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European Journal of Breast Health

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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

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European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

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

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

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

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

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

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

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

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

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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
Current Opinion	300	No abstract	5	No tables	No media

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

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

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

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

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

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

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

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

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

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

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

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Axillary Reverse Lymphatic Mapping in the Treatment of Axillary Accessory Breast Cancer: A Case Report and Review of Management

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ABSTRACT

Accessory breast tissue is a rare aberration of normal breast development, that presents most commonly in the axilla. Similar to normal breast tissue, it can undergo physiologic and pathologic changes, including malignant transformation. We report a rare case of accessory breast cancer, treated with surgical resection and axillary reverse mapping (ARM), and review current literature focusing on management. We report a 68-year-old female with a history of left breast cancer treated with lumpectomy and axillary dissection, who later developed in-breast recurrence treated with re-lumpectomy and sentinel node biopsy which mapped at the contralateral (right) axilla, but was negative. Two years later screening imaging revealed right axillary tail focal asymmetry with two spiculated masses. Core biopsy showed invasive ductal carcinoma (IDC), and histologic examination of the biopsy could not determine whether this represents a new primary breast cancer or axillary metastasis from the contralateral site. She underwent lumpectomy of the two masses and sentinel node biopsy. During surgery, the masses were identified in the axilla itself, rather than the axillary tail. Final pathology revealed IDC, pT1N0(sn), and extensive ductal carcinoma *in situ* (DCIS). Due to positive margins, she underwent re-lumpectomy with ARM. Final pathology revealed residual DCIS with negative new margins. The patient was referred for adjuvant radiotherapy. Accessory axillary breast tissue can be confused with axillary tail tissue. It is necessary for the surgeon to distinguish between them by meticulous physical examination and radiologic evaluation, as resection of axillary breast tissue may warrant reverse lymphatic mapping for lymphedema prevention.

Keywords: Accessory breast tissue, breast cancer, axillary reverse lymphatic mapping

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Key Points

- Accessory breast tissue cancer is extremely rare and associated with a worse outcome due to late diagnosis.
- Early diagnosis should be pursued as it can affect management, including the extent of axillary surgery, and the technique for axillary staging.
- Radiation field recommendations in these patients is a data-free zone.
- Reverse lymphatic mapping should be considered as part of the surgical treatment to prevent lymphedema.

Introduction

Accessory breast tissue (ABT) is a congenital condition in which mammary gland tissue is found outside of the breast. The incidence of ABT is reported to be between 0.3%–6% of females but slightly higher in Asians and Caucasians (1-3). ABT can occur anywhere along the milk line, from axilla to groin, and is thought to result from failure of tissue involution during embryogenesis (4).

ABT can undergo the same physiologic and pathologic changes as normal breast tissue, such as hormonal-induced swelling, inflammatory process, lactational changes, and malignant transformation. Breast cancer originating in ABT represents less than 1% of all breast cancer cases (5, 6). Given its rarity, most of the literature concerning ABT cancer consists of case reports and few case series (7), the largest with 94 patients (8). A second primary invasive carcinoma arising in the contralateral ABT is extremely rare and was described in only one case report previously (7).

Given its location, ABT is not always included in routine screening mammograms, which may lead to delay in diagnosis when cancer develops in it. In addition, due to the proximity of ABT to axillary lymph nodes, ABT cancers have a higher rate of nodal positivity at diagnosis (6), further

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contributing to the worse prognosis in these patients (1, 8-9). The majority of cases reported in the literature underwent axillary lymph node dissection (ALND) as part of their surgical treatment (7).

The management of ABT cancer follows the guidelines for pectoral breast cancer and is largely based on the tumor subtype and stage (10). However, for clinically node negative patients that are not undergoing ALND, the rate of post-surgery lymphedema is unknown, and whether the surgical approach should be attenuated to prevent lymphedema has never been evaluated.

We present a case of node negative ABT cancer that was treated surgically by resection concurrent with a lymphedema-preventative approach, axillary reverse mapping (ARM).

Case Presentation

Clinical course

A 68-year-old female presented with a history of left breast cancer diagnosed 21 years prior to the current presentation. At the original presentation she was treated with lumpectomy and axillary dissection followed by chemoradiation and 10 years of endocrine therapy. She subsequently presented 19 years later with a recurrence in the left breast that was treated with a second lumpectomy, sentinel node biopsy and intraoperative radiation therapy. The sentinel node mapped in the contralateral (right) axilla as well as in the left internal mammary chain, and all lymph nodes were negative. Two years later, after resumption of aromatase inhibitor treatment, a routine diagnostic mammogram revealed a right axillary tail focal asymmetry with two spiculated masses (Figure 1). Ultrasound confirmed two hypoechoic solid masses in the right axilla, measuring 0.8 x 0.8 x 0.4 cm and 0.7 x 0.6 x 0.4 cm (Figure 2). The patient was asymptomatic but on physical exam a 1 x 1 cm axillary tail mass was palpated close to the previous sentinel scar. There was no obvious excess of tissue in the axillary region bilaterally. The rest of her physical exam was unremarkable, except for a well-healed left axillary scar, as well as left lumpectomy and internal mammary lymph node biopsy scars. Ultrasound guided core needle biopsy of one of the masses in the right axilla showed moderately differentiated invasive ductal carcinoma, immunoreactive for estrogen receptor (ER) and progesterone receptor (PR), and not immunoreactive for human epidermal growth factor-2 (HER2). Histologic sections of the biopsy specimen showed no definitive evidence of lymph node and/or mammary parenchyma. Therefore, it could not be determined whether this represented a primary mammary carcinoma in the axilla or a lymph node metastasis.

Workup

Breast magnetic resonance imaging (MRI) was performed and revealed two spiculated homogeneously enhancing masses in the right axillary region measuring 1.6 cm (with biopsy clip in it) and 1.4 cm. In addition, at least eight morphologically abnormal, level 1, right axillary lymph nodes were identified, the largest measuring up to 1.6 cm (Figure 3). Ultrasound guided core biopsy was performed on this node with no evidence of malignancy, confirming reactive nodes secondary to coronavirus disease-2019 (COVID-19) vaccine received recently.

Metastatic workup included brain MRI, chest and abdominal computed tomography (CT) scan and bone scan; all were negative.

Treatment

The case was presented to the multidisciplