1.79 cm (range: 0.5–10 cm). Pathological T staging could be evaluated in 339 patients (82.3%). According to pathological T staging these 339 cases were distributed as follows: pT1 (n = 139; 41%); pT2 (n = 144: 42.5%); pT3 (n = 41; 12.1%); and pT4 (n = 15; 4.4%). The tumor was multifocal in 40 (9.7%), and unifocal in all other cases. Among the cases with precisely known tumor location, the most common location was the upper outer quadrant (38.9%), followed by central (34.2%), upper inner (10.7%), lower inner (7.4%) and lower outer (8.7%) quadrants. Histopathologically tumors were classified as grade 1 in 27 (6.5%), grade 2 in 208 (50.4%), and grade 3 in 177 (42.9%) of cases. A DCIS component was present in 273 (66.3%) tumors and there were no cases of lobular carcinoma *in situ*. Of all the *in situ* components present, 40 (14.6%) were comedoes, 114 (41.8%) were non-comedoes and 119 (43.6%) were comedo+non-comedo mixed *in situ* carcinoma type. Axillary lymph node dissection was performed in 338 (82%) of the cases, and lymph node metastasis was detected in 163 (39.6%). In 112 (68.7%) cases with lymph node metastasis, capsular invasion was present in the metastatic lymph nodes (Table 1).

On IHC studies performed in 412 patients included in the study, estrogen receptor (ER)-positivity was detected in 330 (80.1%), and PR-positivity in 298 (72.3%) cases. Immunohistochemically, c-erbB2, which was applied to evaluate human epidermal growth factor receptor 2 (HER2)/neu amplification and was found to be 1+ or negative in 272 cases (66%), and both groups were considered as HER2-negative. In combined IHC-FISH evaluation, 92 cases (22.3%) were accepted as HER2-positive and all received targeted treatment. Ki67 proliferation index was studied in all cases, and the cut-off level for low/high Ki-67 expression was 15%. In this series the mean Ki67 index was found to be 22.74±18.76% (range: 1-95%). Based on molecular classification, respective number of cases with luminal A (n = 142; 34.4%), luminal B (n = 139; 33.7%), HER2-positive (n = 92: 22.3%), and triple-negative (n = 39; 9.5%) were detected (Table 2). Mean ages of the patients and survival time in different molecular groups were similar ($p = 0.377$). In this series, the longest survival time was found in the luminal A group ($p = 0.003$).

In 218 (53%) cases, there was NGAL expression in tumor cells. In 104 (25.2%) cases, there was KIM-1 expression in tumor cells. NGAL-positive inflammatory cells were seen in tumors of 45 (10.9%) cases. There was no difference in expressions of the two markers between *in situ* and invasive components of the tumors. When comparisons were made by chi-square test, the rate of cases with NGAL expression was higher in HER2 positive tumors compared to other molecular groups ($p = 0.019$). However, there was no significant difference in KIM-1 ($p = 0.100$) expression in tumor cells based on molecular subtype. Similarly, there were no statistical significance in the rate of expression of NGAL or KIM-1 according to the types of *in situ* components. Neither was there a significant relationship between NGAL-positive PNL presence in the tumor microenvironment and other clinicopathological features. However, there was a significant association between the presence of *in situ* carcinoma and the expression of both NGAL ($p = 0.008$) and KIM-1 ($p = 0.020$) in tumor cells (Table 3).

Discussion and Conclusion

Following a number of studies and meta-analyses, breast cancers began to be classified according to the molecular subtype in the 2000s (1-3, 7). It has emerged that 75% of breast tumors contain estrogen and/or progesterone receptors (ER/PR), and therefore belong to the luminal group. However, since tumors in the luminal group manifest diverse behaviors, this group is divided into luminal A and B subgroups according to the their proliferative index (1). Other subtypes are HER2-positive and triple-negative or basal cell-like tumors. HER2 amplification was known as a poor prognostic factor when it was first identified, but with the subsequent development of HER2-targeted therapeutic agents, cases with HER2-positive tumors no longer differ in terms of survival (7). As expected, in the present study, the longest survival time was found in the luminal A group. However, the survival of HER2 positive group was also close to the survival of luminal group

and we attributed this to the fact that all patients in this group received tailored therapy against HER2.

There is an established signaling network between tumor cells and stromal cells (20). This network plays an important role to constitute the tumor microenvironment. The tumor microenvironment can influence behavior of cancer cells in different ways and can promote cancer progression. The tumor microenvironment is composed of various cells of different origins that secrete several soluble factors, including cytokines, growth factors, and microRNAs as well as other factors. Adipocytes also secret NGAL, the main functions of which appear to be activation of the innate immune response and transportation of small hydrophobic molecules (20, 21). In addition, it was determined that NGAL secretion from breast adipose tissue can promote breast cancer progression by increasing EMT (20-25). Surprisingly, the roles of NGAL in carcinogenesis may be contrary. Pro-tumoral effects attributed to NGAL include acting as an intracellular iron carrier and protecting MMP9 from proteolytic degradation in different neoplasms of breast, stomach, esophagus, uterine cervix, and brain. NGAL was also associated with NF-kB which is an important factor involved both in tumor growth and in the link between chronic inflammation and neoplastic development. NGAL, paradoxically, has been reported to have an anti-tumoral and anti-metastatic effect in cancers of colon, ovary, and pancreas (22-27). Some studies have demonstrated that NGAL can inhibit angiogenic factors, such as HIF-1 alpha and vascular endothelial growth factor. In a recent study using a three dimensional spheroid model, it was shown that NGAL contributes to the early events of metastasis *in vitro*. The release of NGAL from macrophages induced an epithelial-mesenchymal transition program in the MCF-7 breast cancer cell line and enhanced local migration as well as invasion into the extracellular matrix. Thus,

Table 1. Demographic and histopathologic data

		n	%
Prognosis	Survived	365	88.6
	Died	47	11.4
Tumor Location	Right	163	47.7
	Left	178	52
	Bilateral	1	0.3
Diagnosis	Invasive ductal carcinoma (IDC)	249	60.4
	Invasive lobular carcinoma	28	6.7
	Invasive papillary carcinoma	11	2.6
	IDC with dominant *in situ* component	102	24.7
	Other histologic variants	22	5.3
Grade	Grade 1	27	6.5
	Grade 2	208	50.4
	Grade 3	177	42.9
Pathologic T stage	pT1	139	41
	pT2	144	42.5
	pT3	41	12.1
	pT4	15	4.4
In situ component	Present	273	66.3
Type of *in situ* component (if any)	Comedo	40	14.6
	Non comedo	114	41.8
	Mixed	119	43.6
Lymph node metastasis	Present	163	39.6
	Absent	175	42.5
Capsular invasion in the lymph node	Present	112	68.7
	Absent	51	31.3
Multifocality	Solid	272	91.3
	Multifocal	40	9.7
Nipple involvement	Present	24	5.8
Dermal/epidermal invasion	Present	38	9.2
Lymphovascular invasion	Present	144	35
Perinueral invasion	Present	104	25.2

Table 2. Immunohistochemical, and molecular findings

Parameters	Status	n	%
ER status	Positive	330	80.1
PR status	Positive	298	72.3
c-erbB2 expression (according to ASCO/CAP 2013 criteria)	Negative or 1+	272	66
	2+	88	21.3
	3+	52	12.6
HER2 amplification (FISH method)	Positive	47	11.4
	Negative	41	10
Molecular type	Luminal A	142	34.4
	Luminal B	139	33.7
	HER2- positive	92	22.3
	Triple negative (Basal-like)	39	9.5
NGAL expression	Positive in inflammatory cells	45	10.9
NGAL expression	Positive in tumor cells	218	53
KIM-1 expression	Positive in tumor cells	104	25.2

ASCO: American Society of Clinical Oncology; CAP: College of American Pathologists; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; FISH: fluorescence *in situ* hybridisation; NGAL: neutrophil gelatinase-associated lipocalin; KIM-1: kidney injury molecule-1

Table 3. Association between NGAL and KIM-1 expression and prognosis

	Presence of NGAL expression (n = 218)	*p*	Presence of KIM-1 expression (n = 104)	*p*
Molecular type	Luminal A (n = 73) Luminal B (n = 69) HER2-positive (n = 62) Triple negative (Basal-like) (n = 14)	**0.019**	Luminal A (n = 35) Luminal B (n = 41) HER2-positive (n = 24) Triple negative (Basal-like) (n = 4)	0.100
Type of *in situ* component (if any)	Comedo (n = 25) Non-comedo (n = 68) Mixed (n = 67)	0.755	Comedo (n = 9) Non-comedo (n = 40) Mixed (n = 30)	0.157
Presence of *in situ* component	Absent (n = 58) Present (n = 160)	**0.008**	Absent (n = 25) Present (n = 79)	**0.020**
Lymph node metastasis	Absent (n = 90) Present (n = 87)	0.720	Absent (n = 43) Present (n = 45)	0.525
Grade of tumor	Grade 1 (n = 14) Grade 2 (n = 110) Grade 3 (n = 94)	0.993	Grade 1 (n = 6) Grade 2 (n = 57) Grade 3 (n = 41)	0.591
Survival	Deceased (n = 30) Alive (n = 188)	0.111	Deceased (n = 12) Alive (n = 92)	0.961

NGAL: neutrophil gelatinase-associated lipocalin; KIM-1: kidney injury molecule-1; HER2: human epidermal growth factor receptor 2

an association between macrophage-released NGAL and breast cancer progression was explored. Therefore one aim of the present study was to attempt an evaluation of the utility of NGAL levels in making an early diagnosis, establishing a prognosis, and predicting response to different treatments (23-30).

A recent study reported a difference in serum levels of NGAL according to breast cancer subtypes with elevated levels of MMP9/NGAL complex in luminal subtypes (31). In contrast, the serum levels of MMP9/NGAL were found to be substantially decreased in Triple Negative and HER2 positive group (31, 32). In contrast, the NGAL-positivity rate increased in HER2 positive group in our study, although we did not measure blood concentrations of NGAL. It has been reported that high cytoplasmic and low nuclear localization of NGAL was associated with the worst survival outcome in breast cancer patients (27). In our study, prominent nuclear NGAL expression was

absent and most NGAL expression was cytoplasmic in the tumor cells. Therefore, although we found a strong correlation between the presence of *in situ* carcinoma and the presence of both nuclear and cytoplasmic NGAL expression, we cannot draw any conclusions about the relationship between the location of NGAL expression and prognosis.

Earlier studies have suggested that the phagocytic function of KIM-1 to remove apoptotic bodies in injured proximal tubules reduced antigen exposure to inflammatory cells and prevented over-reaction of the immune system. However, as apoptotic bodies are phagocytosed by antigen presenting cells (APCs), these cells subsequently activate regulating T cells and cytotoxic T lymphocytes to attack target cells. In addition, renal cell carcinomas (RCCs), derived from the proximal tubules, express KIM-1, which implies some phagocytotic activity in RCC cells. Therefore, it was suggested that the phagocytotic function of KIM-1 may be adapted by RCC cells to clear tumor apoptotic bodies, thus preventing the activation of APCs and T lymphocytes against RCC cells. In other words, KIM-1 may play a scavenger role in RCC against potential immune reactions and may be a key factor in the tumor microenvironment for the survival and development of RCC (14-17). KIM-1 overexpression in the cells of clear cell and papillary RCC has for a long time been known as a special feature of kidney tumors, but data concerning the clinical significance of increased KIM-1 expression in the extra-renal tumors are ambiguous. For example, Liu et al. (17), reported that elevated expression of KIM-1 mRNA is associated with unfavorable prognosis and low sensitivity to chemotherapy in stomach cancer. Similarly, Zheng et al. (18) found that increased KIM-1 protein expression was also associated with worse survival in non-small cell lung cancers. Inactivation of KIM-1 in lung cancer cells suppresses proliferation, migration activity, and invasion and is also accompanied by a rise in the level of tumor suppressor protein PTEN and inhibition of the pro-oncogenic PI3K/Akt signaling pathway. In contrast, Wang et al. (19) reported that overexpression of KIM-1 mRNA in colon cancer tissue was associated with a longer recurrence-free survival of patients. In addition, high KIM-1 expression rates have been reported in clear cell carcinoma of the ovary (93.8%), nephroblastomas (74%), primary lymphomas of the central nervous system (54%), germ cell tumors (50%), and endometrium carcinomas (33.3%). However, there is no firm correlation between the level of KIM-1 expression in cancer cells and clinical and morphological characteristics of each specific malignant disease, which indicates independent prognostic significance of this indicator (12, 14-19). Similarly to these studies, we could not find a relationship between KIM-1 expression and invasive breast tumors. However, unlike the others, we found higher KIM-1 positivity in breast cancer with a ductal *in situ* component.

Today, widespread mammographic screening has led to the increasing diagnosis of DCIS and *in situ* carcinomas now comprise 20-25% of all breast carcinoma diagnoses. DCIS shares many of the epidemiological, hormonal and genetic risk factors with invasive breast cancer (IBC). Although DCIS is usually treated with surgical excision, chemoradiotherapy may be added depending on the extent of the lesion or the team that will administer the treatment. Despite the increase in the diagnosis and treatment of DCIS, there is no decrease in the diagnosis of IBC. This has led to the suggestion that the *in situ* carcinomas may never become invasive tumors and that the surgical wide-excision, hormone therapy, or radiotherapy are over-treatment (4-6).

Based on our results, we speculate that the reason for detecting high NGAL and KIM-1 expression in tumors with *in situ* carcinoma in this study may be associated with the behavior of DCIS. We think that the NGAL and KIM-1 positivity rates of tumor cells were found to the higher in the tumors with DCIS. Therefore, breast cancers expressing NGAL and/or KIM-1 may form a mass, may invade, and metastasize earlier. One of the most important limitations of this study is that NGAL and KIM-1 expressions were not investigated in DCIS cases without invasive cancer. If our speculation is correct, then it could be expected that NGAL and KIM1 positivity rates would be found to be significantly lower in patients without invasive carcinoma in their follow-up and repeat investigations.

This study has demonstrated higher positive expression rates of NGAL and KIM-1 in breast cancer with *in situ* components. Considering the development of anti-KIM1 therapies, the presence of KIM-1 expression may have increased importance in clinical practice, especially in *in situ* component-rich tumors. It remains for these findings to be confirmed in larger series which should also include DCIS with no evidence of invasion.

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Authorship Contributions

Surgical and Medical Practise: C.K.; Concept: G.D., A.G.P., D.S.K., U.V., S.S., D.A., C.K.; Design: G.D., A.G.P., D.S.K., U.V., S.S., D.A., C.K.; Data Collection and/or Processing: G.D., A.G.P., D.S.K., U.V., S.S., D.A.; Analysis and/or Interpretation: G.D.; Literature Search: G.D., A.G.P., D.S.K., U.V., S.S., D.A., C.K.; Writing: G.D., A.G.P., D.S.K., U.V., S.S., D.A., C.K.

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Original Article

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Unexpectedly High Coexistence Rate of *In Situ*/Invasive Carcinoma In Phyllodes Tumors. 10-Year Retrospective and Review Study

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ABSTRACT

Objective: Phyllodes tumors (PTs) are a rare group of breast tumors. Most malignant transformations are *in situ* carcinomas that are extremely rare and are limited to individual cases in the literature. The presence of *in situ*/invasive carcinomas is important as this may alter clinical judgment and management. In this study, we aimed to determine the association of *in situ*/invasive carcinomas among PTs.

Materials and Methods: This retrospectively designed study included cases diagnosed with PTs between 2011 and 2020 in the pathology department of a tertiary level hospital. Tumors were grouped into benign, borderline and malignant, according to stromal overgrowth, stromal atypia, stromal cellularity and mitotic activity. In addition, age, location, type of operation, tumor diameter, and surgical margin information were recorded. *In situ* and/or invasive carcinoma foci accompanying the PTs were assessed.

Results: A total of 29 patients diagnosed with PTs were identified, among whom 14 (48.2%) had benign PTs, 10 (34.4%) had borderline PTs, and 5 (17.2%) had malignant PTs. Of the patients with PTs, 3 (10.3%) had coexistent invasive carcinoma and 1 (3.4%) had carcinoma *in situ*. In this cohort the incidence of coexistence of PT and carcinoma was 4/29 (13.7%), which is much higher than previously reported (1.1% and 6%). The incidence of carcinoma was 2/5 (40%) in malignant PT patients and 2/10 (20%) in borderline PT patients. The coexistence of malignant PTs and carcinoma was significantly higher than those of benign and borderline PTs (p<0.05).

Conclusion: The multidisciplinary team dealing with breast diseases has a great responsibility in both diagnosis and treatment. We anticipate that these rates will increase with an increase in the awareness and importance of this coexistence of carcinoma and PTs.

Keywords: Phyllodes tumors; breast; *in situ*; intraductal carcinoma; malignant

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Key Points

- Although the diagnosis of phyllodes tumor (PT) is not challenging, a comprehensive histopathological examination with multiple sampling when considering the coexistence with carcinoma is necessary.
- Not only full examination of the stromal component, but also meticulous microscopic examination, may be useful to detect a possible invasive focus of epithelial origin.
- The presence of ductal carcinoma in PTs is clinically significant as it may alter treatment.
- Surgeon, radiologist and pathologist should take great care in phyllodes tumors larger than 4 cm and showing sudden growth.

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Introduction

Phyllodes tumors (PTs) are a rare group of breast tumors involving a biphasic proliferation of the stroma and breast epithelium. They usually appear as a fast-growing, painless, unilateral, mobile mass with regular margins. Histologically, they display an intracanalicular growth pattern and form a typical leaf-like appearance, usually with a benign course (1).

Fibroadenoma (FA) is a frequently diagnosed lesion in clinical pathology. In the presence of increased stromal cellularity, tru-cut biopsy may be difficult to definitively distinguish FA from benign PT. In such cases, the term "fibroepithelial lesion" is used and excision is typically done for definitive classification (1, 2). Older age at diagnosis of FA, presence of radiologically synchronous masses in other regions of the breasts, and continued enlargement of the lesion are other potential "red flags" (3).

Taking sufficient amount of tru-cut biopsy pre-operatively and sampling the excision material with multiple paraffin blocks by the histopathologist will reduce the risk of missed diagnosis when PTs exhibit tumor heterogeneity and may even occur in some FAs (4).

Triple evaluation, including physical examination, radiological and histopathological evaluation, has been shown to result in increased pretest probabilities, reduced false positive and false negative results, and better identification of lesions requiring excision or further treatment (5, 6). The primary purpose of most tru-cut biopsies is to exclude malignancy. Management of malignancy is well known and continues to evolve. However, the diagnosis of benign diseases, such as FA or fibroepithelial lesions, can sometimes pose a management challenge for the breast multidisciplinary team within the current diagnostic paradigm, especially due to the lack of good evidence to guide the need for excision (6).

Based on World Health Organization (WHO) 2019 criteria (2), PTs are classified as benign, borderline, or malignant according to histological parameters, including stromal hypercellularity, cellular pleomorphism, mitotic activity, margin status, and stromal overgrowth. Malignant transformation usually occurs in the stromal part of the tumor, but the epithelial component of PTs may also transform into a malignancy (3). Most of these are *in situ* carcinomas and are extremely rare, <1% (4). Similarly, the coexistence of malignant PTs and invasive ductal carcinomas (IDC) is limited to individual cases (7-40). In this article, we investigated the rate of ductal carcinoma among PTs diagnosed in a single center.

Materials and Methods

A retrospective review to identify phyllodes cases between 2011-2020 was conducted in the Department of Medical Pathology at the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The study was approved by the clinical trials ethics committee of the referred hospital (PN 381/2020). Clinical data were retrieved from the database for analysis. All patients who underwent core biopsy followed by complete surgical excision and were subsequently diagnosed with PT by histopathology were included in the study. Tumors were reviewed according to WHO criteria by two pathologists (S.A., Ö.G.), one of whom is board certified (S.A.). To illustrate, a phyllodes tumor was diagnosed when the tissue showed an exaggerated intracanalicular pattern of leaf-like protrusions into cystically enlarged spaces accompanied by fibroepithelial architecture and stromal hypercellularity. A benign phyllodes tumor differed from a fibroadenoma by showing slightly increased stromal cellularity, minimal nuclear atypia and pushing borders, mitoses in ≤5/10 high magnification field (HPFs) compared to a fibroadenoma. In stromal overgrowth; the criterion of epithelial-free stroma was based on at least one low magnification field with the x4 microscope objective.

Malignant phyllodes tumor, on the other side of the histopathological spectrum, was generally recognized by easily defined stromal overgrowth, prominent stromal cellularity and atypia, permeative borders, and mitotic activity of at least 10/10 HPF. Phyllodes tumors with intermediate features were included in the borderline category.

Ducts that appeared to be entrapped within the phyllodes tumor and were suspicious for tumor were evaluated with p63 immunohistochemistry for the presence/absence of myoepithelial cells.

In addition, age, location, type of operation, tumor maximum diameter, and surgical margin information were recorded. The occurrence of concomitant *in situ* and/or invasive foci was investigated.

SPSS, version 22.0, was used in the analysis of data (IBM Inc., Armonk, NY, USA). Comparative analysis of the groups was made with Fisher's Exact test.

Results

A total of 29 patients diagnosed with PTs were identified from the database (Table 1). All patients were female, with an age range of 17-81 years, with a mean age of 42.8±16.2 years. Core biopsy revealed fibroepithelial lesions in 21 patients and it was noted that core biopsy in 12 of these patients could be PTs. All patients underwent surgical resection. Three patients underwent total mastectomy due to the tumor/breast tissue ratio, one patient underwent modified radical mastectomy, nine patients underwent breast-conserving surgery, while wide local excisions (WLEs) were performed in 15 patients. Benign PTs were identified in 14 patients (48.2%), borderline PTs were found in 10 patients (34.4%) while malignant PTs were detected in five patients (17.2%) (Table 2). The incidence of carcinoma (both *in situ* or invasive carcinoma) was 40% (2/5) in malignant PT patients and 20% (2/10) in borderline PT patients. The coexistence of malignant PTs and carcinoma was significantly higher than in patients with benign and borderline PTs (p<0.05). There were three patients (10.3%) in whom invasive carcinoma also revealed a PT and one patient (3.4%) had carcinoma *in situ* with PT. These case are briefly presented below to provide a better understanding of the series (Table 3).

Case No. 20: A 25x25 mm mass was detected at the 10 o'clock position in the right breast of a 45-year-old patient in 2018. The tru-cut biopsy performed in the outer center was reported as FA. This mass, which was excised locally, was diagnosed as borderline PT. In the post-op breast US performed at our center in the same year, a new mass of 41x20 mm was detected at the 3 o'clock position in the left breast, and a tru-cut biopsy was performed. Left WLE was carried out upon detection of an IDC focus in this biopsy. A grade 2 IDC with a size of 30x20 mm was detected in the WLE material. In the immunohistochemical assay performed on this subject, estrogen receptor (ER) was detected as 100% positive, progesterone receptor (PR) was 90% positive, while the c-erbB2 score was 1 negative. No relapse and/or metastasis was detected during the 22-month follow-up period after treatment.

Case No. 23: A 50x35 mm mass at the 3 o'clock position was detected in the left breast of a 69-year-old patient in 2014. Fibroadenomatoid-phillodes like changes were detected via a tru-cut biopsy, and WLE was performed. A 45x35 mm borderline PT was detected in the WLE material, but the lesion persisted within surgical margins. Therefore, re-excision was performed with clear margins and a solid type ductal carcinoma *in situ* (DCIS) was identified in the re-excision material. The patient could not be followed up after treatment.

Case No. 28: A 60x55 mm mass was detected at the 1 o'clock position of the left breast in the US performed in 2019 on a 45-year-old patient with a history of excision of FA in the left breast in 2018. PT was diagnosed in the tru-cut biopsy while a benign PT diagnosis was made in the WLE performed afterward. A mass with a size of 120x110 mm was detected in the left breast at 3 o'clock position in the follow-up US and a malignant PT was diagnosed in the re-performed segmentary mastectomy, but the tumor was observed in the CSs in the surgical

Table 1. Summary of the clinicopathologic characteristics of the 29 patients described in the current series

Patient no	Age	PT Type	Localization	PT size (cm)	Margins	Operation	Axillary Surgery
1	46	Benign	Left	10x10	Clear	WLE	(-)
2	17	Benign	Right	2.5x2.3	Clear	WLE	(-)
3	45	Benign	Right	3.5x3.5	Clear	WLE	(-)
4	55	Benign	Right	5x4	Clear	WLE	(-)
5	29	Benign	Right	6x5.5	Clear	WLE	(-)
6	42	Benign	Left	9x7	Clear	WLE	(-)
7	23	Benign	Right	7x6	Clear	WLE	(-)
8	48	Benign	Right	13x9.5	Clear	WLE	(-)
9	26	Benign	Right	5x4	Clear	WLE	(-)
10	41	Benign	Right	4x4	Clear	WLE	(-)
11	35	Benign	Right	4.5x4	Clear	WLE	(-)
12	20	Benign	Right	6.5x3.5 3x2.5	Clear	WLE	(-)
13	57	Benign	Left	5x2.2	Clear	WLE	(-)
14	22	Benign	Right	5x4.5	Clear	WLE	(-)
15	30	Borderline	Right	NA	Clear	WLE	(-)
16	81	Borderline	Left	8x6	Clear	WLE	(-)
17	49	Borderline	Right	11x0.5	Clear	TM	(-)
18	73	Borderline	Right	2x2	+	WLE	(-)
19	45	Borderline	Left	7x5	Clear	WLE	(-)
20*	45	Borderline	Right	2.5x2.5	Clear	WLE	(-)
21	57	Borderline	Right	3.5x3.5	Clear	WLE	(-)
22	39	Borderline	Left	5.5x4.5	Clear	WLE	(-)
23*	69	Borderline	Left	4.5x3.5	Clear	WLE	(-)
24	25	Borderline	Left	1.3x1.3	Clear	WLE	(-)
25	31	Malign	Left	24.5	Clear	MRM	(-)
26	39	Malign	Right	5x4	Clear	WLE	(-)
27	45	Malign	Right	5.5x5.5	Clear	TM	(-)
28*	45	Malign	Left	12x11	Clear	WLE	(-)
29*	63	Malign	Left	20x16	Clear	TM	(-)

PT: phyllodes tumor; WLE: wide local excision; MRM: modified radical mastectomy; TM: total mastectomy, *coexisting with carcinoma

Table 2. Histological type and age distribution of the 29 patients described in the current series

n (%)	PT type	Median age (Range)	Coexisting with carcinoma n (%)	*p*-value
14 (48.2)	Benign	36.1 (17–57)	0 (0)	
10 (34.4)	Borderline	51.3 (25–81)	2 (20)	
5 (17.2)	Malign	44.6 (31–63)	2 (40)	0.038

PT: phyllodes tumor

Table 3. Summary of the pathologic characteristics of the four patients described with PT coexistent with *in situ*/invasive carcinoma)

Patient no	Pre- op core bx	PT type	Carcinoma	Carcinoma size (cm)	Mitotic rate	ER (%)	PR (%)	HER2
20	FEL	Borderline	IDC (G2)	3X2	5/10 HPF	100 +	90 +	Score 1 (Negative)
23	FEL	Borderline	LCIS, DCIS	0.5X0.5 and 0.4x0.3	5/10 HPF	90 +	70 +	Score 1 (Negative)
28	Likely PT	Malign	IDC (G2)	0.8X0.8	>20/10 HPF	90 +	90 +	Score 2 (FISH negative)
29	FEL	Malign	IDC (G1)	0.8X0.8	>10/10 HPF	100 +	70 +	Score 2 (FISH negative)

PT: phyllodes tumor; ER: estrogen receptor; PR: progesterone receptor; FEL: fibroepithelial lesion; IDC: invasive ductal carcinoma; DCIS: ductal carcinoma *in situ*; LCIS: lobular carcinoma *in situ*; NA: not available; HPF: high powered field; FISH: fluorescent *in situ* hybridization; HER2: human epidermal growth factor receptor 2

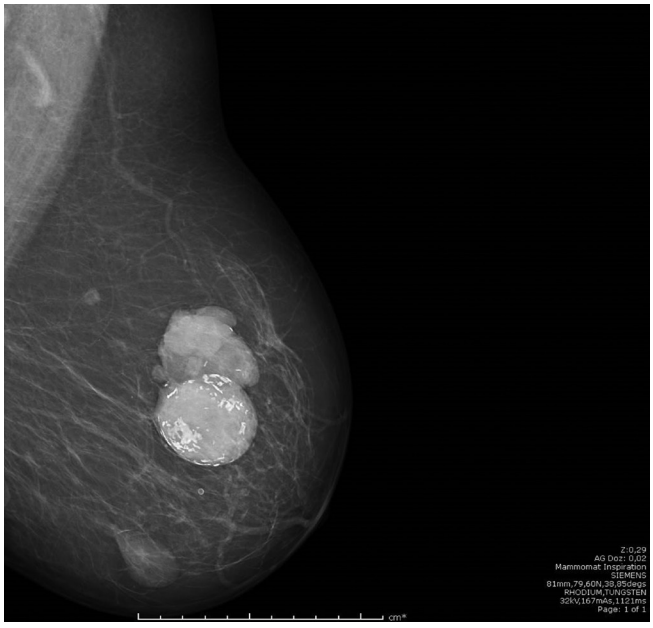

Figure 1. LMLO mammogram. In the upper-outer quadrant of the left breast, there is a 51 mm diameter, well-defined, radio-dense lesion in which extensive, coarse calcifications are superposed, and two radio-dense lesions 25 mm and 22 mm in diameter are located adjacent to it

margins. Therefore, in addition to a malignant PT, a grade 2 IDC with a diameter of 8 mm was detected on re-excision, and no lesions were observed in CSs. Immunohistochemical assay showed ER 90% positive, PR 90% positive, and the c-erbB2 score was 0 negative. No relapse and/or metastasis was detected during the 10-month follow-up period after treatment.

Case No. 29: A 63-year-old patient had been operated for endometrial adenocarcinoma in 2015. During the follow-up in 2017, a mass was detected in the left breast. On LMLO (left mediolateral oblique view) mammography, there was a 51 mm diameter, well-circumscribed radio-dense lesion in which dense, coarse calcifications overlapped and there were adjacent radio-dense lesions 25 mm and 22 mm in diameter in the upper-outer quadrant of the left breast (Figure 1). The patient, whose

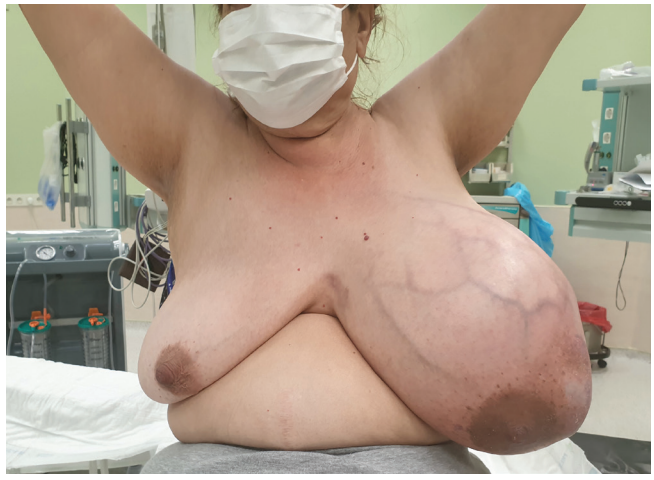

Figure 2. Preoperative picture of patient. Red, hard, fluctuating mass covering more than 50% of the left breast

breast tru-cut biopsy could not be performed in February 2017, was admitted in March 2020 with a mass that filled the entire breast. She had a red, hard, fluctuating mass covering more than 50% of the breast in her left breast (Figure 2). The preoperative magnetic resonance imaging (MRI) revealed a cystic-solid mass of 160x120 mm with an irregular, lobular contour and intense contrast enhancement in the solid component after the left breast was filled with intravenous contrast media almost completely and was evaluated as BI-RADS category 4C (Figure 3). Mammogram in 2017 and preoperative MRI in 2020 and US examination did not suggest the presence of ductal carcinoma. On the cut surface of the mastectomy specimen a dirty yellow-white tumoral lesion with cystic-solid appearance, which was hemorrhagic-necrotic and filled almost the entire breast was seen (Figure 4). In the samples prepared from the mastectomy specimen, a tumor with infiltrative margins, prominent stromal cellularity and stromal cellular atypia, characterized by necrosis and mitosis (>10/10HPF) was observed (Figures 5,6). Total mastectomy revealed a malignant PT of 20x16 cm and grade 1 IDC with a diameter of 0.8 cm in a focus (Figure 7). On p63 immunohistochemical staining, ducts that do not show immunoreactivity were observed in myoepithelial cells (Figure 8). The axillary staging was N0 via sentinel lymph node

biopsy. Immunohistochemical assay showed ER 100% positive, PR 70% positive, while the c-erbB2 score was suspicious positive 2. Fluorescence in situ hybridization-negative adjuvant radiotherapy (RT) was performed. No relapse and/or metastasis was detected during the 9-month follow-up period after treatment.

Discussion and Conclusion

The term "Philodes" comes from the latin root "Philodes" meaning leaf-like, describing the appearance of "Phyllodium" on microscopic examination (1). Johannes Müller, a German physician, first described PTs as cystosarcoma phyllodes in 1838, despite the rare cystic component of these tumors and the rarity of malignancy (1, 2). PTs, which make up 0.5-1% of all breast tumors, have a younger age at diagnosis than breast carcinoma, which occurs at an average age of 40 years (1, 41). Although typically diagnosed after palpation of a breast mass on physical examination, 20 percent of patients are initially detected by radiographic imaging, such as mammography (41). In our series, the mean age was 36.1 years which is somewhat younger than

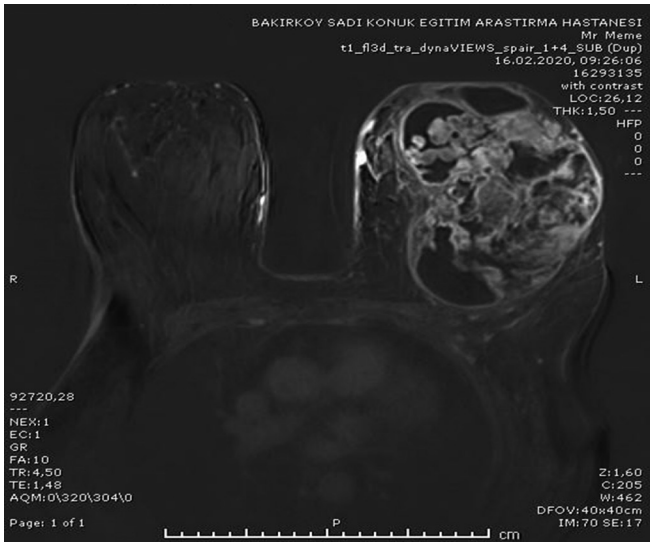

Figure 3. T1-weighted dynamic magnetic resonance imaging. It is seen that the volume of the left breast is increased compared to the right. A 16x12 cm sized, irregular lobule-contoured, cystic-solid mass that almost completely fills the left breast is notable, with intense contrast enhancement in its solid component after intravenous contrast material

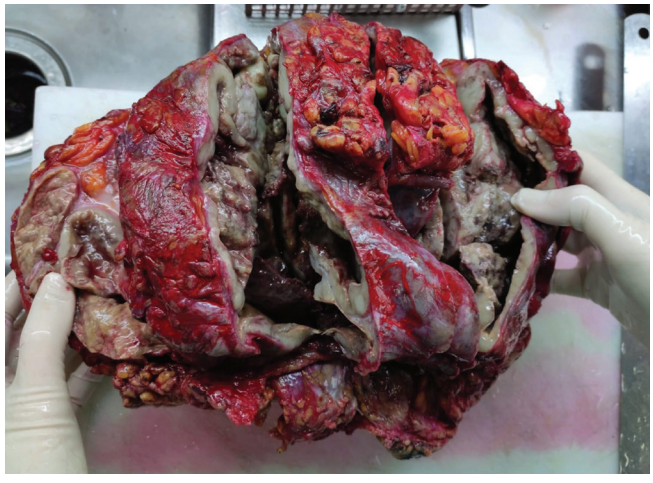

Figure 4. Postoperative macroscopic picture. On the cut surface, a dirty yellow-white tumoral lesion with cystic-solid appearance and hemorrhage-necrosis is seen

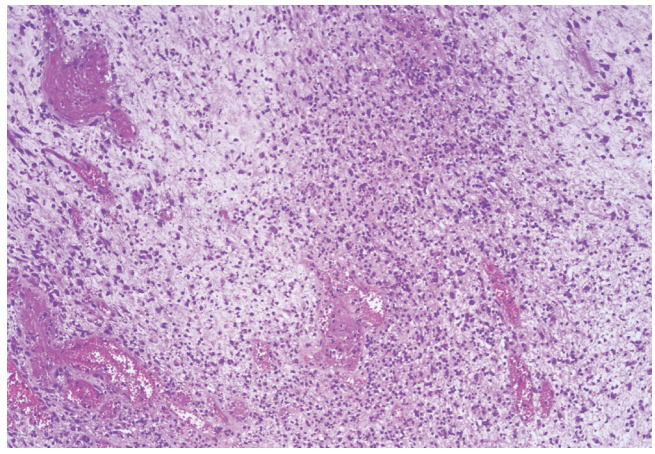

Figure 5. Microscopic evaluation reveals atypical spindle cells with stromal cellularity within large areas of necrosis (H&E, x100)

H&E: hematoxylin and eosin stain

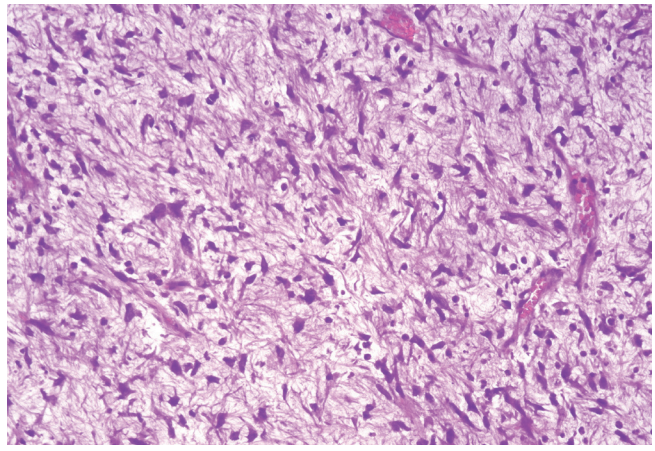

Figure 6. The picture shows cellular tumor tissue characterized by mitotic figures formed by prominent cellular atypia (H&E, x200)

H&E: hematoxylin and eosin stain

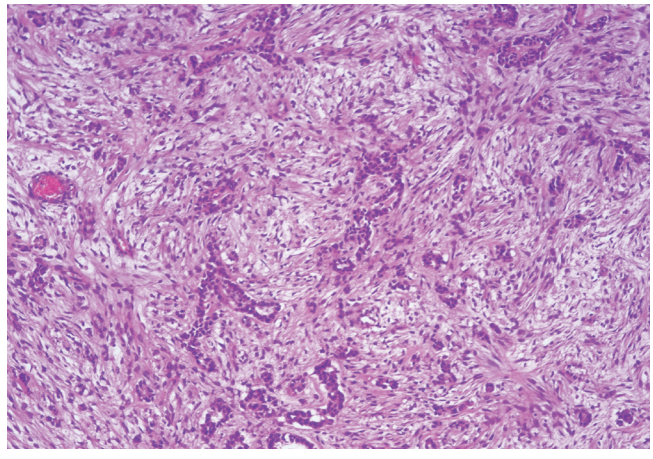

Figure 7. The picture shows areas of invasive carcinoma, some of which forms a well-formed tubule in the stroma (H&E, x100)

H&E: hematoxylin and eosin stain

the reported 40 years in benign PTs, while it was over 40 years in borderline and malignant PTs (51.3 and 44.6 years, respectively).

Diagnosing these lesions as malignant or benign by fine-needle aspiration remains difficult preoperatively, with an accuracy of 63% (5). Although high sensitivity rates have been reported, diagnostic difficulties may also be experienced with core needle biopsy (41).

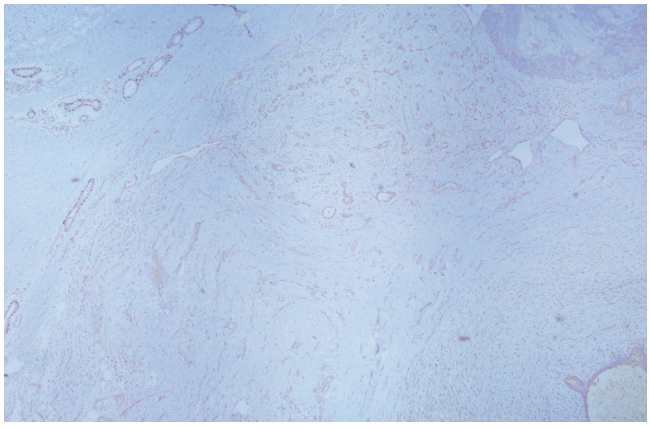

Figure 8. On p63 immunohistochemical staining, ducts that do not show immunoreactivity are observed in myoepithelial cells. Please compare with normal breast tissue in the upper left corner (x40)

However, since surgical excision provides the most definitive diagnosis, if there are findings that may raise clinical suspicion for phyllodes, such as rapid growth, excisional biopsy should be performed regardless of the results of core needle biopsy. Tru-cut biopsy was performed in case 20 for rapidly growing mass in the same year, and a focal invasive ductal carcinoma was detected in the WLE performed subsequently.

It is noted in the WHO breast tumor classification that PTs may include *in situ* and/or invasive carcinoma due to the presence of epithelial components (2). Although their mechanism of development is not fully understood, when carcinoma is detected within the PT it is believed that the epithelial component, stimulated by systemic growth factors, is responsible for this (3). Some investigators believe that the carcinoma begins in the breast parenchyma adjacent to the PT (4). In the cases in our study, the coexistence was detected in the ipsilateral breast. However, since there are reports of carcinoma in the contralateral breast, we suggest that mechanisms other than stimulation of the epithelial component must also be present.

Breast ductal carcinomas arise from the terminal lobular unit, while PTs arise from the stroma (1, 2). However, there is no evidence that when these two tumors coexist, stromal genetic changes lead to the neoplastic transformation of the epithelium, although this mechanism is plausible (4). It is unclear whether malignant transformation of the epithelium is due to stroma-epithelial interactions within the PT or whether it represents cancerization of a PT by carcinoma arising in

Table 4. Malign PTs coexisting with *in situ* carcinoma

Report	Carcinoma	Age	Tumor size (mm)	Localization (PT-Carcinoma)	Outcome
Seemayer et al. (8)	DCIS	27	60	Ipsilateral	NA
Huntrakoon (9)	DCIS	31	90	Ipsilateral	AW at 24 months
Christensen et al. (10)	LCIS	42-58	NA	Ipsilateral	DA 12 months from metastatic PT
Schwickerath et al. (11)	DCIS	47	20	Ipsilateral	NA
Morimoto et al. (12)	LCIS	49	110	Contralateral	AW at 132 months
Powell and Rosen (13)	DCIS	17–71	8–100	Ipsilateral	NA
Powell and Rosen (13)	LCIS	17–71	8–100	Contralateral	NA
Padmanabhan et al. (14)	LCIS	47	75	Ipsilateral	AW at 6 months
Nishimura et al. (16)	DCIS	80	105	Ipsilateral	DA 3 months from metastases
Lim and Tan (19)	DCIS	45	120	Ipsilateral	DA 108 months from unrelated cause
Tan et al. (20)	DCIS	NA	NA	Ipsilateral	NA
Nomura et al. (22)	DCIS	75	35	Ipsilateral	AW at 32 months
Korula et al. (25)	DCIS	51	210	Ipsilateral	AW at 11 months
Sin et al. (31)	DCIS	45	120	Ipsilateral	AW at 43 months
Sin et al. (31)	LCIS	48	50	Ipsilateral	AW at 43 months
Widya et al. (34)	DCIS	75	50	Ipsilateral	AW at 53 months
Widya et al. (34)	DCIS	49	40	Ipsilateral	AW at 53 months
Widya et al. (34)	LCIS	53	10	Ipsilateral	AW at 53 months
Co et al. (35)	DCIS	52	10	Ipsilateral	AW at 70 months
Co et al. (35)	DCIS	48	5	Ipsilateral	AW at 70 months
Hasdemir et al. (39)	DCIS	15–75	1.5–12	Ipsilateral	NA
Nistor-Ciurba et al. (40)	DCIS	45	60	Ipsilateral	NA

PT: phyllodes tumor; DCIS: ductal carcinoma *in situ;* LCIS: lobular carcinoma *in situ;* AW: alive and well; NA: not available; DA: died after

Table 5. Malign PTs coexisting with invasive carcinoma

Report	Carcinoma	Age	Tumor size (mm)	Localization (PT-Carcinoma)	Outcome
Powell and Rosen (13)	ILC	17–71	8–100	Ipsilateral, Contralateral	NA
Kasami et al. (15)	ILC	47	NA	Contralateral	NA
Gebrim et al. (17)	ILC	58	300	Contralateral	AW at 84 months
Auerbach (18)	IDC	69	NA	Ipsilateral	DA 51 months from metastases
Tokudome et al. (21)	Undifferentiated	59	35	Ipsilateral	AW at 5 months
Merck et al. (23)	IDC	NA	NA	Contralateral	AW at 32 months
Kefeli et al. (26)	IDC	26	45	Ipsilateral	DA 12 months
Choi et al. (29)	ICC	62	165	Ipsilateral	AW at 24 months
Shin et al. (30)	Invasive carcinoma, NOS and MC	45	240	Ipsilateral (Invasive), Contralateral (MC)	NA
Zhao et al. (32)	IDC	44	100	Contralateral	NA
Muthusamy et al. (36)	Invasive carcinoma, NOS	51	155	Ipsilateral	NA
Co et al. (35)	IDC	45	4,8	Ipsilateral	AW at 70 months
Kaur et al. (38)	NEC	26	90	Ipsilateral	NA
Hasdemir et al. (39)	IDC	15–75	1.5–12	Ipsilateral	NA
Hasdemir et al. (39)	IDC	15–75	1.5–12	Contralateral	NA
Nistor-Ciurba et al. (40)	IDC	71	50	Ipsilateral	AW at 39 months
Current study (Case no: 20)	IDC	45	NA	Contralateral	AW at 22 months
Current study (Case no: 28)	IDC	45	120	Ipsilateral	AW at 10 months
Current study (Case no: 29)	IDC	63	200	Ipsilateral	DA 2 months from unrelated cause

PT: phyllodes tumor; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; NEC: neuroendocrine carcinoma; ICC: invasive cribriform carcinoma; MC: metaplastic carcinoma; AW: alive and well; NA: not available; DA: died after

Table 6. Malign PTs coexisting with *in situ* and invasive carcinoma

Report	Carcinoma	Age	Tumor size (mm)	Localization (PT-Carcinoma)	Outcome
Widya et al. (34)	DCIS	75	2	Ipsilateral	AW at 53 months
Widya et al. (34)	DCIS	49	40	Ipsilateral	AW at 53 months
Widya et al. (34)	LCIS	53	3	Ipsilateral	AW at 53 months
Sugie et al. (24)	IDC, DCIS	54	60	Ipsilateral	DA 40 months from metastatic PT
Abdul Aziz et al. (27)	IDC, DCIS, LCIS	43	35	Ipsilateral	AW at 12 months
Macher-Goeppinger et al. (28)	IDC, DCIS	70	60	Ipsilateral	NA
Warrier et al. (33)	ILC, DCIS	50	110	Contralateral (ILC), Ipsilateral (DCIS)	AW at 24 months
To et al. (37)	ILC, LCIS	48	65	Ipsilateral	NA
Nistor-Ciurba et al. (40)	IDC, DCIS	50	110	Ipsilateral	AW at 132 months
Nistor-Ciurba et al. (40)	IDC, DCIS	75	40	Ipsilateral	DA 1 months from metastases

PT: phyllodes tumor; DCIS: ductal carcinoma *in situ;* LCIS: lobular carcinoma *in situ;* IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; AW: alive and well; NA: not available; DA: died after

the immediately adjacent breast tissue (39). This coexistence is usually found incidentally as it is often unnoticed in the limited evaluations provided by tru-cut biopsies and preoperative radiological evaluations. Therefore, although the diagnosis of PT is not challenging, we believe that a comprehensive histopathological examination with multiple sampling upon considering the coexistence with carcinoma is critical. The presence of ductal carcinoma in combination with PT is clinically important because it can alter the diagnostic process and the management of the patient.

Before 1970, mastectomy was the treatment of choice, regardless of PT subtypes (5, 43). Since then the type of operation to be selected in the surgical treatment of PTs varies depending on whether the tumor is benign, borderline, or malignant. While the absence of a tumor at the surgical margin is sufficient in benign tumors, a wide excision and >1 cm surgical margin is recommended in borderline and malignant tumors (41, 43). *National Comprehensive Cancer Network* guideline therapy recommends complete surgical excision with 1 cm margins without sentinel lymph node biopsy for or malignant phyllodes tumor (43). Axillary dissection is not routinely recommended because lymph node involvement is very rare, occurring in <1% of patients (43-45). However, the prognosis of patients with lymph node metastasis tends to be poor (46). The general surgical approach for giant PTs is simple mastectomy (44).

The coexistence of invasive carcinoma and PTs in patients undergoing breast-conserving surgery, adjuvant RT, chemotherapy, and targeted therapy may be performed in addition to surgical treatment, depending on immunohistochemical findings. However, this coexistence is quite rare and limited to individual cases in the literature (8-40). In our study, the incidence of the coexistence of PTs and carcinoma was 13.7% (4/29). This rate was higher than the previously reported incidence rates (Tables 4,5,6). In a multicenter study the rate of coexistence of PT and carcinoma was 1.07% (6/557) (35). In another single-center study (34), the rate of *in situ*/ invasive carcinoma was 6.01% (11/183) among all phyllodes. The largest study on this subject was performed by Co et al. (35) and their series consisted of 557 PTs. In the study, which included a large population (Hong Kong and Southern China) and included five hospitals over a period of 20 years, only 6 cases show the coexistence of phyllodes tumor and ductal carcinoma. In our tertiary center, the number of PTs over 10 years was only 29, and the association with ductal carcinoma was found in 4 (4/29=13.7%). This high rate of association may be due to small study numbers. However, considering that the association of phyllodes and ductal carcinoma reported from our country is limited to case reports (26, 39), there will not be a significant decrease. Perhaps more importantly, breast cancer incidences differ by ethnicity and are about four-fold higher in Western Europeans (90.7) compared to South Central Asia (26.2), possibly due to Western lifestyle and diet (47). Another reason may be that we oversampled tumor tissues for resident training.

In our study, the incidence of carcinoma, both *in situ* and invasive carcinoma, was 40% (2/5) in malignant PT patients and 20% (2/10) in borderline PT patients. The coexistence of benign PT and carcinoma was not detected. The coexistence of malignant PTs and carcinoma was significantly higher than those of benign and borderline PTs (p<0.05). In the series of Co et al. (35) and Widya et al. (34) the rate of carcinoma in malignant PT patients was 4.6% (3/64) and 27.2% (3/11) while this rate was 0.7% (1/130) and 45.4% (5/11) in borderline and 0.5% (2/363) and 27.2% (3/11) in benign PT patients, respectively. This coexistence was detected in the same breast in all cases in the study of Co et al. (35), while PT and carcinoma were found in the same breast in 3 of the 4 cases (75%) with PT coexistent with carcinoma in our study and one case (25%) had contralateral breast tumor. IDC was detected in 0.1% (1/557) of patients with concomitant PT, and DCIS was detected in 0.8% (5/557) of patients, while these rates were 3.4% (1/29) for DCIS, 3.4% (1/29) for LCIS and 10.3% (3/29) for IDC in our study. Human epidermal growth factor receptor 2 (HER2) was negative in all patients and ER positivity was detected in 50% (3/6) of the patients in the study by Co et al. (35), while HER2 was 50% (2/4) positive and ER was 75% (3/4) positive in our study. In the present series and in those of Co et al. (35) and Widya et al. (34) all PT diameters were >4 cm, with the exception of one patient in each.

There is a general lack of standardization in the treatment of PT, although there are rare cases of malignant epithelial transformation. As the association of PT with carcinoma influences patient management decisions, a multidisciplinary approach is needed with data from breast cancer surgeons, histopathologists, medical oncologists, and radiation oncologists to personalize treatment. In the adjuvant systemic and local treatment decision-making process, axillary nodal staging, pathological stage, borderline status and careful pathological examination are important.

We present a series that has found the highest rate of this rare association in the literature, to the best of our knowledge. However, a weakness of the present study is the low number of cases. Further limitations include the retrospective and single center nature of the study. However, we anticipate that the rate of coexistence of PT and breast carcinoma will increase as the importance of this assocaition is recognized. The multidisciplinary team dealing with breast diseases has a great responsibility in both diagnosis and treatment stages. Future studies with larger case numbers and patients with long-term follow-up data will provide better evidence concerning optimal management of this patient group.

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Authorship Contributions

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Original Article

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Pure Mucinous Breast Carcinoma With a Favorable Tumor Biology and Clinical Outcomes

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ABSTRACT

Objective: A few studies suggest that mucinous breast carcinoma (MBC) is a rare breast carcinoma with good prognostic features. Therefore, the aim of this study was to evaluate biological features and clinicopathological characteristics of pure mucinous breast carcinoma (PMBC) to determine clinical outcome in PMBC.

Materials and Methods: The data of 87 patients diagnosed with PMBC between November 2004 and February 2022 were retrospectively analyzed in terms of clinicopathological and demographic characteristics, management, and outcome.

Results: The majority of the patients in this study were female, with a median (range) age of 63 (28–90) years. Out of 87 patients, 60 had breast conserving surgery, 27 had a mastectomy, 58 had sentinel lymph node biopsy (SLNB), and 24 had axillary dissection due to a positive SLNB or clinical axilla. Due to age and comorbidities, five patients were not suitable for axillary surgery. The median largest tumor diameter was 23 (5–100) mm. Only 23 patients (26.4%) received adjuvant chemotherapy, whereas almost all patients received hormone therapy. The median duration of follow-up was 53 (6–207) months. There was no local or systemic recurrence in any of the patients. Only 10 patients (11.5%) died from non-cancer causes during the follow-up and treatment period. In this study, tumor diameter was significantly higher in grade II/III tumors (p = 0.039) and in patients under the age of 50 (p = 0.027). Furthermore, lymph node metastasis was statistically significantly more likely in patients under the age of 50 (60% *versus* 40%, p = 0.013). Patients who had not received chemotherapy or radiotherapy tended to be older than 50 years (p = 0.002).

Conclusion: In this study, the majority of patients were in the luminal subgroups with excellent prognosis and low incidences of lymph node metastasis. As a result, PMBC has favorable tumor biology. We believe that minimal axillary surgery would be the most appropriate approach during patient treatment, due to the low rate of lymph node involvement and favorable prognosis in PMBC patients.

Keywords: Mucinous carcinoma; molecular subtype; prognosis

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Key Points

- Few studies suggested that mucinous breast carcinoma is a rare breast carcinoma with good prognostic factors. Therefore, in this study, biologic features and clinicopathological characteristics of pure mucinous breast carcinoma were investigated to determine its clinical outcome.

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Introduction

Mucinous breast carcinoma (MBC) is relatively uncommon subtype of breast cancer, representing about 2% of all invasive breast cancers (1). In general, MBC presents at a mean age of 65 years, with 1% incidence in women under the age of 35 years. MBC patients are generally diagnosed through physical examination or mammography (2). MBC is characterized with the presence of tumor cells floating in extracellular mucin pools. Based on mucin contents, MBC is further divided into pure and mixed subgroups. Pure mucinous breast carcinoma (PMBC) contains a higher content of mucin than mixed mucinous breast carcinoma (MMBC). In this study, we considered tumors with more than 90% mucin content to be PMBC and less than 90% mucin contents to be MMBC (3). MBC patients have some features that differ from those of patients with invasive ductal carcinoma not otherwise specified. MBC has a lower incidence of nodal involvement, favorable histological grade (HG) and higher estrogen receptor (ER) and progesterone receptor (PR) expression (4). Breast carcinoma is a heterogeneous tumor with many clinical features that could be prognostic factors for patients. Despite the good prognosis of MBC, its clinical, histological, immunohistochemical characteristics and prognostic factors are still debatable. The purpose of this study was to report the last 18-year experience of the Department of Breast Surgery of the Istanbul Faculty of Medicine of Istanbul University regarding MBC with its histological and immune-histochemical characteristics and patient outcomes.

Materials and Methods

This study was based on an analysis of a large mono-institutional series of breast cancer patients treated in a high-volume reference center with widely standardized treatment and management. A multidisciplinary team had discussed each case individually after surgery, and all decisions about adjuvant treatment were made at these meetings.

Patient Selection and Follow-up

The study population was constituted at the Department of General Surgery, Breast Surgery Unit, and consisted of 87 female patients who had undergone surgical operations in the General Surgery Department. In addition, the PMBC diagnosis was assumed retrospectively. From the prospectively collected data between November 2004 and February 2022, we analyzed patients' demographics and pathologic features.

All cases' histological types were strictly controlled, and cases other than PMBC were excluded. Clinical and pathological factors, such as tumor size, surgical procedure, presence of loco-regional recurrence or distant metastasis, pathological characteristics, nodal staging, adjuvant treatment, and survival were analyzed. Personal contact with patients, including routine correspondence and telephone calls, was used to follow the patients. Follow-ups were performed at Istanbul University's Department of General Surgery, Breast Surgery Unit, every three months for the first two years, every six months for the next two years, and once a year after that. Patients were treated with either mastectomy or lumpectomy and axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) with local radiotherapy. After completion of the surgery, adjuvant treatments were administered as indicated based on international guidelines.

SLNB Method

Intraoperative visual blue dye (isosulfan blue) detection procedure was used. A frozen section procedure was employed, so if neoplasia was detected in the lymph node, a further lymph node dissection was performed. ALND was defined as a dissection of at least anatomical levels I and II including at least ten nodes, as shown in Figure 1.

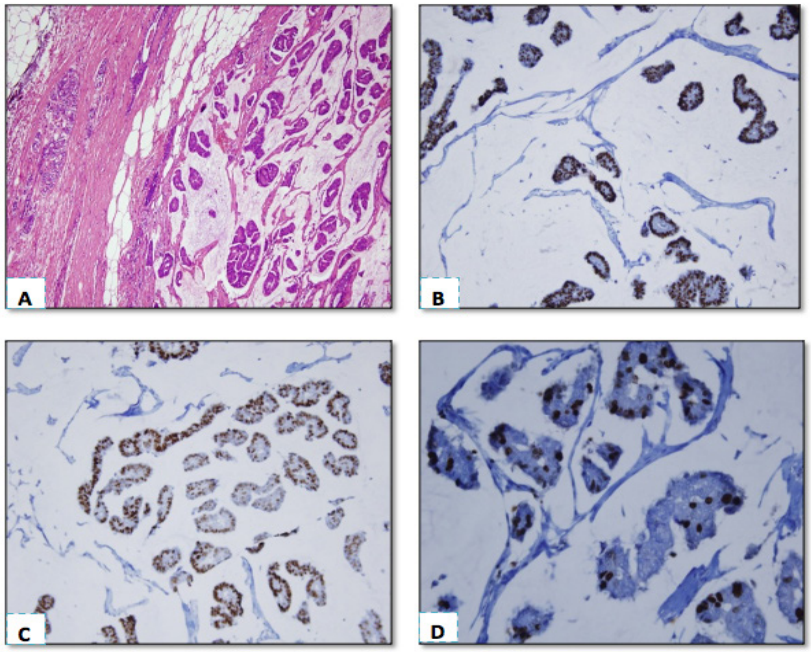

Figure 1. A. Neoplastic cells form papillary and glandular structures within extracellular mucin pools (Hematoxylin and eosin x10), **B.** Diffuse and strong intranuclear immunoreaction for estrogen receptor antibody in a case of mucinous carcinoma of the breast [Diaminobenzydin (DAB)-anti estrogen receptor-Mayer's hematoxylin x20], **C.** Moderately intense nuclear expression of progesterone receptor in nearly three quarters of neoplastic cellular nuclei (DAB-anti progesterone receptor-Mayer's hematoxylin x20), **D.** Low proliferative rate, as shown by anti-Ki67 labelling of neoplastic cells (DAB-anti Ki 67-Mayer's hematoxylin x40)

The pathological tumor stage was assessed according to the American Joint Committee on Cancer's 7th Staging System. PMBC was defined as having a mucinous component more than 90% and specialized pathologists with extensive experience in breast pathology performed a pathologic slide review. As recently revised (5, 6), the intrinsic subtypes of the tumor were defined as follows: luminal A, ER(+) or PR(+), human epidermal growth factor receptor 2 (HER2)-neu (-), Ki67 20%; luminal B, ER(+) or PR(-/+), HER2-neu (-/+), Ki67 >20%; HER2-enriched, ER(-) PR(-) HER2-neu (+); triple-negative, ER(-) PR(-).

Statistical Analysis

For statistical analysis, the Statistical Package for the Social Sciences (SPSS), version 25.0, was used (IBM Corp., Armonk, NY, USA). The data obtained from each continuous variable were analyzed using various descriptive, graphical, and statistical methods to determine whether or not they were normally distributed. In addition to descriptive statistical methods (number, percentage, mean, median, standard deviation, etc.), quantitative data was compared using the independent sample t-test. For qualitative comparisons between groups, the chi-square test (Pearson chi-square, continuity correction, Fisher's Exact test) was used. The significance of the results was determined using a 95% confidence interval.

Results

Patients and Tumors Characteristics

The patients were all female, with a median (range) age of 63 (28–90) years. The median tumor size was 23 (5–100) mm. Out of 87 patients, 60 (69%) had breast-conserving surgery (BCS), while 27 (31%) had mastectomy (Table 1). Only 15 of the patients with axillary staging had lymph node metastasis, 11 of which were N1 and four of which were N2.

As can be seen in Table 1, 58 patients (66.7%) had SLNB, and 24 had axillary dissection due to positive SLNB or positive clinical axilla. Only two of the 15 patients who had a positive SLNB and underwent axillary dissection had non-sentinel positivity. Due to age and comorbidities, five patients were not suitable for axillary surgery.

From all the tumors that were included in this study, 11 (12.6%) had lympho-vascular invasion (LVI), whereas 37 tumors (42.5%) were HG 1, 45 tumors (51.7%) were HG 2, and only 5 tumors (5.7%) were HG 3. Necrosis was seen in only six (6.9%) of the patients. Almost all patients were in the luminal group (95.4%).

Only five patients (5.7%) had HER2-neu positive tumors, while 83 tumors (95.4%) were ER-positive and 77 tumors (88.5%) were PR-positive. The majority of patients with Ki67 index (n = 56) had a Ki67 score less than 20% (71.4%).

Adjuvant Systemic Therapy

Adjuvant chemotherapy was given to only 23 patients (26.4%). With the exception of four patients, all patients had hormone therapy since their tumors were ER negative.

Outcome Analysis

The median follow-up time was 53 (6–207) months. None of the patients had a local or systemic recurrence. Only 10 out of 87 patients (11.5%) died during the follow-up and treatment period due to non-cancer causes.

As shown in Table 2, in this study we found that tumor diameter and LVI were statistically significantly higher in grade II/III tumors (p = 0.039 and p = 0.021, respectively). Also, we found that necrosis was only seen in grade II/III tumors (p = 0.036). Additionally, tumor diameter was larger (p = 0.027) and lymph node metastasis was more likely (p = 0.013) in patients younger than 50 years. Moreover, HER2 positivity was statistically significantly more common in patients younger than 50 years (p = 0.026). In a similar way, Ki67 less than 20% was statistically significant in grade I tumors and in patients older than 50 (p = 0.006 and p = 0.033, respectively). Furthermore, patients who had not received chemo/radiotherapy were older than 50 years (p = 0.002).

Radiological Investigation Results

Our radiological investigations were the same as reported in previous studies. Mammographically, PMBC tends to present as a well-circumscribed lesion (7-9), which is echogenic to the breast fat on ultrasonography (10). Thus, a significant number of lesions could be misinterpreted as benign on screening mammograms (10, 11).

Interestingly, a delay in the diagnosis may not cause a significant adverse outcome for most women (2). On magnetic resonance imaging, PMBC is associated with a very specific appearance, showing a gradually enhancing contrast pattern with rim or heterogeneous enhancement and a very high signal intensity on T2-weighted images (12, 13), as we show in Figure 2.

Discussion and Conclusion

Mucinous carcinoma is a rare type of cancer that can arise in mucin-producing epithelial tissues. MBC is rarely seen in clinical practice, comprising approximately 2% of all invasive breast cancers (1). In the literature, Di Saverio et al. (14) and Vo et al. (15) presented multivariate analysis results. These studies indicate that independent factors such as age, tumor size, lymph node status, and ER status are associated with a particularly good prognosis in MBC patients. PMBC is a cancer of older women, with only 1% of PMBC patients being under the age of 35 years (2, 16). The median age of the patients included in this study was 63, which is similar to a study done by Zhou et al. (17).

Previous studies have shown that sentinel lymph node metastasis is the most important prognostic factor for disease-free survival (1, 18, 19). In this study, a small number of patients (15/87) had lymph node metastasis, and a favorable prognosis was noted for patients who had no metastasis to lymph nodes. Compared to the other studies, nodal positivity was detected in 17.2% of our study patients whereas in other series, this percentage ranged from 2% to 20% (17-20). Only two of the 15 patients (2/15; 13.3%) who had a positive SLNB and underwent axillary dissection had non-sentinel positivity. According to the findings of the ACOSOG Z0011 study, axillary curettage would be unnecessary for patients with sentinel lymph node positivity in the pure mucinous carcinoma patient group (21).

We found that tumor diameter in PMBC was significantly larger in grade II/III tumors and in patients under the age of 50, which was consistent with the findings of Tahmasebi et al. (22). In a group of 111 patients with MBC, Diab et al. (23) observed a correlation between the size of the primary tumors and the status of the lymph nodes. When the tumor size was less than 2 cm, metastasis to lymph nodes was not indicated in 90% of the patients, which is in agreement with our study results of 83%. Another study by Skotnicki et al. compared the clinical characteristics and treatment results of 70 patients with PMBC and 40 patients with MMBC, treated at a single institution for 25 years.

Table 1. Patients and tumors characteristics (n = 87)

Characteristic	Category	n	%	Median (range)
Age (years)	All	87	100.0	63 (28–90)
Age group	<50 years	26	29.9	
	≥50 years	61	70.1	
pT stage	pT1	36	41.4	
	pT2	44	50.6	
	pT3	7	8.0	
pN stage	pN0	72	82.8	
	pN1	11	12.6	
	pN2	4	4.6	
Tumor diameter (mm)	All	87	100.0	23 (5–100)
Breast surgery	BCS	60	69.0	
	Mastectomy	27	31.0	
	Not done	5	5.7	
Axillary surgery	SLNB	58	66.7	
	ALND	24	27.6	
Grade	I	37	42.5	
	II	45	51.7	
	III	5	5.7	
LVI	Positive	11	12.6	
	Negative	76	87.4	
Necrosis	Positive	6	6.9	
	Negative	81	93.1	
ER	Positive	83	95.4	
	Negative	4	4.6	
PR	Positive	77	88.5	
	Negative	10	11.5	
HER2	Positive	5	5.7	
	Negative	82	94.3	
Ki-67 (n=56)	<20%	40	71.4	10 (2–50)
	≥20%	16	28.6	
Molecular subtype	Luminal	83	95.4	
	Non- Luminal	4	4.6	
Adjuvant therapy	None*	14	16.1	
	RT	50	57.5	
	CT+RT	23	26.4	
Follow-up time (months)	All	87	100.0	53 (6–207)
Relapse	Yes	0	0.0	
	No	87	100.0	
Mortality	Yes**	10	11.5	
	No	77	88.5	

ER: estrogen receptor; PR: progesterone receptor; CT: chemotherapy; RT: radiotherapy; LVI: lymph vascular invasion; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; *: they received only hormone therapy, **: all deaths were due to non-cancer causes

Table 2. Patient characteristics according to grade and age (n = 87)

		Grade			Age		
		I (n = 37)	II/III (n = 50)		<50 (n = 26)	≥50 (n = 61)	
Characteristic	**Category**	**n (%)**	**n (%)**	***p***	**n (%)**	**n (%)**	***p***
Age#	All	61.22±13.38	59.42±16.48	0.588[a]	41.08±6.76	68.33±9.26	-
Age group	<50	9 (34.6)	17 (65.4)	0.461[c]	-	-	
	≥50	28 (45.9)	33 (54.1)		-	-	
pT stage	pT1	19 (52.8)	17 (47.2)	0.160[c]	10 (27.8)	26 (72.2)	0.902[c]
	pT2/3	18 (35.3)	33 (64.7)		16 (31.4)	35 (68.6)	
pN stage	pN0	31 (43.1)	41 (56.9)	0.999[c]	17 (23.6)	55 (76.4)	**0.013[c]***
	pN1/2	6 (40.0)	9 (60.0)		9 (60.0)	6 (40.0)	
Tumor diameter (mm)#	All	23.32±15.33	30.98±17.83	**0.039[a]***	33.92±18.72	25.08±15.87	**0.027[a]***
Breast surgery	BCS	26 (43.3)	34 (56.7)	0.999[c]	18 (30.0)	42 (70.0)	
	Mastectomy	11 (40.7)	16 (59.3)		8 (29.6)	19 (70.4)	
Axillary surgery	Not done	2 (40.0)	3 (60.0)	0.98[db]	0 (0.0)	5 (100.0)	0.246[b]
	SLNB	25 (43.1)	33 (56.9)		17 (29.3)	41 (70.7)	
	ALND	10 (41.7)	14 (58.3)		9 (37.5)	15 (62.5)	
Grade	I	-	-		9 (24.3)	28 (75.7)	0.461[c]
	II/III	-	-		17 (34.0)	33 (66.0)	
LVI	Positive	1 (9.1)	10 (90.9)	**0.021[d]***	5 (45.5)	6 (54.5)	0.393[c]
	Negative	36 (47.4)	40 (52.6)		21 (27.6)	55 (72.4)	
Necrosis	Positive	0 (0.0)	6 (100.0)	0.036[d]*	2 (33.3)	4 (66.7)	0.999d
	Negative	37 (45.7)	44 (54.3)		24 (29.6)	57 (70.4)	
ER	Positive	36 (43.4)	47 (56.6)	0.633[d]	24 (28.9)	59 (71.1)	0.580[d]
	Negative	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)	
PR	Positive	34 (44.2)	43 (55.8)	0.507[d]	23 (29.9)	54 (70.1)	0.999[d]
	Negative	3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)	
HER2	Positive	0 (0.0)	5 (100.0)	0.069[d]	4 (80.0)	1 (20.0)	**0.026[d]***
	Negative	37 (45.1)	45 (54.9)		22 (26.8)	60 (73.2)	
Ki-67(n = 56)	<20%	22 (55.0)	18 (45.0)	**0.006[d]***	9 (22.5)	31 (77.5)	**0.033[c]***
	≥20%	2 (12.5)	14 (87.5)		9 (56.3)	7 (43.7)	
Molecular subtype	Luminal	36 (43.4)	47 (56.6)	0.633[d]	24 (28.9)	59 (71.1)	0.580[d]
	Non-Luminal	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)	
Adjuvant therapy	Didn't receive	6 (42.9)	8 (57.1)	0.052[b]	1 (7.1)	13 (92.9)	**0.002[b]***
	RT	26 (52.0)	24 (48.0)		12 (24.0)	38 (76.0)	
	CT+RT	5 (21.7)	18 (78.3)		13 (56.5)	10 (43.5)	
Mortality	Yes	3 (30.0)	7 (70.0)	0.507[d]	2 (20.0)	8 (80.0)	0.716[d]
	No	34 (44.2)	43 (55.8)		24 (31.2)	53 (68.8)	

*: p<0.05, #: Mean ± Standard deviation; [a(t)]: independent sample t-test; x^2: chi-square tests ([b]: pearson chi-square, [c]: continuity correction, [d]: fisher's exact test)

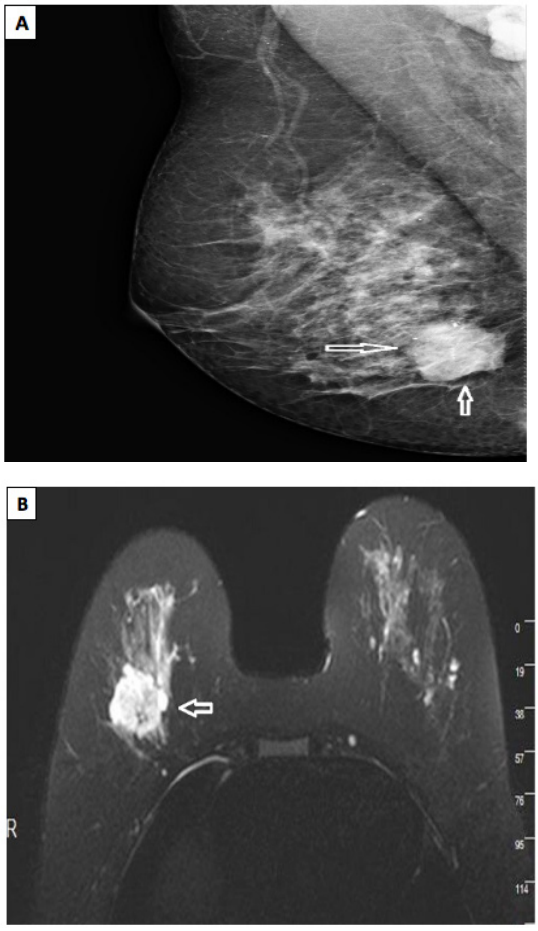

Figure 2. A. Mucinous breast carcinoma mammography, **B.** Magnetic resonance imaging

*Images had taken from our diagnosed patients

Their results demonstrated that the only difference between PMBC and MMBC was nodal status, as MMBC showed a significantly higher incidence of axillary nodal metastasis compared to PMBC (25% *versus* 10%) (17).

Furthermore, a recent study found that PMBC and MMBC were clinicopathologically distinct in terms of gross findings and lymph node status. The average length of follow-up was 24.5 months. MMBCs were highly proliferative, with more complications compared to PMBC. Lymph node involvement is the most important prognostic factor, and it is independent of other prognostic factors, such as tumor size, patient age, and hormonal receptor status (24). According to our findings, lymph node involvement, mean tumor diameter, high Ki67 expression, and HER2 positivity were all significantly increased in the group under 50 years old. These findings are consistent with the earlier reports of young-age aggressive tumor structure. However, no local, regional, or systemic recurrence was found in this study. This could be explained by the distinctive structure of mucinous carcinomas.

The PMBC data shows a high percentage of hormone receptor expression. These findings are consistent with Saverio's findings from large data, which reported a rate of positivity of 94% for ER and 81% for PR (14). A high rate of hormone receptor expression and old age were associated with a favorable prognosis in patients. Patients over the age of 50 did not receive chemo/radiotherapy, which explains their high sensitivity to hormone therapy and lack of lymph node metastasis.

Compared to other breast carcinoma forms, mucinous carcinoma has less genetic instability (25). Several studies have shown that PMBC has clinicopathological heterogeneity (26), but 95.4% of patients in this study were in the luminal subgroups. We couldn't classify luminal subgroups because we didn't have the values for Ki67 expression for all patients. Moreover, it is genetically heterogeneous and lacks any sort of pathognomonic genetic alterations (26, 27). Further clinical trials with larger sample sizes, as well as molecular and genetic studies, need to be conducted to get a better understanding of the molecular biology and clinical outcomes of PMBC.

In conclusion, MBC is a rare type of breast cancer with a favorable prognosis. Patients with MBC have a low rate of lymph node metastasis and almost all patients are in the luminal subgroups. PMBC has a lower incidence, smaller tumor size, benign lesion-like characteristics, low axillary lymph node metastasis, low grade, low recurrence rate, and a higher survival rate. We believe that minimal axillary surgery would be the most appropriate approach during patient treatment due to the low rate of lymph node involvement and favorable prognosis in PMBC patients.

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Ethics Committee Approval: This study was based on an analysis of a large mono-institutional series of breast cancer patients treated in a high-volume reference center with widely standardized treatment and management.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.E., N.C., E.O.; Design: S.E., S.K., N.C., E.O., M.M.; Data Collection and/or Processing: S.E., M.T., S.O., M.M.; Analysis and/ or Interpretation: S.E., M.T., S.K., H.K., S.O., V.O., N.C., E.O., R.Y., M.M.; Literature Searching: S.E.; Writing: S.E., M.T., S.K.

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Original Article

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The Clinicopathologic Features of 22 Cases With Primary Invasive Papillary Carcinoma of the Breast Identified in 1153 Cases With Invasive Breast Carcinoma: Single-Center Experience

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ABSTRACT

Objective: Invasive papillary carcinoma (IPC) of the breast is an uncommon histologic subtype with limited data in the literature. The aim of this study was to increase the evidence base by presenting clinicopathological findings of cases diagnosed as IPC.

Materials and Methods: Hematoxylin and eosin sections and immunostaining of surgical excision specimens diagnosed as invasive breast carcinoma were re-evaluated, retrospectively.

Results: IPC was detected in 22 cases (1.9%), of which 7 (0.6%) had pure and 15 (1.3%) had mixed morphology. Histologic types accompanying IPC were: Invasive ductal carcinoma (IDC) (15/15); invasive micropapillary carcinoma (3/15); and pleomorphic lobular carcinoma (1/15). Patient ages ranged between 36 and 89 (median 56.5) and the tumor size from 8 to 70 mm (median 19 mm). The histologic grade was 3 in five cases, 2 in 13, and 1 in four cases. The nuclear grade was 3 in 10 cases and 2 in 12. The values of positivity for estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2, and Ki-67 index indicated Luminal B phenotype in 16 (72.7%), triple-negative in 5 (22.7%), and Luminal A in 1 case (4.6%). Ductal carcinoma *in situ* was noted in 19 cases (86.4%).

Conclusion: IPC was mostly detected as an accompanying carcinoma to IDC at postmenopausal ages and was mostly Luminal B phenotype with intermediate-to-high grade features.

Keywords: Invasive papillary carcinoma; breast; histopathological findings; clinical features

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Key Points

- Invasive papillary carcinoma (IPC) of the breast is a rare type of tumor with usually Luminal B molecular phenotype.
- IPC is frequently detected as an accompanying carcinoma to invasive ductal carcinoma.
- Before diagnosing as IPC of the breast, metastases from other sites must be excluded.
- Encapsulated and/or Solid PC of the breast with invasive foci should not call as IPC.
- Most patients present in the early stages of breast cancer at postmenopausal age.

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Introduction

Papillary neoplasms of the breast comprise a wide spectrum of lesions from benign intraductal papilloma to invasive papillary carcinoma (IPC). This group of lesions were described in the last two editions of World Health Organization guidelines as intraductal papilloma, papillary ductal carcinoma in situ (DCIS), encapsulated papillary carcinoma, solid papillary carcinoma and IPC (1-4). Intraductal papilloma defines a benign breast lesion arising within a duct either in a central (solitary) or peripheral (multiple) location. This lesion, generally composed of broad papillary projections with fibrovascular cores, is covered by epithelial and myoepithelial cell layers. Some of the intraductal papillary lesions may include a mixed type of epithelial cell proliferation composed of luminal epithelial, myoepithelial, and immature cells, histologically estrogen receptor + (ER+) and CK5/6+ complementary patchy staining, and so these lesions are described as "intraductal papilloma with usual hyperplasia" (3, 5). Beyond this, some intraductal papillary lesions may demonstrate monotonous epithelial cell proliferation (ER+, CK5/6-). When the extent of this epithelial proliferation is <3 mm, they are called intraductal papilloma with atypical ductal hyperplasia (5). When this extent is ≥3 mm, they are then called intraductal papilloma with DCIS (5). Papillary DCIS, another type of lesion, defines a morphological subtype of DCIS composed of delicate branching fibrovascular cores lined with neoplastic ductal epithelium without myoepithelial cells in papillae. Since these lesions are a subtype of DCIS, the myoepithelial cell layer is retained in the periphery of the lesion (4).

Encapsulated papillary carcinoma is a carcinoma present within a cystic space surrounded by a fibrous capsule. The lesion is composed of fine fibrovascular stalks covered by a neoplastic epithelium of low or intermediate nuclear grade. Myoepithelial cells are usually not found along the papillae or periphery of the lesion. Encapsulated papillary carcinoma with high-grade nuclear features, however, should be graded, staged, and managed as an invasive breast carcinoma (6). Solid papillary carcinoma is characterized by a solid growth pattern with inconspicuous delicate fibrovascular cores. This tumor may show neuroendocrine differentiation, as well as intracellular or extracellular mucin production. Myoepithelial cells may be present or absent within the solid papillary proliferation or on the periphery of the nodules. Both encapsulated papillary carcinoma and solid papillary carcinomas may display clearly invasive foci of breast carcinoma. In this situation, it is important not to label these foci as IPC. These invasive foci generally exhibit a non-papillary morphology (7). Since some papillary lesions have been misidentified in the past, resulting in conflicting data in the literature (8, 9).

IPC is an invasive carcinoma with fibrovascular cores covered by neoplastic epithelial cells. IPC of the breast is an extremely rare type of breast tumor. Therefore, there is limited knowledge of the histopathologic and clinical features of this tumor. Before diagnosing a tumor as IPC of the breast, metastasis from other sites to the breast must be excluded (3, 10). The previous history of the patient and radiologic findings provide information for accurate differential diagnosis. Additionally, the presence of a DCIS component, as well as positive immunostaining for ER, PR, and GATA-3, and negative immunostaining for PAX8, TTF-1, and thyroglobulin are useful tools for supporting a breast origin. In this study, we aimed to determine the incidence and clinicopathological features of primary IPC of the breast.

Materials and Methods

Data Collection

We retrospectively reviewed the slides of cases with primary invasive breast carcinoma to define the invasive papillary morphology within these tumors. For this purpose, we obtained hematoxylin and eosin (H&E) sections of surgical excision specimens of cases diagnosed between 2010 to 2018 and then re-evaluated them microscopically. Clinical features of the patients were obtained from patient files and clinicians.

We used the definition of "pure IPC" for invasive carcinoma that consists of papillary structures in ≥90% of the tumor (11).

Exclusion-Inclusion Criterion

After re-examining the slides, 23 cases with invasive papillary morphology were identified, either as pure IPC or as IPC as a component within a mixed-type breast carcinoma. One of these cases was excluded due to retraction artefact around the groups of tumor cells that mimic papillary appearance.

One case had a history of neoadjuvant therapy. Secondary changes due to therapy were not prominent in this case. Following neoadjuvant chemotherapy, the nuclear grade of the tumor changed from 2 to 3 in the excision specimen (Case #20). The ER, progesterone receptor (PR), human epidermal growth factor 2 (HER2) and Ki-67 status of this tumor were similar to that of previous core needle biopsy and thus the molecular subtype stayed the same.

Two out of 22 cases with IPC showed no DCIS in the adjacent areas. Both cases showed pure-type IPC morphology (one was 100% of the tumor, the other 90%). The clinical history and radiographic findings of these cases were checked and then immunohistochemical staining was performed, including GATA3 (for breast origin), PAX8 (for Mullerian origin), TTF-1 (for lung origin), and Thyroglobulin (for thyroid origin) to exclude possible metastatic origin. Both cases showed positivity for GATA3 and were negative for PAX8, TTF-1, and Thyroglobulin; thus, several possible metastatic origins were excluded.

Eventually, a total of 22 cases, 1 of which had a history of neoadjuvant therapy, were included in the study. This project was approved by the Ethical Committee (protocol number: 1888-28/06/2019).

Results

Statistical and Clinical Characteristics

Review of 1153 invasive breast carcinomas, diagnosed in our clinic from 2010 to 2018, identified only 22 cases that showed an invasive component as found in a papillary form (22/1153; 1.9%). The invasive papillary morphology composed 10% of the tumors in two cases, 10-50% of the tumor in 11 cases, 50-90% of the tumor in a further two cases, and ≥90% of the tumor in seven cases. Therefore, pure-type IPC was found in 7 of 22 cases (7/1153; 0.6%) and identified as a component within mixed type carcinomas in 15 out of 22 cases (15/1153; 1.3%). The other invasive histologic types accompanying IPC were: IDC (15/15; 100%), micropapillary carcinoma (3/15; 20%), and pleomorphic-type lobular carcinoma (1/15; 6.7%). One case (Case #9) had two invasive foci, of which one was mixed-type histology (IPC + IDC + invasive micropapillary carcinoma) and the other was IPC only.

One of the 22 cases was male (4.5%). The ages of the patients with IPC ranged from 36 to 89 years (median 56.5), from 36 to 89 years for mixed-type IPC (median 52) and from 47 to 79 years for pure-type IPC alone (median 61). The tumor size was 8 to 70 mm (median 19 mm). The presenting features of the patients were palpable mass (15 cases), radiologic abnormality by mammographic screening and magnetic resonance imaging (5 cases), and bloody nipple discharge (2 cases; 1 accompanying to a palpable mass). Four of these cases also had a history of familial breast cancer.

The tumor was located in the left breast in 16 cases (72.7%) and the right breast in six (27.3%). Tumor locations were upper outer quadrant (n = 12), lower outer quadrant (n = 4), upper inner quadrant (n = 4), and the retroareloar region (n = 2). Five of these cases had multiple foci.

The previous diagnoses of the core needle biopsy specimens (CNBS) in these cases were invasive ductal carcinoma (IDC) (n = 9), invasive breast carcinoma (n = 5), mixed-type invasive ductal and IPC (n = 2), invasive breast carcinoma with focal micropapillary growth pattern (n = 2), invasive breast carcinoma with extensive papillary growth pattern (n = 1), invasive breast carcinoma with apocrine differentiation (n = 1), and invasive adenocarcinoma consistent with breast primary (n = 1). The latter case showed prominent desmoplastic stroma in between irregular-shaped glandular structures, reminiscent of Mullerian-type serous carcinoma. However, the neoplastic glandular epithelium was positive for GATA3 and negative for PAX8, TTF1, and Thyroglobulin.

None of the cases in this study showed positivity for PAX8, TTF1, and Thyroglobulin. However, all cases were positive for GATA3, which supported breast origin. The CNBS of one case was interpreted as "a lesion consistent with papillary neoplasia" and offered surgical excision with a clear margin. This biopsy was composed of a monotonous cell proliferation of low-grade nuclei in fibrovascular stalks; however, this neoplastic fragment was 1 mm in size. The second CNBS performed in this case revealed invasive breast carcinoma (Case #1). As a result, all cases but one demonstrated a clearly invasive morphology in the first CNBS, and IPC morphology was described in 3 of these 22 (13.6%) cases.

Breast conserving surgery was performed in 13 cases (with sentinel lymph node dissection in eight and axillary dissection in five cases); simple mastectomy in three cases (with sentinel lymph node dissection), and modified radical mastectomy in six cases. The follow-up time of the patients ranged between 7 to 108 months, with one patient dying 7 months after diagnosis. Follow-up time (months) and clinic status, as well as other clinicopathologic features of the patients are summarized in Table 1.

Histopathologic Characteristics

The distribution of histologic grade was as follows: Grade 3 in five cases, grade 2 in 13 cases, and grade 1 in four cases. Nuclear grade was 3 in 10 cases and 2 in 12 cases. Lymphovascular invasion was noted in nine cases (9/22, 40.9%), perineural invasion in two (2/22, 9.1%), and DCIS in 19 (19/22, 86.4%). The DCIS patterns were noted in decreasing order as cribriform (12/19), micropapillary (10/19), solid (8/19), papillary (7/19), and flat type (3/19). Comedonecrosis was seen in 17 of 19 cases (89.5%). Tumor-associated microcalcification (for both invasive and *in situ* component) was seen in 10 of 22 cases. Different appearances of tumor in IPC are displayed through Figure 1a,b to Figure 5a,b.

The T-stages of the cases were as follows: pT1 n = 13, pT2 n = 8, pT3 n = 0, and pT4 n = 1. Axillary lymph node status was as follows: pNx n = 1, pN0 n = 10, pN1 n = 7, pN2 n = 2, and pN3 n = 2. Whereas lymph node metastasis was determined in 2 out of 7 pure-type IPC (28.6%), it was identified in 10 out of 15 mixed-type carcinomas (66.6%).

The histopathological findings determined within the surrounding breast parenchyma were as follows: ductal hyperplasia with atypia (n = 1), ductal hyperplasia without atypia (n = 3), columnar cell lesions with atypia/flat atypia (n = 6), columnar cell lesions without atypia (n = 9), complex sclerosing lesions (sclerosing adenosis, radial scar and/or papilloma, n = 3), papilloma only (n = 2), fibrocystic changes (n = 15), apocrine metaplasia (n = 10), ductal ectasia (n = 11), fibroadenoma or fibroadenomatoid nodules (n = 4), pseudoangiomatous stromal hyperplasia (PASH; n = 2), capillary hemangioma (n = 1), pseudolactational changes (n = 1), and fat necrosis (n = 1). There were no prominent changes in the non-tumoral breast tissue in seven cases.

Immunohistochemical Findings

Seventeen cases showed positive immunostaining for ER and PR (Luminal phenotype; 17/22, 77.3%). The ER/PR/HER2/Ki-67 status for each case can be viewed in Table 2. The HER2 expression was found to be negative by immunohistochemistry in 19 cases (score 0 or 1) and positive by immunohistochemistry and/or the silver *in situ* hybridization (SISH) method in three cases (3/22; 13.6%). Among 22 cases, 20 showed a Ki-67 proliferation index ≥20% and the remaining two cases were <20%. According to the values of ER, PR, HER2, and Ki-67, the distribution of cases in the molecular subgroups were: 16 cases (72.7%) Luminal B (ER/PR/HER2 positive or ER/PR+, HER2- but Ki67 ≥20%), five cases (22.7%) triple negative (ER/PR/HER2 negative), and one case (4.6%) Luminal A (ER/PR+, HER2- and Ki67 <20%). There was no case in the HER2 subgroup (ER/PR- and HER2+). Pure-type IPC cases showed Luminal B phenotype in five cases and triple-negativity in two cases. Histopathologic and immunohistochemical findings are summarized in Table 2.

Cases With Exceptional Findings

A prominent lymphocytic inflammatory cell infiltration was noted within the tumor in one of the cases (Case #8). This case showed mixed-type histology of IPC + IDC + invasive micropapillary carcinoma and high-grade nuclear and histologic features with triple negative phenotype. Axillary lymph node metastasis was found in seven out of 14 lymph nodes. The patient died 17 months after diagnosis.

An apocrine cytonuclear feature was described in one case (Case #3). This case showed mixed-type histology (IPC + IDC) in all invasive foci (four tumor foci) and Luminal A molecular phenotype as well as positive immunostaining for Androgen and GCDFP-15. Axillary lymph node metastasis was identified in one out of 18 lymph nodes.

A pagetoid involvement of large ducts and nipple dermis was identified in one case (Case #16). This case had two invasive tumor foci, one of which was located in the retroareolar region. The tumor (both foci) showed a mixed-type histology (IPC + IDC) and Luminal B molecular phenotype. Axillary lymph node metastasis was identified in 3/8 lymph nodes. The axillary metastases were of non-papillary IDC morphology.

Table 1. Clinical characteristics of the patients

	Sex	Age	Clinical history	Location	Tumor size (mm)	Histologic type	Mixed component	Follow-up time (months)	Survey (dead or alive)	Local reccurence (LR)/ Metastasis (month)
Case 1	F	62	Palpable mass	R-UIQ	20	IPC	-	108	Alive	-
Case 2	F	52	Palpable mass	L-Retroareolar	18-15 (two foci)	Mixed carcinoma	30% IPC + 70% IDC	92	Alive	-
Case 3	F	45	Palpable mass	L-UOQ	16-12-11-3 (multiple foci)	Mixed carcinoma	50% IPC + 50% IDC	67	Alive	-
Case 4	F	47	Palpable mass	L-UOQ	21	IPC	-	74	Alive	Lung and bone met (53 m)
Case 5	F	61	Palpable mass (Family history+)	L-LOQ	20	IPC	-	32	Dead	Lung, bone and infra+supra-diaphragmatic LN met (21 m)
Case 6	F	64	Palpable mass (Family history+)	R-UOQ	22	Mixed carcinoma	10% IPC + 90% IDC	72	Alive	-
Case 7	F	42	Palpable mass	R-UOQ	22	Mixed carcinoma	30% IPC + 70% IDC	55	Alive	-
Case 8	F	53	Palpable mass	L-UOQ	30	Mixed carcinoma	45% IPC + 45% IDC + 10% IMPC	17	Dead	LR (+)/multiple LN met (+malign pleural effusion) (17 m)
Case 9	F	55	Bloody nipple discharge + palpable mass	L-UOQ and UIQ	14-6.5	1. Mixed carcinoma 2. IPC	1. 45% IPC + 45% IDC + 10% IMPC 2. IPC	49	Dead	Brain, bone and infra+supra-diaphragmatic LN met (46 m)
Case 10	F	58	Palpable mass	L-UOQ	16	Mixed carcinoma	35% IPC + 30% IDC + 35% IMPC	55	Alive	-
Case 11	F	70	Palpable mass	L-UOQ	8	Mixed carcinoma	30% IPC + 70% IDC	63	Alive	-
Case 12	M	70	Palpable mass	L-Retroareolar	15	IPC	-	58	Alive	-
Case 13	F	89	Palpable mass, prolabed to skin (Family history+)	L-UOQ	70	Mixed carcinoma	40% IPC + 50% IDC + 10% IMPC	12	Dead	Bone and supradiaphragmatic LN met (7 m)
Case 14	F	36	Mammographic screening	R-UOQ	26	Mixed carcinoma	30% IPC + 70% IDC	42	Alive	-
Case 15	F	61	Mammographic screening (Family history+)	L-UIQ	14	IPC	-	48	Alive	-
Case 16	F	63	Radiologic examination (MRI)	L-UOQ and retroareolar	15-10	Mixed carcinoma	50% IPC + 50% IDC	41	Alive	-

Table 1. Continued

	Sex	Age	Clinical history	Location	Tumor size (mm)	Histologic type	Mixed component	Follow-up time (months)	Survey (dead or alive)	Local reccurence (LR)/ Metastasis (month)
Case 17	F	79	Bloody nipple discharge	R-LOQ	25	IPC	-	7	Dead - IDC in the left breast (31 m) *	-
Case 18	F	39	Palpable mass	L- UOQ	14-12	Mixed carcinoma	10% IPC + 80% IDC + 10% PLC	33	Alive	-
Case 19	F	41	Mammographic screening	L-UOQ	25	Mixed carcinoma	60% IPC + 40% IDC	31	Alive	-
Case 20	F	50	Mammographic screening	L-LOQ	17	Mixed carcinoma	40% IPC + 60% IDC	36	Alive	-
Case 21	F	64	Palpable mass	L-UIQ	16	Mixed carcinoma	20% IPC + 80% IDC	38	Alive	-
Case 22	F	40	Palpable mass	R-LOQ	26	Mixed carcinoma	70% IPC + 30% IDC	25	Alive	-

F: female; M: male; MRI: magnetic resonance imaging; R: right; L: left; UIQ: upper inner quadrant; UOQ: upper outer quadrant; LOQ: lower outer quadrant; IPC: invasive papillary carcinoma; IDC: invasive ductal carcinoma; IMPC: invasive micropapillary carcinoma; PLC: pleomorphic lobular carcinoma; m: month; LN: lymph node, *metachronous tumors

Discussion and Conclusion

Differential Diagnoses and Controversies in the Literature

IPC of the breast was rare and poorly defined before 2003. Therefore, collecting reliable data for this tumor type is quite difficult. Before making a diagnosis of IPC, some important issues should be clarified. First, a possible metastasis to the breast must be excluded by clinical, radiological, and histopathological examination. Differential diagnosis comprises mostly gynecologic tractus, lung, and thyroid malignancies in women and prostate, lung, colon, and bladder carcinomas in men (1, 4, 12). Prostate-specific antigen has a limited value to differentiate between primary and metastatic carcinoma of the breast in men, since it may also show positive staining in breast carcinomas (1). The presence of a DCIS component, as well as positive staining for ER and/or PR receptors and GATA3 support breast origin. Second, if the tumor exhibits encapsulated papillary carcinoma or solid papillary carcinoma morphology associated with invasive breast carcinoma, these tumors should not be classified as IPC, but categorized according to the individual invasive component, which is generally non-papillary (6, 7, 9). The favorable prognosis for IPC reported in the literature mainly originates from cases of encapsulated papillary carcinoma and solid papillary carcinoma associated with invasion (9, 13). Moreover, IPC should be differentiated from invasive micropapillary carcinoma, which is a separate entity in terms of biological behavior and morphological appearance (3).

Clinicopathologic Statistics

In the current study, whereas the median age of the patients with mixed-type IPC was 52, it was 61 for pure-type IPC. However, there was no significant difference in terms of patient age (p = 0.149) between mixed or pure types of IPCs. Patient age at tumor diagnosis was reported as older in IPCs than in IDC in previous studies (14-16). The median size of tumor was 19 mm. IPC is more common in males than in females, accounting for approximately 2 to 4% of cases (11). One of the patients in our study was male. The presence of more papillary-type carcinoma in the male patient was explained by a less well-developed terminal duct lobular unit as well as the presence of more large ducts in the male breast (17, 18). Most of the cases in this study presented as a palpable breast mass and others were detected by routine clinic-radiologic examinations. Two cases had a history of bloody nipple discharge. Although the tumor was located mostly in outer quadrants, in almost one-third of the cases, it was located in the inner quadrant or retroareolar region. Multiple tumor foci were also identified in 23% of the cases. Similarly, in previous studies, the presentation of patients with IPC were reported as a palpable breast mass, nipple discharge, or radiographic abnormality (19). IPC may exhibit growth as a single nodule in the central portion of the breast or as multiple nodules that extend out from the retroareolar region to the periphery of the breast (20, 21). Therefore, tumor location in the central region (retroareolar/subareolar) or inner quadrants and the presence of multiple foci of tumor should indicate papillary neoplasms of the breast.

Invasive papillary morphology was determined in 1.9% of the cases diagnosed as primary invasive breast carcinoma in this study. Whereas invasive papillary morphology was identified in 10-90% of the tumor in 1.3% of the cases, pure-type IPC (in which the tumor showed invasive papillary morphology in ≥90%

of the tumor) was found in 0.6% of the cases. The other histologic types accompanying IPC were IDC (15 cases), invasive micropapillary (3 cases), and pleomorphic lobular carcinoma (1 case). The overall incidence of IPC was reported as low, accounting for less than 1 to 2% of the cases with invasive breast carcinoma in the literature, as in this study (1, 22). IDC, invasive micropapillary carcinoma, and invasive lobular carcinoma have also been reported as other histologic types accompanying IPC (13). Lobular neoplasia was present in one case with mixed type breast carcinoma (IDC + pleomorphic type invasive lobular carcinoma + IPC). DCIS was identified in most of the cases (86.4%) in this study and both the nuclear grade and the patterns of DCIS were consistent with primary invasive breast carcinoma. Tumor-associated microcalcification was found at a higher frequency (45.4%).

Contrary to other studies, in the present study most of the cases with IPC showed intermediate to high-grade nuclear and histological features (13, 19, 22). We partially explain this due to the high number of cases with mixed-type histology in which each component (IPC

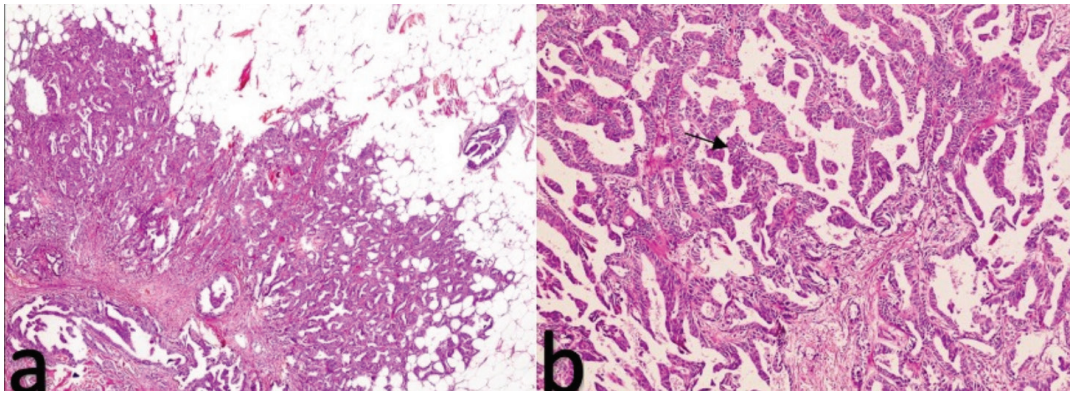

Figure 1a. Tumor shows infiltration within the adipose tissue (H&Ex100), **b.** Papillary structures lined by single or more layered cells with moderate nuclear atypia (H&Ex200)

H&E: hematoxylin and eosin

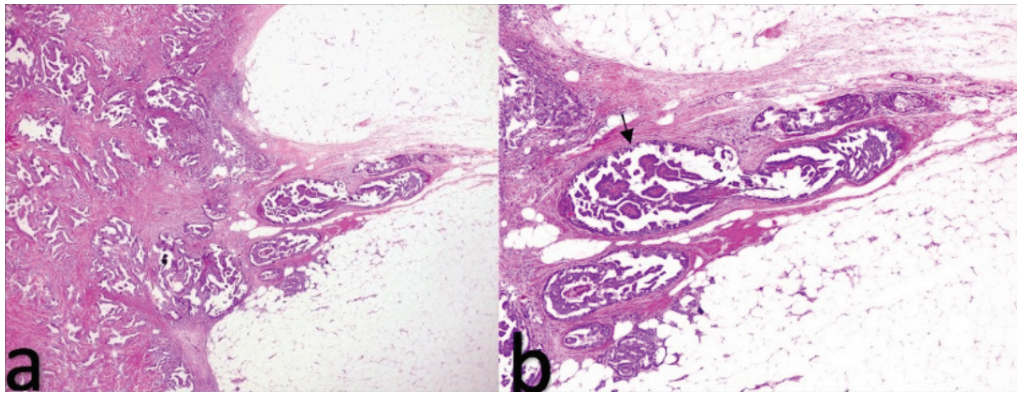

Figure 2a. Irregularly dilated invasive glands including papillary structures within their lumen are seen in the left part of the image (H&Ex40), **b.** Papillary type DCIS is seen (H&Ex100)

H&E: hematoxylin and eosin, DCIS: ductal carcinoma in situ

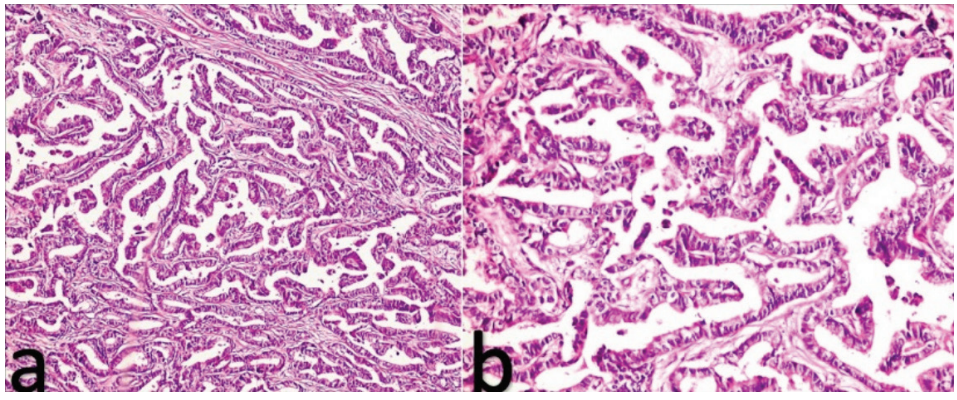

Figure 3a, b. Papillary structures within the irregularly dilated glands in a desmoplastic stroma (a: H&Ex200, b: H&Ex400)

H&E: hematoxylin and eosin

with IDC and/or invasive micropapillary and/or pleomorphic lobular carcinoma) might have similar grade features. In pure-type IPC (n = 7), the high-grade nuclear feature was found in almost half of the cases (3 cases) and intermediate-grade histologic feature in four. Although IPC generally was reported as a lower-grade tumor, information for tumor grade was not available in a significant number of patients in some published studies. In one of the largest studies, based on Surveillance, Epidemiology and End Results population, the histologic grade of tumor was reported as 1 in 32.6% of the cases, 2 in 31.9% of the cases, 3 in 14.5% of the cases, and unknown in 21% of the cases (22).

Most of the cases presented in this study were in the early stages of breast cancer (pT1-2, N0-1) as in the other studies (13, 19). Previous studies reported characteristic clinical and pathologic features of IPC to be patients at older age presentation (≥50), tumors presenting with smaller size, lower grades, reduced involvement of axillary lymph nodes, positive staining for hormone receptors (ER PR), and better survival rates (13, 14). In a study by Zheng et al. (22), the demographics and tumor characteristics of IPC (n = 524) were compared to those of IDC (n = 232,647). According to this study, patients with IPCs presented with smaller tumors (tumor size <20 mm, 67.4% *versus* 63.9%), more grade 1 disease (32.6% *versus* 18.6%), lower rate of LN involvement at diagnosis (11.6% *versus* 32.6%), more frequently presented with Stage I disease (61.5% *versus* 50.2%), a higher rate for ER positivity (87.2% *versus* 76.6%), a higher rate for PR positivity (80.7% *versus* 66.5%), a lower rate for HER amplification (2.1% *versus* 5.6%), higher rates for lumpectomy (68.7% *versus* 60.2%), and a lower rate for adjuvant radiotherapy (48.5% *versus* 56.6%) (22).

Comparison of survival rates between IPC and IDC demonstrated that disease-specific survival (DSS) was better in IPC patients than in the overall IDC population, with 5-year DSS rates in IPC and IDC 97.5% and 93%, respectively (22). Univariate analysis revealed that prognostic indicators included age, year of diagnosis, race, laterality, tumor grade, tumor size, LN status, and ER/PR/HER2 status (22). The type of treatment (radiation and surgery) was significantly associated with DSS so IPC histology was found to be a protective factor. Multivariate analysis also confirmed the prognostic factors identified in univariate analysis. However, histologic type was not found to be an independent prognostic factor after adjusting for other factors in multivariate analysis (22).

In the study by Liu et al. (13), the clinicopathological features and survival status of patients with IPC (n = 284) were compared to those with IDC (n = 300). The authors found that patients with IPC presented with an older age at diagnosis (postmenopausal), a low to intermediate grade of tumor, lower involvement of axillary lymph nodes, and a better 5-year overall survival (OS) and DSS than those of IDC. Additionally, tumors with Luminal A molecular phenotype showed a better 5-year OS and DSS than the other phenotypes. Therefore, the authors concluded that IPC was more favorable in terms of patient outcome than IDC. In addition, 11 out of 284 patients with IPCs were reported to have died from breast cancer. In these 11 patients, seven showed mixtures of other invasive histologic components such as IDC (n = 5), invasive micropapillary carcinoma (n = 1), and invasive lobular carcinoma (n = 1). Four of these 11 cases

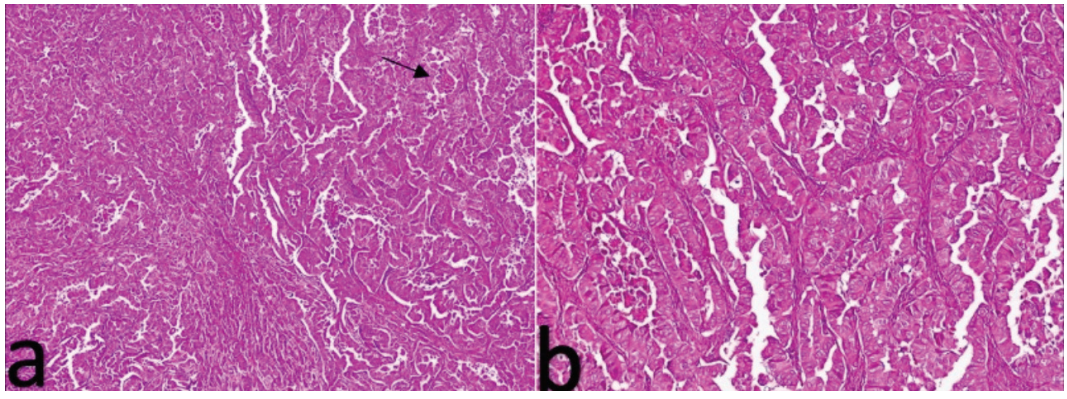

Figure 4a. IPC with focal areas of comedonecrosis (H&Ex200), **b.** Tumor cells show high-grade cytonuclear features, such as pleomorphic vesicular nuclei with prominent nucleoli as well as ample eosinophilic cytoplasm (H&Ex400)

H&E: hematoxylin and eosin, IPC: invasive papillary carcinoma

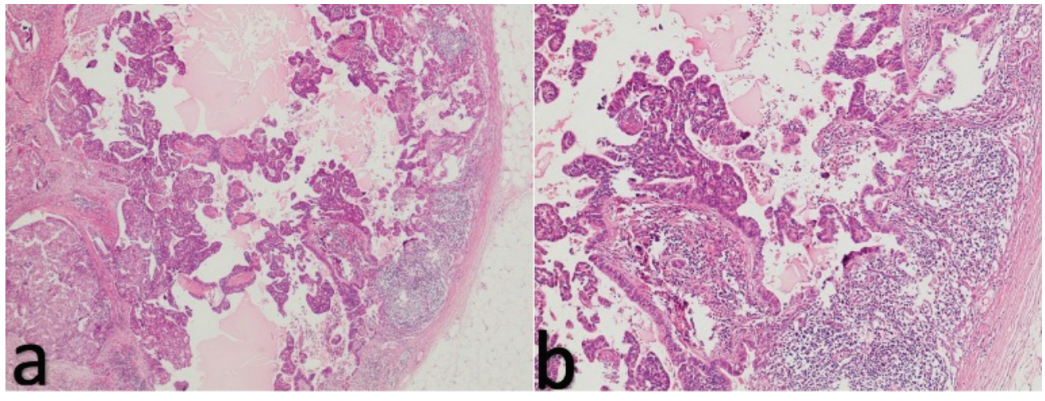

Figure 5a, b. Although most of the axillary lymph node metastases were detected in IDC morphology, a few cases (as seen above) maintained their papillary appearance in lymph node metastasis (a: H&Ex40, b: H&Ex 100)

 H&E: hematoxylin and eosin, IDC: invasive ductal carcinoma

Table 2. Histopathologic and immunohistochemical findings of the patients

	Surgical Procedure	Histologic Type	Focality	Mixed Component	NG	HG	LVI	PNI	Axillary LN	ER* %; intensity	PR* %; intensity	HER2	Ki-67 (%)	AR
Case 1	BCS+AD	IPC	U	-	2	2	-	-	0 / 20	90 +++	10 ++	-	60	NA
Case 2	MRM	Mixed carcinoma	M	30% IPC + 70% IDC	3	2	-	-	+ 3 / 11	50 ++	20 ++	-	30	NA
Case 3	MRM	Mixed carcinoma	M	50% IPC + 50% IDC	3	2	+	-	+ 1 / 18	95 +++	90 ++	-	10	+
Case 4	BCS+AD	IPC	U	-	3	2	+	-	+ 6 / 13	100 +++	30 ++	+	17,5	NA
Case 5	BCS+SLN	IPC	U	-	3	2	+	+	0 / 2	-	-	-	90	NA
Case 6	BCS+AD	Mixed carcinoma	U	10% IPC + 90% IDC	2	1	-	-	+ 3 / 17	100 +++	60 ++	-	22,5	NA
Case 7	BCS+SLN	Mixed carcinoma	U	30% IPC + 70% IDC	3	3	-	-	0 / 4	-	-	-	90	-
Case 8	BCS+AD	Mixed carcinoma	U	45% IPC + 45% IDC + 10% IMPC	3	3	+	-	+ 7 / 14	-	-	-	80	-
Case 9	SM+SLN+AD	1. Mixed carcinoma 2. IPC	M	1. 45% IPC + 45% IDC + 10% IMPC 2. IPC	3	3	+	-	+ 1 / 17	-	-	-	50	NA
Case 10	BCS+SLN	Mixed carcinoma	U	35% IPC + 30% IDC + 35% IMPC	2	2	-	-	+1 / 1 (<2 mm)	100 +++	85 +++	-	22	NA
Case 11	BCS +SLN	Mixed carcinoma	U	30% IPC + 70% IDC	2	2	-	-	0 / 1	-	< 5% +	-	80	-
Case 12	MRM	IPC	U	-	2	2	-	-	0 / 10	100 +++	100 +++	+	25	NA
Case 13	SM	Mixed carcinoma	U	40% IPC + 50% IDC + 10% IMPC	2	2	+	-	Malignantcytology	100 +	-	-	27,5	NA
Case 14	BCS+AD	Mixed carcinoma	U	30% IPC + 70% IDC	3	3	+	-	+ 10 / 11	15 +++	60 +	-	40	NA
Case 15	BCS+SLN	IPC	U	-	2	2	-	-	0 / 1	100 +++	95 +++	-	35	NA
Case 16	MRM	Mixed carcinoma	M	50% IPC + 50% IDC	3	2	-	-	+ 3 / 8	100 +++	80 +++	-	24	NA
Case 17	SM+SLN	IPC	U	-	2	1	-	-	0 / 3	100 +++	13 ++	-	37,5	NA
Case 18	BCS+SLN	Mixed carcinoma	M	10% IPC + 80% IDC + 10% PLC	2	2	-	-	0 / 3	95 +++	85 ++	+	40	NA
Case 19	MRM	Mixed carcinoma	U	60% IPC + 40% IDC	2	2	+	-	+ 2 / 9	90 ++	90 +++	-	30	NA

Table 2. Continued

	Surgical Procedure	Histologic Type	Focality	Mixed Component	NG	HG	LVI	PNI	Axillary LN	ER* %; intensity	PR* %; intensity	HER2	Ki-67 (%)	AR
Case 20	MRM (+Neoadjuvant therapy)	Mixed carcinoma	U	40% IPC + 60% IDC	3	3	+	-	+ 11 / 32	100 +++	90 +++	-	20	NA
Case 21	BCS+SLN	Mixed carcinoma	U	20% IPC + 80% IDC	2	1	-	+	0 / 3	100 +++	100 +++	-	27,5	NA
Case 22	BCS+SLN	Mixed carcinoma	U	70% IPC + 30% IDC	2	1	-	-	0 / 4	100 +++	95 +++	-	25	+

NG: nuclear grade; HG: histologic grade; LVI: lymphovascular invasion; PNI: perineural invasion; ER: estrogen; PR: progesteron; AR: androgen; BCS: breast-conserving surgery; AD: axillary dissection; MRM: modified radical mastectomy; SLN: sentinel lymph node dissection; SM: simple mastectomy; U: unifocal; M: multifocal; NA: not available, IPC: invasive papillary carcinoma; IDC: invasive ductal carcinoma; HER2: human epidermal growth factor 2, *for ER and PR intensity: strong staining (+++); moderate staining (++); weak staining (+). HER2 (+): score 3 immunostaining or amplification detected by SISH

showed pure-type IPC. Liu et al. (13) found that patients with pure-type IPC had significantly more favorable prognoses than IDC. In other words, patients with mixed-type IPC appeared to have a poorer outcome.

In the current study, 5 out of the 22 patients died (Table 1). While 3/5 cases showed mixed-type histology (IPC+ IDC+ invasive micropapillary carcinoma) the remaining two showed pure-type IPC. However, one of these pure-type IPC cases (Case #17) had a history of IDC with Paget's disease in the other breast two years earlier (metachronous breast carcinoma). The previous breast carcinoma showed different tumor morphology and molecular subtype (ER-/PR-/HER2+) and there was no lymphovascular invasion or axillary nodal metastasis.

Molecular Phenotypes

The distribution of cases by molecular phenotype in this study was Luminal B in 16 cases (72.7%), triple-negative in 5 cases (22.7%), and Luminal A in 1 case (4.6%). Although three cases showed HER2 positivity by immunohistochemistry and/or SISH methods, there was no case in the HER2 molecular subgroup. The Ki-67 proliferation index was ≥20% in most of the cases (90.9%). The pure IPC cases showed Luminal B phenotype in five and triple-negative in two cases. In recent studies, the majority of patients with IPC were found to be positive for ER and PR receptors and negative for HER2 (13). In terms of the four molecular subtypes, some studies reported Luminal A to be the most frequent subtype, in the current study and others Luminal B was found to be most common (13, 23). A considerable number of IPC cases showed triple negative phenotype in some other studies, as in this study (13).

Darvishian et al. (23) described a variant of papillary carcinoma called breast carcinoma with tubulopapillary features. This tumor exhibited a predominant (≥50%) tubulopapillary morphology characterized by infiltrating, gaping, and anastomosing tubules and small cysts in a retiform arrangement within a dense, abundant, sclerotic stroma. The tubules were lined with cuboidal to short columnar cells with moderate to high-grade nuclear atypia and occasional hobnail cells reminiscent of serous papillary carcinoma of Mullerian origin. They found that this type of IPC tends to have a significantly higher mitotic rate, higher Ki-67 proliferation index, nuclear grade 3 features, lymphovascular invasion, p53 overexpression, and axillary nodal involvement compared to the control group. Therefore, the authors concluded that invasive breast carcinoma with tubulopapillary features showed a significant correlation with adverse prognosis compared to ordinary papillary carcinomas. Their study group was composed of 12 cases, in which the molecular subtype was Luminal B in five, Luminal A in three, triple-negative in three, and HER2 in one case (23). One of our cases (Case #4) showed a morphology similar to this type of breast tumor, with tubulopapillary features. The CNBS of this case was described as "Invasive Adenocarcinoma" and after clinical-radiology evaluation and immunostaining results, it was reported as "tumoral proliferation compatible with breast primary." A similar morphology of tumor was also seen in the surgical excision material.

Individual Cases

Individual cases in this study showed tumor with a prominent lymphocytic inflammatory cell infiltration or tumor with apocrine cytonuclear features, or tumor in association with pagetoid involvement of large ducts and nipple dermis. The coexistence of IPC and Paget's disease was reported in only one case in previous studies (24). The authors indicated unfavorable histological features for this case, contrary to IPC. Pagetoid involvement was identified in one of the cases in this study (Case #16). This case showed two invasive tumor foci and at the time of writing was alive and disease-free after 41 months of follow-up.

Lymphocyte-predominant breast cancer was defined by the presence of more than 50% of lymphocytes within the tumoral stroma (25). It has been recognized as an important prognostic and predictive factor, particularly for ER-negative carcinomas (25). One of the cases in this study (Case #8) showed mixed-type

histology and high-grade tumor features with triple-negative phenotype. However, after 17 months of follow-up, local recurrence, lymph node involvement and multiple visceral organ metastasis were detected and soon after, the patient died.

Apocrine differentiation in breast carcinoma was seen in IDC, tubular, lobular, micropapillary, and medullary carcinomas (1). These tumors may demonstrate solid-tubular or papillary growth patterns (1). However, an "apocrine molecular signature," androgen receptor (AR) (+), GCDFP-15 (+), ER (-), PR (-), and HER2 (+), was described in almost half of the tumors that showed these morphologies (1, 26). One of our cases showed apocrine cytonuclear features and positivity for AR. However, the tumor showed Luminal A phenotype (ER+ PR+ HER2- and Ki-67 index 10%). The AR is a nuclear steroid hormone receptor and differentially expressed in breast cancer subgroups (27). Higher expression rates for AR were found in ER-positive breast carcinomas than for those of ER-negative tumors (27). AR expression was found in association with favorable clinicopathological features, such as lower grade, lower pT stage, and positivity for PR in ER-positive breast cancers (27).

Histopathological Findings Within Non-Tumoral Breast Parenchyma

We also described several findings within the non-tumoral breast parenchyma of patients with IPC. Columnar cell changes with or without atypia, apocrine metaplasia (mostly in the form of cystic papillary apocrine hyperplasia), fibrocystic changes, and ductal ectasia were the most frequent findings noted in surrounding breast parenchyma.

In conclusion, we retrospectively reviewed the H&E slides of cases diagnosed as invasive breast carcinoma between 2010 and 2018 and described the clinicopathological findings of the cases with pure and mixed-type IPC in our department. Consequently, IPC was detected in 1.9% of all the cases with invasive breast carcinoma, of which 0.6% was of the pure-type form and 1.3% exhibited a mixed-type histology. IPC was detected mostly as an accompanying carcinoma to IDC and showed Luminal B molecular phenotype with intermediate-to-high grade features. DCIS was usually coexistent with IPC. The patients mostly presented in the early stages of breast cancer with palpable breast mass and/or radiographic abnormality at postmenopausal age. Tumor location in the retroareolar region or inner quadrant and multiple tumors were detected at a higher frequency. Columnar cell changes, apocrine metaplasia, fibrocystic changes, and ductal ectasia were the most frequent findings within the non-tumoral breast parenchyma.

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of Istanbul Education and Research Hospital (protocol number: 1888, date: 28.06.2019).

Informed Consent: Informed consent information haven't been obtained since the methods currently used for diagnostic purposes were used in this study and no additional method without proven benefit was applied.

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Authorship Contributions

Surgical and Medical Practices: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Concept: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Design: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Data Collection and/or Processing: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Analysis and/ or Interpretation: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Literature Searching: C.K.T., B.Y.E., Y.C.; Writing: C.K.T., B.Y.E., Y.C.

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

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Case Report

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Co-Existence of Two Rare Entities in the Male Breast: Intraductal Papilloma and Angiolipoma

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ABSTRACT

Intraductal papilloma and angiolipoma lesions are very rare in male breasts and gynecomastia is the most common male breast pathology.

A 52-year-old healthy Caucasian male patient with right nipple pain for one month and two subareolar and periareolar masses had no other abnormal clinical or laboratory findings. After ultrasound examination, pull-through excision was made with a circumareolar incision in both lesions and the samples were sent for pathological examination. Histopathological examination revealed intraductal papilloma and angiolipoma on the basis of gynecomastia.

This case is unique because both lesions are extremely rare and this is the first report of concurrent occurrence in a male breast.

Keywords: Papilloma, intraductal; angiolipoma; gynecomastia; male; breast

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Key Points

- Both intraductal papilloma and angiolipoma are extremely rare entities in males. To the best of our knowledge, this is the first report of concurrent occurrence of intraductal papilloma and angiolipoma in a male breast on the background of gynecomastia.

Introduction

Morphologically male breasts are composed of glandular and fatty tissues, as in females. These glandular units only consist of ducts that are typically delimited below the nipple-areolar complex (1).

Gynecomastia is the most common male breast pathology, and its prevalence in males with breast-related disorders varies between 32% and 100% according to age groups (1, 2).

Intraductal papilloma is a proliferative lesion of the mammary ducts and is usually completely benign, but can sometimes contain atypical or even malignant cells. The benign intraductal papilloma consists of abundant stroma containing both luminal epithelium and myoepithelial cells, forming several broad fronds (2-4).

Angiolipoma is an unusual vascular variant of the lipoma, the etiology of which is controversial and represents 5%–17% of all benign fatty tumors. This lesion is mostly localized in the subcutaneous tissues of the trunk and extremities, and breast angiolipoma is extremely rare. In addition, differential diagnosis of breast angiolipomas can be difficult as they can be confused with malignant lesions clinically, radiologically and pathologically (5, 6).

Both intraductal papilloma and angiolipoma lesions in male breasts are very rare and a few cases have been reported in the literature (1-3, 7).

Here, a case in which the co-existence of intraductal papilloma and angiolipoma in the male breast with gynecomastia is presented with the help of ultrasonographic and pathological images. In addition, the relevant literature is reviewed.

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Case Presentation

A 52-year-old healthy Caucasian male patient was admitted to the surgical outpatient clinic with complaints of right nipple pain and two subareolar and periareolar masses for one month. Physical examination revealed firm, tender, well-circumscribed, nodular masses of approximately 2 cm and 1 cm in diameter, which could be palpated in the right retroareolar region. The remaining breast areas were symmetrical and had normal nipple-areolar complex. No erythema or pitting of the skin was observed. No palpable bilateral axillary or supraclavicular lymph nodes were found. Except for anti-arterial hypertension drugs, he had no history of local trauma, recent weight loss, or use of anabolic steroids or other drugs that could cause gynecomastia. There was no relevant family history. The patient had no other abnormal clinical or laboratory findings.

Mammography could not be performed because the breast of the case was not large enough and was extremely painful. Ultrasound examination revealed a hypoechoic solid mass with a maximum diameter of 2 cm in the right retroareolar region with coarsely lobulated contours (Figure 1) and a well-circumscribed hyperechoic solid mass with a maximum diameter of 1 cm immediately medially (Figure 2).

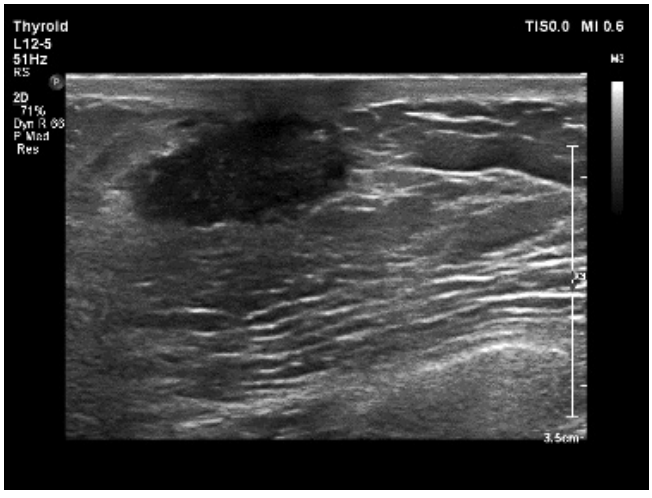


Figure 1. Ultrasound image shows a retroareolar, hypoechoic solid mass with coarse lobulated contours

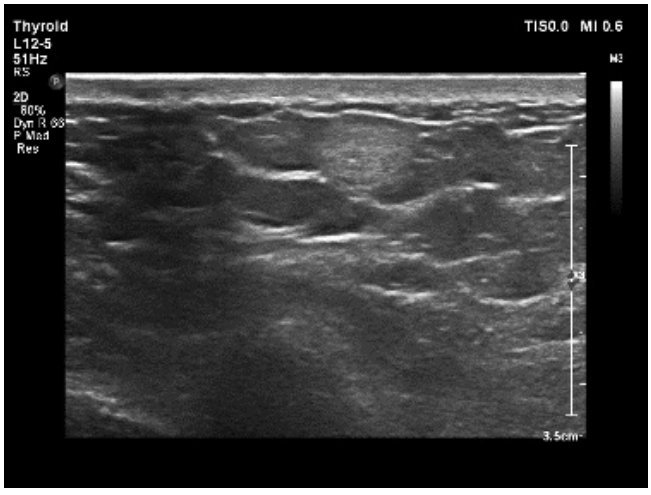


Figure 2. Ultrasound image shows a medial retroareolar, hyperechoic solid mass with well circumscribed

Total pull-through excision with circumareolar incision was performed for both lesions and the samples were sent for pathological examination.

Histological examination revealed an intraductal papilloma (Figure 3) in the large lesion, with no evidence of atypia or malignancy, on a background of gynecomastia (Figure 4), and an angiolipoma (Figure 5) in the small lesion.

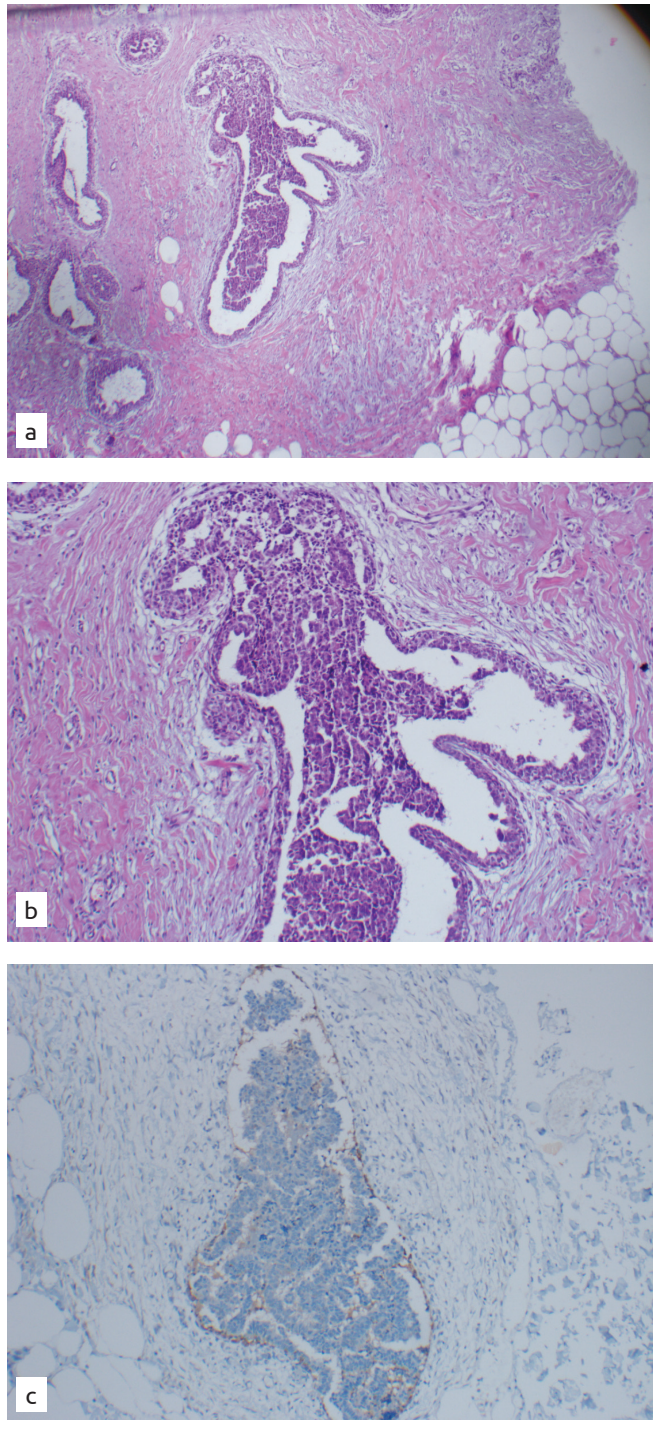
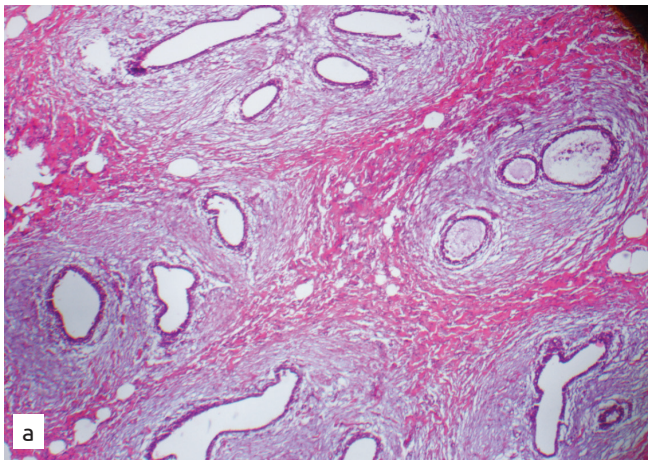
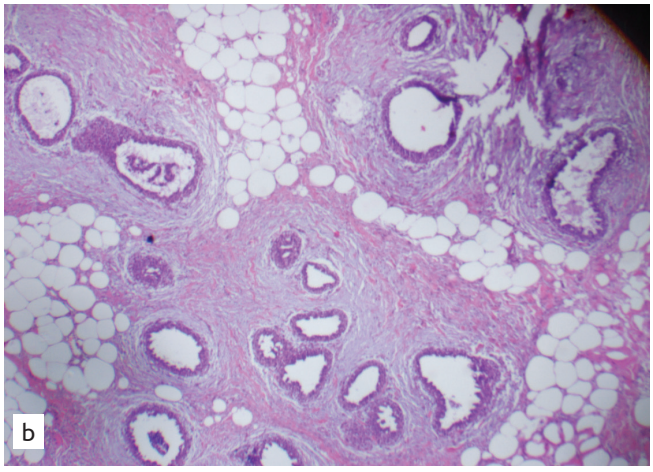


Figure 3. Intraductal papilloma. **a)** It is observed that papillary structures with fibrovascular cores in the enlarged duct are lined with epithelial and myoepithelial cells (H&E, x10) and **b)** (H&E, x20). **c)** Immunohistochemical staining of myoepithelial cells with p63 was observed in intraductal papilloma areas (H&E, x10)

H&E: hematoxylin and eosin stain





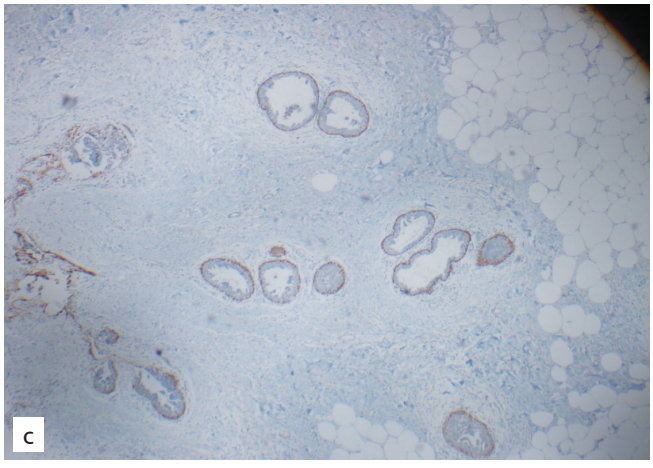
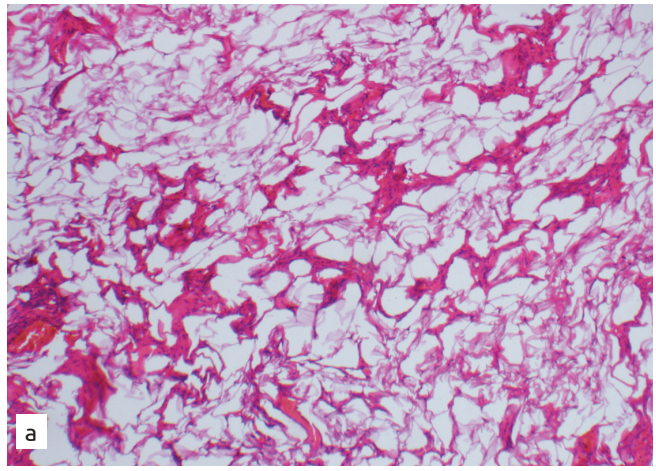


Figure 4. Florid type gynecomastia. **a)** Budding is seen in the proliferating ducts in the fibroblastic stroma (H&E, x20). **b)** In addition to the surrounding fibroadipose tissue, budding is also seen in the proliferating ducts in the fibroblastic stroma (H&E, x20). **c)** Immunohistochemical staining of myoepithelial cells with p63 is observed in areas with gynecomastoid changes (H&E, x10)

H&E: hematoxylin and eosin stain



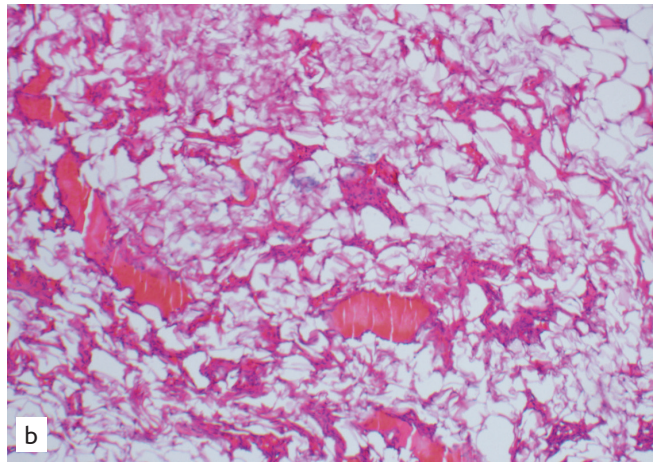


Figure 5. An encapsulated nodular lesion (angiolipoma) containing mature adipose tissue and vascular tissue proliferation. **a)** Mature adipose tissue contains thick-walled vessels with branching capillaries and pericytes (H&E, x20). **b)** Fibrin thrombi were seen in the lumen of some vascular structures (H&E, x20)

H&E: hematoxylin and eosin stain

Discussion and Conclusion

Male breast disease is often not recognized due to rarity, lack of awareness, and the scarcity of epidemiological data in the literature when compared to the female breast. Male and female breasts are similar at birth. Subareolar ducts in males are histologically similar to those in prepubertal females. An adult normal male breast usually consists of large ducts that do not extend beyond the central subareolar segment without the formation of lobules and acini. These ducts are embedded in the fibrous stroma and adipose tissue (8).

Gynecomastia can occur in any age group, and the risk factors for all the same breast lesions are similar. These include age, family history, medications, obesity, endocrine and hormonal imbalance, systemic disease, liver disease, neoplasm, history of orchitis or thoracic radiotherapy, and genetic predisposition in patients with Klinefelter syndrome, or *BRCA2* and the *P53* gene positivity (8).

In males, a retroareolar mass can be benign, such as an intraductal papilloma or any soft tissue tumor, or sometimes malignant. Intraductal papillomas of the male breast are rare, in contrast to females (3, 8).

The clinical presentation of intraductal papilloma and malignant lesions is similar, with a unilateral bloody or serous discharge associated with a palpable, unilateral, firm, fixed lesion in the subareolar region in males. It may be associated with skin changes or axillary lymphadenopathy (8).

The diagnostic approach to intraductal papillary lesions includes physical examination, mammography, ultrasonography, magnetic resonance imaging, and more rarely, breast ductoscopy or ductography. When there is discharge, cytological examination of discharge material may also be required. Differential diagnosis between benign intraductal papilloma and a carcinoma with atypia or even malignancy is not possible with imaging alone. Therefore surgical excision and histological confirmation are required (3).

Microscopically, intraductal papilloma appears as an epithelium containing both luminal and myoepithelial cells and abundant stroma forming several broad leaves (8).

Lipomas are encapsulated proliferations of mature adipocytes but the cause of angiolipoma is unknown. Breast angiolipomas may present as solitary or multiple breast masses, and angiolipomas do not have a typical imaging appearance. The diagnostic key may be the homogeneous echogenic sonographic appearance, which is unusual for breast masses. However, in the differential diagnosis of masses with increased echotexture, focal acute hemorrhage or acute hematoma, focal fibrosis, hemangioma, spindle cell lipoma and malignancy are included, in addition to angiolipoma. The histological appearance of angiolipoma in the subcutaneous tissue of the breast is not different from comparable lesions at other subcutaneous locations. Microscopically, angiolipomas consist of mature adipose cells separated by a network of branching small vessels. Diagnosis of cellular angiolipoma can potentially lead to diagnostic pitfalls involving better-known formations such as angiosarcoma or Kaposi's sarcoma of the breast region (5).

In this case, intraductal papilloma with angiolipoma was observed, together with gynecomastia in the right breast. This case is unique because both lesions are extremely rare and are reported here for the first time in a male breast with gynecomastia. The diagnosis was confirmed by histological analysis as intraductal papilloma and angiolipoma without any atypia or evidence of malignancy.

The proportion of men with breast complaints is increasing day by day, and although mammography plays an important role in distinguishing between benign and malignant breast diseases (9), especially in the elderly, mammography examination could not be performed in our case.

In conclusion, both intraductal papilloma and angiolipoma lesions in male breasts are very rare in the literature. A systematic search in PubMed, Web of Knowledge, and EBSCO found only a few cases of intraductal papilloma and a few angiolipomas in the breast in males, but not together. Here, the co-existence of intraductal papilloma and angiolipoma in the breast of a male patient with gynecomastia is presented as an extremely rare case that has not, to the best of our knowledge, been described before.

Informed Consent: The authors certify that they have received a consent from the patient. The form gave consent for patient pictures and other clinical information to be reported in the journal.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Case Report

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Gastrointestinal Tract Metastases of Invasive Lobular Carcinoma of the Breast: An Immunohistochemical Survey Algorithm

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ABSTRACT

Invasive lobular carcinoma (ILC) accounts for almost 15% of all breast carcinomas. The potential of ILC to metastasize to the gastointestinal system is significantly greater than that of invasive ductal carcinoma. Gastric metastasis occurred in the ninth year of the follow-up in a patient who was operated on the right breast due to ILC. The patient was investigated for simultaneous masses in the stomach and colon, and a random mass was found in her right breast.

Keywords: Breast cancer; colonic metastasis; gastric metastasis; gastrointestinal tract metastasis; invasive lobular carcinoma

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Key Points

- The histopathological findings are similar in invasive lobular carcinoma of the breast and poorly cohesive carcinoma of the stomach. Therefore, the possibility of metastasis should be kept in mind in multiple erosions or linitis plastica type gastric lesions.
- In breast cancer patients who develop gastrointestinal tract metastases, determining the nature of the tumor (primary or metastatic) is extremely important in terms of treatment.
- The importance of histopathological examination is critical and is highlighted in this report.
- Possible diagnostic errors can be avoided by making immunophenotypic evaluation of endoscopic biopsy material with an appropriate immunohistochemical panel.

Introduction

Invasive lobular carcinoma (ILC) accounts for almost 15% of all breast carcinomas (1, 2). Since the 1960s, many case reports about gastrointestinal tract (GIT) metastases of ILCs have been reported (3-6). The susceptibility of ILC to metastasize to GIT is many times greater than invasive ductal carcinoma (IDC) (4.5% *versus* 0.2%, respectively, $p<0.05$) (1).

Isolated GIT metastasis of ILC is extremely rare and at least 60% of ILC patients with GIT metastases have had concurrent bone (7,8) and, less frequently, other organ metastasis (5, 9-11). The pattern of metastasis is often diffuse and infiltrative so that it essentially presents as multiple erosions (7, 8) or often linitis plastica type in the stomach (6, 7, 12). Since molecular profiling and immunophenotyping methods were not available in the past, the diagnosis of GIT metastases of ILC was based almost entirely on histological evaluation (3, 13). However, in the recent literature, there are few case reports in which differential diagnosis was made by immunohistochemical (IHC) methods (8, 10).

In this study, we evaluated two patients treated in our clinic. The first had ILC in the breast and subsequently developed gastric metastasis (Case 1). In the second patient, an incidental mass was found in the right breast while investigating simultaneous masses in the stomach and colon (Case 2).

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In addition, using current and specific immunohistochemical methods, we examined the staining pattern of poorly cohesive carcinoma of the stomach (PCCS), including signet ring cell carcinoma and gastric metastasis of ILC.

Case Presentations

Case 1: A 76-year-old female patient was admitted to our service nine years previously, due to a mass in her right breast. The tru-cut needle biopsy was reported as ILC. Following radiodiagnostic studies, the patient underwent right mastectomy and axillary dissection upon detection of carcinoma metastasis in the sentinel lymph node (1/3). Histological examination of the breast revealed two separate tumor foci (3.0 and 1.8 cm) with signet-ring cell component. The number of metastatic lymph nodes was 1/12.

Immunohistochemistry showed positive estrogen receptor (ER) and negative progesterone receptor (PgR), human epithelial growth factor receptor type 2 protein (Cerb-B2), p53 and e-cadherin staining.

The patient had had T2N1M0 Stage 2B tumor. She received six courses of adjuvant consisting of tri-weekly TEC regimen (75 mg/m^2 docetaxel + 75 mg/m^2 epirubicin + 600 mg/m^2 cytoxan) followed by radiotherapy.

In the ninth year of follow-up, an increase in tumor markers was detected (CEA = 29.7 U/mL, CA15-3 = 1019 U/mL). The abdominal ultrasound and computed tomography revealed free intraperitoneal fluid accumulation, hypermetabolic implants in the peritoneum (peritoneal carcinomatosis) and a diffuse but asymmetric gastric wall thickening reaching 17 mm. The patient underwent gastroduodenal endoscopy. There were numerous infiltrative nodular lesions in the gastric corpus and antrum mucosa and multiple biopsies were taken. On positron emission tomography/computed tomography (PET/CT), a possibly metastatic lymph node in the left axillary region with a size of 16x13 mm [(maximum standardized uptake value (SUV_{max}: 4)] was seen and a tru-cut biopsy was performed. Endoscopic gastric biopsies and left axillary lymph node biopsies were evaluated together with previous right mastectomy and axillary dissection material for pathological evaluation.

The endoscopic biopsy sample of the stomach revealed a non-cohesive tumor with an infiltrative pattern between the normal gastric glands in the lamina propria. Considering the medical history of the patient, an IHC panel was simultaneously applied to primary breast adenocarcinoma and gastric endoscopic biopsy specimen in order to rule out possible metastasis.

In the breast biopsy samples, tumor cells were ER 100% (3+), GATA 3 (+), PR (-), CerbB2 score 1, Ki-67 25% (+), e-cadherin (-), mammoglobulin (+), GCDFP15 focal (+), CDX2 (-). In the stomach biopsy samples, tumor cells were ER 100% (3+), GATA 3 (+), PR (-), e-cadherin (-), mamoglobulin (+), GCDFP15 focal (+), CDX2 (-). CerbB2 and Ki-67 assessments were suboptimal (Figure 1).

A sample of primary malignant gastric carcinoma and its staining pattern for comparison with metastatic gastric carcinoma is shown in Figure 2. With histological and immunohistochemical findings, both breast mass and infiltrative nodular gastric lesions were evaluated as "infiltrating lobular carcinoma".

First line endocrine therapy (aromatase inhibitor) was started. The patient died 11 months after metastasis was detected.

Case 2: A 65-year-old female patient was admitted to our clinic in December 2020 with nausea, vomiting and intermittent colic abdominal pain, resembling incomplete mechanical bowel obstruction. On abdominal CT, an irregular wall thickening in an approximately 8 centimeters long segment of the proximal transverse colon was observed. Chest CT revealed multiple lymph nodes in the right axillary region with a maximum dimension of 30x24 mm and diffuse sclerotic metastatic lesions in the bony structures.

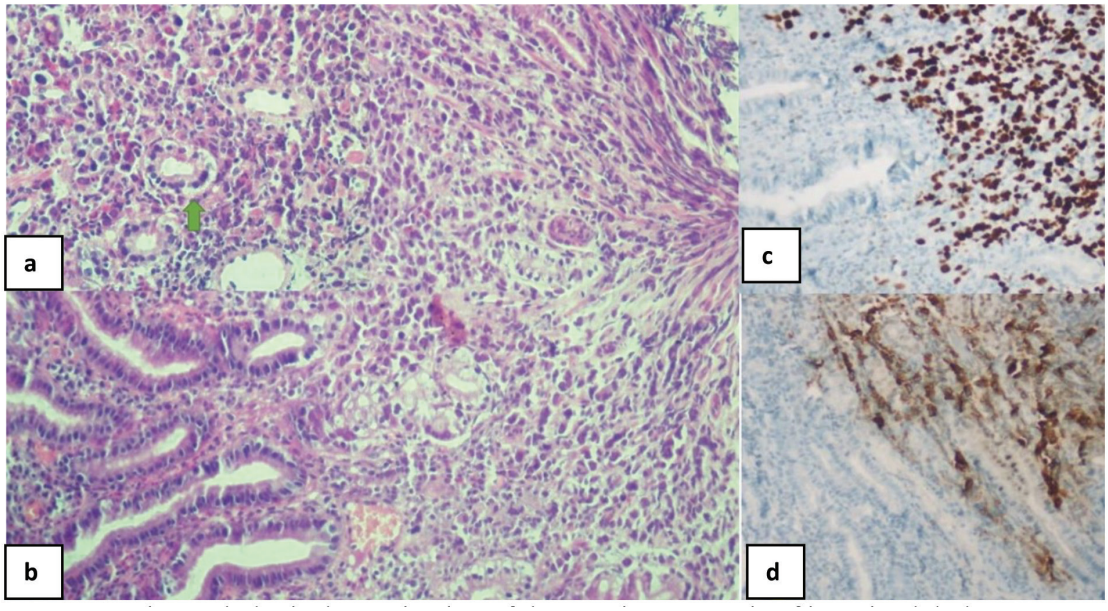

Figure 1. Histopathological examination of the gastric metastasis of invasive lobular carcinoma of the breast. **a)** Tumoral infiltration in the lamina propria of stomach (H&E, x200). **b)** Dyscohesive tumor cells (H&E, x400) around the usual stomach glands (arrow). **c)** GATA3 nuclear positivity in tumor cells and gland epithelium without staining (IHC, GATA3). **d)** Tumor cells with Mammoglobin staining and gastric gland epithelium without staining immunohistochemical (IHC, Mammoglobin)

H&E: hematoxylin and eosin stain; ICH: immunohistochemical

In the colonoscopic examination of the patient, there was an ulcerovegetan mass encircling the lumen and multiple biopsies were taken. In the same session, upper GI tract endoscopy was also performed and a few biopsies were taken from erosive lesions in the stomach.

In the histopathological examination, there was atypical tumoral infiltration showing loss of cohesion in the lamina propria of both colon and gastric epithelium. In tumor cells, ER was 80% (3+), PR (-), GATA3 (+), CK7 (+) Pancytokeratin diffuse (+), CD20 (-), CD3 (-) and CDX-2 (-), LCA (-), Synaptophysin (-), Chromogranin (-), Vimentin (-), OCT3 (-), SOX10 (-), PAX8 (-), CK20 (-), S100 (-) (Figure 3).

With the described IHC findings, metastasis of breast carcinoma to the colon and stomach was strongly considered. Afterwards, breast

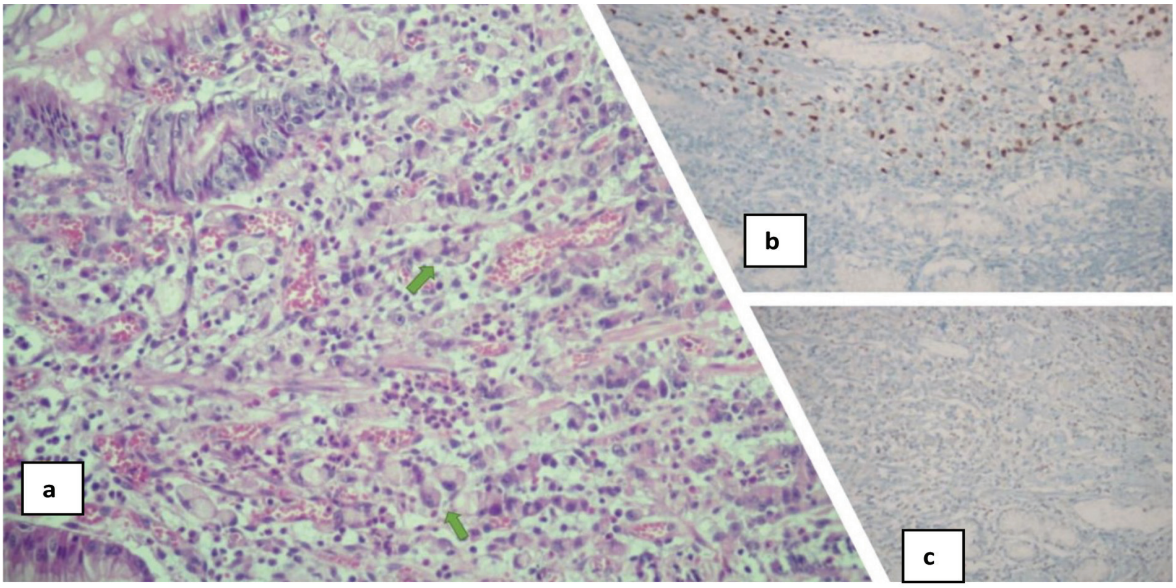

Figure 2. The histology of primary malignant (poorly cohesive) gastric carcinoma and its' immunohistochemical (IHC) staining pattern. **a)** Cohesive carcinoma cells between gastric glands (arrow) (H&E, x200). **b)** CDX2 positivity in tumor cells (IHC, CDX2). **c)** GATA3 negativity in both stomach gland epithelium and tumor cells (IHC, GATA3)

H&E: hematoxylin and eosin stain; ICH: immunohistochemical

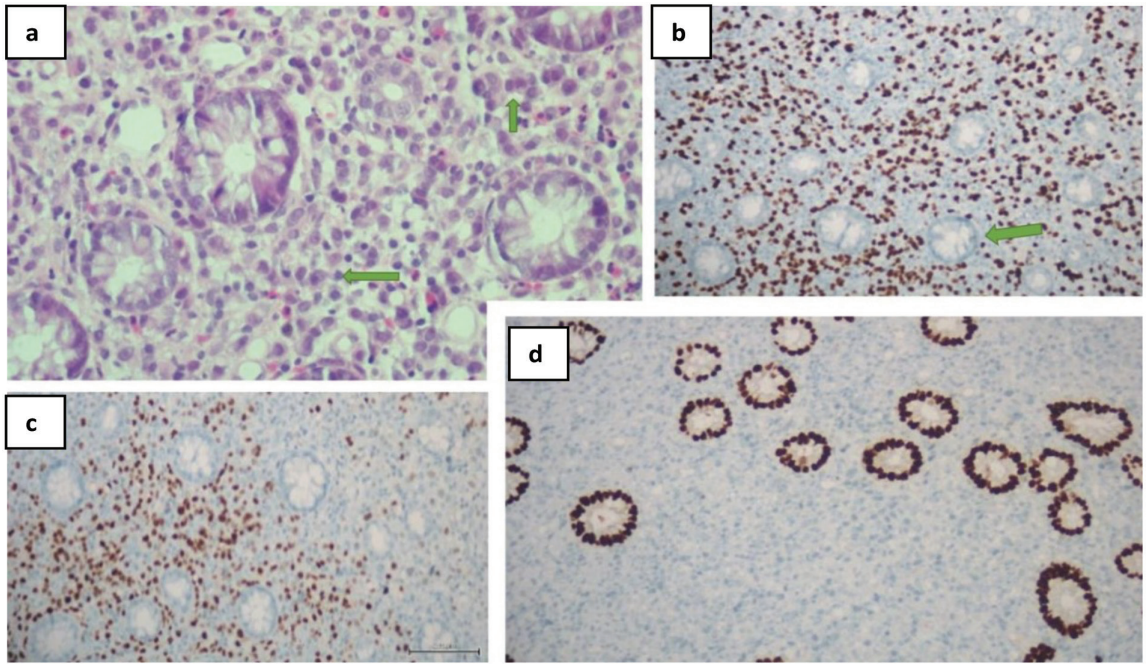

Figure 3. Breast carcinoma metastasis to the colon.

a) Poorly cohesive carcinoma cells (arrow) between the glands of colonic epithelium (H&E, x200). **b)** GATA3 stained tumor cells and unstained glandular epithelium of the colon (arrow) (IHC, GATA3). **c)** ER positivity in tumor cells in the lamina propria (IHC, ER). **d)** CDX2: Negative staining in tumor cells and positive nuclear staining in colonic epithelial cells (IHC, CDX2)

H&E: hematoxylin and eosin stain; ICH: immunohistochemical; ER: estrogen receptors

magnetic resonance imaging (MRI), mammography and breast ultrasonography (USG) examinations were performed. On ultrasound examination, there was an irregularly circumscribed area in the right breast that did not show a clear mass formation. MRI examination revealed an irregular and spicular mass located in the retroareolar and mid-quadrant area of the right breast, with a size of 16x11 mm. The mass was classified as Breast Imaging Reporting and Data System (BI-RADS) 4-C. The MRI images of the right axilla was compatible with adjacent and numerous pathological lymph nodes ≤33 mm in size. Ultrasound guided tru-cut biopsy and fine needle aspiration biopsy (FNAB) was performed from the mass in the right breast and the axillary lymph node, respectively.

In the right breast tru-cut biopsy specimen, an invasive tumor was observed that developed as individual cells and short cell lines with scanty cytoplasm. In the tumor cells, ER was 100% (+++), PR 40% (++++), cerbB2 (-), Ki-67 5%, p53 (-), e-cadherin (-), P63 (-). Findings were consistent with "invasive lobular carcinoma" as the most likely diagnosis. In addition, cytomorphological and immunocytochemical findings (GATA 3 positivity in tumor cells) in axillary lymph node FNAB were interpreted as breast carcinoma metastasis. In the light of IHC findings, it was reported that the tumor was not primary colon carcinoma and the primary focus was most likely the breast. Thus, in this case, the diagnosis of ILC of the breast was reached based on the GI tract metastases.

In terms of treatment, the patient had first-line systemic hormonotherapy; + CDK4-6 inhibitor treatment was started in January 2021. The patient is still using palbociclib 125 mg/d for 21 days in combination with letrozole 2.5 mg/d. In addition, she is regularly receiving Denosumab 60 mg (recombinant human monoclonal IgG2 antibody) subcutaneously every 6 months.

Discussion and Conclusion

In our clinic, the number and percentage of patients with ILC (excluding mixed-type tumors) among 2000 patients with primary breast carcinoma was 162 and 8.1%, respectively. Among these, the number of ILC patients with gastrointestinal organ metastasis was only two (1.2%). In patients dying of breast carcinoma, gastric metastasis was found in 6–18% at autopsy. This might be due to the diffuse nature of the disease (ILC) and some predilection for gastric involvement (3, 14, 15). In one study, metastatic disease secondary to breast cancer was detected in 12,000 patients over a 15-year period. The number of patients with GIT metastases in this series was only 23 (0.2%). In this series, the prevalence of ILC was 12 percent, however it was significantly increased (54%) in patients with GIT metastases and carcinomatosis ($p<0.001$) (16). The metastasis of ILC to the colon is less common compared to the stomach, and it is frequently encountered in the literature as single case reports (4, 10, 17, 18).

In published breast cancer patient series, when the surviving patients are compared to those deceased and autopsied, a significant difference was observed in the frequency of GIT metastasis. This suggests that clinicians failed to notice the GI tract metastases during the follow-up of these patients. Patients with breast cancer very rarely have isolated GIT metastases. On the contrary, in almost all of them, multiple metastases are observed, most commonly in the bone (about 60%) before or simultaneously with the GIT metastasis (5, 7-11, 17). This perhaps causes clinicians to focus on the more common metastases with more prominent symptoms and may result in failure to recognize possible GIT metastases.

In our study, in the first patient who had gastric metastasis after ILC, there were simultaneous metastasis in the locoregional lymph nodes, and in the second case, multiple bone metastases were demonstrated concurrently with colon metastasis.

In breast cancer patients who develop GI tract tumors, histopathological examination is extremely important in determining the nature of the tumor and for optimal treatment planning. In this study, direct histopathological examination of H&E stained specimens of metastatic ILC were characterized by poorly cohesive tumor cells around the epithelial glands located in the lamina propria. This infiltration was sometimes patchy or diffuse. Poorly cohesive ILC cell infiltration in the lamina propria has also been reported in different studies (11, 19). In these cases, the use of immunomarkers, alone or in combination, significantly increased the sensitivity and specificity for diagnosing metastatic ILC in the GIT. We used CDX2 to differentiate adenocarcinoma of intestinal or breast epithelial origin. *CDX2* gene encodes a nuclear transcription factor relatively specific for the development of intestinal epithelium from duodenum to rectum (20). In an immunohistochemical survey study, CDX2 monoclonal antibody was expressed uniformly in 76%–100% of tumor cells in 183 of 184 tumors originated from esophagus to the colon (21). However in our patients, tumor cells from gastric and colon biopsies were CDX2-negative, thus effectively excluding primary GI adenocarcinomas.

In both of our patients, an immunohistochemical survey with ER and GATA3 was used in all biopsies obtained from the breast, axillary lymph nodes, stomach and colon to prove that tumors were of breast origin. GATA3 is a transcription factor important in the differentiation of breast epithelia and urothelia. As expected, ER expression in tumor cells was 100% positive in breast, axillary lymph node and stomach biopsies and 80% in colon biopsy while GATA3 was strongly and uniformly expressed in all four biopsy specimens. Several case series have been reported about high ER-positivity (5, 10, 12, 17, 22) and GATA3 expression (11, 23) in both primary and metastatic tumor foci of ILC of the breast. In one study GATA 3 was immunohistochemically examined in 268 patients with primary or metastatic IDC and ILC of the breast. GATA3 positivity was observed in 97.3% (251 of 268 tumors) and was strongly expressed in 100% of primary ILC cases (23). In another study, primary breast and gastrointestinal carcinomas showing signet ring features were reviewed with respect to expression patterns of several immunohistochemical markers. The specificity of ER and GATA3 expression was 100% and 98% in primary breast carcinomas and the specificity of CDX2 was 100% for tumors of gastrointestinal origin. Thus, these markers successfully discriminated ILC and gastric signet ring carcinomas (24). These findings were supported in a different study in which ER and GATA3 expression were positive in 82% of the patients with metastatic ILC (mILC) and were helpful in distinguishing mILC from primary diffuse gastric adenocarcinoma (25).

Estrogen receptor expression in gastric carcinoma may sometime lead to misdiagnosis. It has been reported that some isoforms of ER-alpha (ERα) are highly expressed in cases with gastric cancer. Furthermore, the incidence of ER-alpha 66 isoforms is significantly higher, especially in diffuse type and poorly differentiated gastric adenocarcinomas (26). However, there are still inconsistencies regarding the effects of estrogen receptors on the development and/or progression of gastric cancer (27).

In our study, as a comparison group, we immunohistochemically surveyed the pathological specimens of five malignant (poorly

cohesive) gastric adenocarcinoma cases operated in our clinic. As seen in Figure 2, CDX2 was positive and GATA3 expression was negative in gastric tumor cells in all cases. In addition to the IHC stains presented above, we also used mammoglobin and GCDFP15 molecular markers in our first patient. Mammoglobin was reported to have higher expression, particularly in ILC and ER-positive tumors than IDC (28). These two markers were expressed both in primary breast tumor (50%–70%) and its gastric metastasis and this strengthened our diagnosis of gastric metastasis of primary ILC of the breast. Here, we do not intend to specifically recommend these last two molecular markers to be routinely used in differential diagnosis of GI tract metastasisof ILC of the breast. However, there are publications stating that these two markers are very useful to distinguish primary GI tract adenocarcinomas from gastrointestinal metastases of ILC (5, 9).

As a result, ER-α positivity can be reliably used to diagnose gastric metastasis of hormone receptor positive ILC of the breast. Simultaneous GATA3 positivity in both primary and metastatic foci significantly increases diagnostic accuracy. Negative CDX2 staining in gastrointestinal tumor cells fairly specifically excludes GI origin.

Also, in our second case presentation, the malignant primary focus was elucidated during the investigation of the metastatic masses. Therefore, since the histopathological findings are similar in ILC of the breast and poorly cohesive carcinoma of the stomach, the possibility of metastasis should definitely be kept in mind in cases with multiple erosions or linitis plastica type gastric lesions, even if there is no history of breast carcinoma in the medical records of the patient. Possible diagnostic errors can be avoided by implementing immunophenotypic evaluation in endoscopic biopsies with the IHC panel described above.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and/or Medical Practices: B.Z., D.Ç., Ö.Ö., F.T., M.K., C.Ş.; Concept: B.Z., D.Ç., A.U.; Design: B.Z., D.Ç., F.T., A.U.; Data Collection and/or Processing: B.Z., D.Ç., Ö.Ö., F.T., M.K., C.Ş.; Analysis and/or Interpretation: B.Z., D.Ç., Ö.Ö., F.T., A.U.; Literature Search: B.Z., D.Ç., Ö.Ö., F.T., A.U.; Writing: B.Z., A.U.

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

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Case Report

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Large Desmoid Tumor in the Setting of Prior Cosmetic Breast Augmentation

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ABSTRACT

Desmoid tumors of the breast are rare, comprising 0.2% of all breast tumors. They may be locally invasive but do not metastasize. The etiology is multifactorial including surgical trauma in the setting of prior cosmetic augmentation breast implants. We submit a case of a large desmoid tumor in the breast following silicone implant placement three years prior to patient presentation. The patient was treated with wide local excision to negative margins and implant exchange. A follow up breast magnetic resonance imaging at 3 and 6 months did not detect a recurrence thus far.

Keywords: Breast implant; breast mass; desmoid; fibromatosis; aggressive

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Key Points

- Desmoid tumors of the breast may be due to surgical trauma (i.e. prior breast augmentation surgery).
- Initial treatment could be surveillance depending on presentation.
- If the tumor is complicated, large, invasive, or painful, surgical excision with negative margins (at least 3 cm) is the recommended treatment.

Introduction

Desmoid tumors are locally aggressive tumors that arise from connective tissue. These tumors commonly occur in the abdominal wall, intra-abdominal mesentery and extremities. They do not metastasize. The rate of local recurrence is high at 24–65% in 10 years (1). Desmoid tumors of the breast are rare, comprising about 4% of extra-abdominal desmoid tumors and 0.2% of all breast tumors (2). Breast implants are a potential risk factor for desmoid tumors of the breast. This publication discusses management of a breast implant-related desmoid tumor.

Case Presentation

A 34-year-old healthy female presented with a rapidly growing, painful right breast mass. She had a history of elective bilateral breast augmentation with silicone retropectoral implants, three years prior to development of the mass.

On physical exam an intact right breast implant was detectable. An 8 cm mass occupied the upper inner quadrant of the right breast, partially fixed to the lateral border of the sternum. It was tender to palpation.

Diagnostic work up included a right breast ultrasound, which showed a silicone retropectoral implant and a heterogeneous hypoechoic mass measuring 5.5x3.0x6.0 cm, centered at the 3 o'clock position and 7 cm from the nipple (Figure 1). An ultrasound-guided core needle biopsy of the mass was performed. Pathology was consistent with fragments of desmoid fibromatosis. It appeared to be arising from the implant capsule, as both normal benign breast and skeletal muscle were evident separately from the fibromatosis. A breast magnetic resonance imaging (MRI) study revealed a well-circumscribed enhancing mass centered the 3 o'clock position and 7 cm from the nipple, measuring 3.5x5.5x8.5 cm. The mass was located within the fibrous capsule of the implant and the silicone implant was displaced

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anteriorly by the mass (Figures 2-4). Computed tomography of the chest was performed, revealing no evidence of osseous, extrapleural/pleural or pulmonary invasion. Family history was unknown as the patient was adopted. Genetic testing with an 84 gene panel was performed; results were negative for a pathogenic mutation.

Following multidisciplinary discussion with surgical oncology and plastic surgery, resection of the mass with reconstruction was recommended, due to symptoms and the size of the mass. Intra-operative findings included that the tumor was well encapsulated in the retropectoral space and adherent to the capsule on the chest wall (Figures 5, 6). The existing 295 mL silicone implant was removed along with radical resection of the tumor, including portions of the pectoralis major, minor, and intercostal muscles from ribs 2–5, and the anterior rectus sheath. A subtotal capsulectomy was performed. Reconstruction consisted of placement of a 310 mL cohesive silicone implant. On final pathology, the right breast mass was consistent with desmoid fibromatosis, measuring 9.1x6.5x3.9 cm, with negative margins (Figures 7, 8).

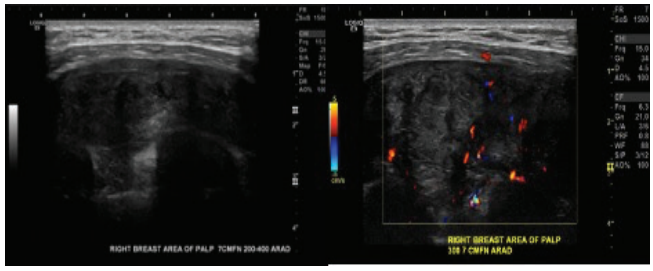
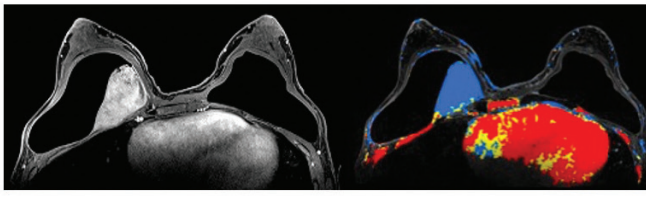
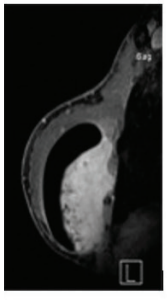


Figure 1. Right breast ultrasound showed a silicone retropectoral implant. There is a heterogeneous, hypoechoic mass, measuring 5.5x3.0x6.0 cm, centered at the 3 o'clock position and 7cm from the nipple. Color Doppler image shows increased vascularity within the mass





Figures 2-4. Contrast-enhanced axial and sagittal bilateral breast MRI showed a silicone retropectoral implant in the right breast and a well-circumscribed enhancing mass centered at the 3 o'clock position and 7 cm from the nipple, measuring 3.5x5.5x8.5 cm. The mass is within the fibrous capsule of the implant. The silicone implant is displaced anteriorly by the mass. The mass demonstrates persistent kinetics

MRI: magnetic resonance imaging

Planned follow up includes the patient initially undergoing a breast MRI every three months to monitor closely for evidence of recurrence. Her first three-month post-operative MRI was negative for any abnormalities (Figures 9, 10).

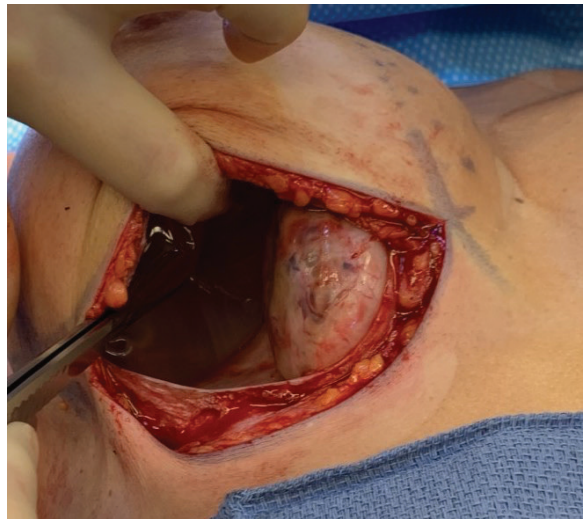


Figure 5. Intraoperative view of desmoid tumor adjacent to implant, through an inframammary incision

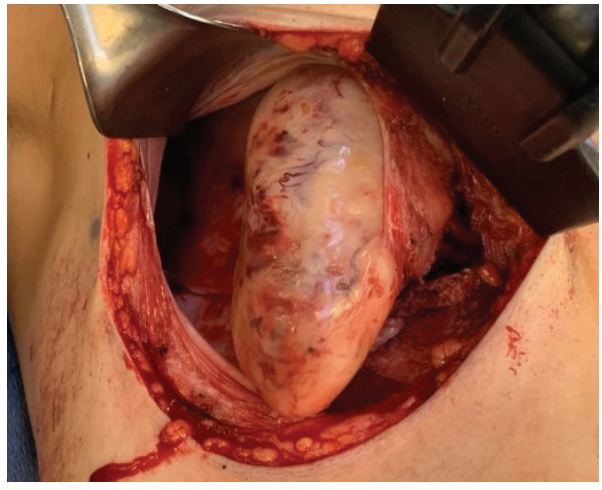


Figure 6. Desmoid tumor adherent to the fibrous capsule adjacent to the implant

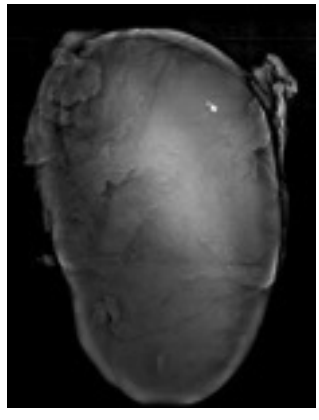


Figure 7. This is the specimen mammogram depicting the mass with the biopsy clip

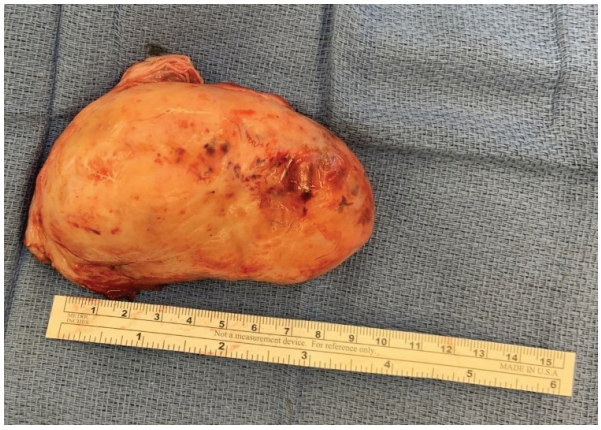


Figure 8. Desmoid tumor following removal, measuring 9.1x6.5x3.9 cm

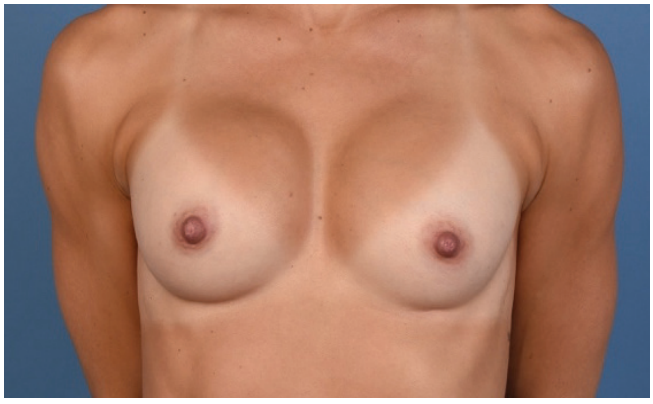


Figure 9. On initial presentation the patient has fullness on the right superior/medial aspect of the breast near the chest junction

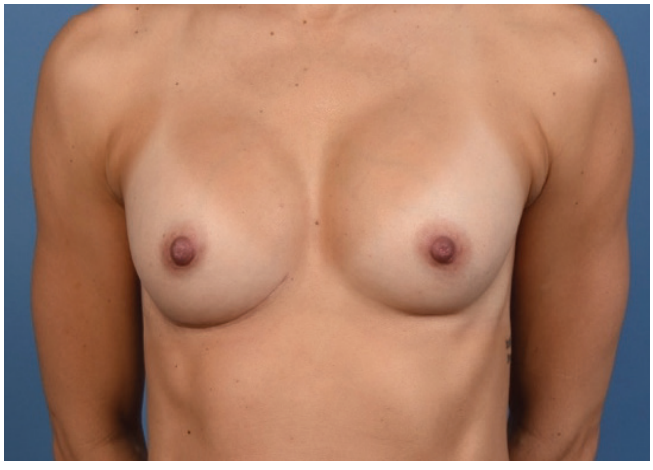


Figure 10. At two months post-operatively, the right superior medial breast near the chest wall junction appears softer

Discussion and Conclusion

The case we have reported is a rare presentation of desmoid tumor. Breast fibromatosis has been frequently associated with trauma from prior surgery. Breast fibromatosis is thought to arise from the fibrous capsule surrounding the breast implant (3, 4). Prior publications have reported an average time for detecting a tumor from the time of implant placement to be approximately 3 years (4).

Clinical presentation of desmoid tumors can resemble breast carcinoma. On physical exam this can include a hard mass with skin dimpling (5). On diagnostic imaging desmoid tumors can also mimic malignancy. Fibromatosis may present as a mass with circumscribed or irregular margins on mammogram (4, 6). On ultrasound, desmoid tumors usually present as solid masses with posterior acoustic shadowing and the margins may appear microlobulated, spiculated, or irregular (6). Breast MRI is the imaging modality of choice to evaluate extent of disease (4, 6). In most cases, fibromatosis presents as a hypointense to isointense mass on T1 weighted images and heterogeneously hyperintense on T2 weighted images (4, 6). Fibromatosis typically demonstrates persistent kinetics, in contrast to invasive breast cancer which typically demonstrates washout kinetics (6).

Treatment for desmoid tumors is multimodal. The initial treatment for all desmoid tumors is active surveillance as the majority of tumors will remain stable in size. In one case series 88% of patients had stability of disease or regression (7). Other options for non-surgical treatment include non-steroidal anti-inflammatory medications, hormone therapy (tamoxifen), and chemotherapy. If there is enlargement of the tumor or complications related to local invasion, surgery (wide excision) with negative margins is the treatment of choice (1, 2). Radiation is another treatment modality that is typically utilized in cases of a future recurrence after surgery (1). The recurrence rate of breast fibromatosis is lower than that of other sites of fibromatosis, reported at 21–27% compared to 30–65% (4).

In a study by Costa et al. (7), a total of eighty patients with breast desmoid tumors in the setting of prior breast implants at their institution and other cases reported in the literature were analyzed. Patients underwent the following treatments: 82% had a surgical resection; 12% underwent chemotherapy; 4% received Sorafenib; 14% received hormonal therapy; and 4% underwent active surveillance. Breast implants were removed in 50% of patients, replaced in 27%, and kept in place in 23%. In patients who underwent resection, the recurrence rate was 24% within three years. Removal or replacement of the implant did not significantly affect the risk of progression. The standardized incidence ratio (SIR) was calculated to examine if there was a connection between breast implants and breast desmoid tumors. The SIR was 482 to 823, correlating to a 482–823 times higher risk of developing a breast desmoid tumor after breast implant placement compared to the general population (7).

In conclusion, breast fibromatosis may mimic invasive carcinoma on presentation, but it is a locally aggressive benign tumor. The initial treatment recommended is surveillance. If there is enlargement of the tumor or a complication due to the tumor, surgical excision with negative margins is advised. Following definitive resection, surveillance is essential in detecting early recurrence. Given the rarity of this disease a world registry with documented clinical information has been suggested to add to the accuracy of predicting incidence and results of treatment (2).

Informed Consent: It was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: K.K., T.H., A.R.M., S.S.T., R.W.; Design: K.K., T.H., A.R.M., S.S.T., R.W.; Data Collection and/or Processing: K.K., T.H., A.R.M., S.S.T., R.W.; Analysis or Interpretation: K.K., S.S.T., R.W.; Literature Search: S.S.T., R.W.; Writing: K.K., S.S.T., R.W.

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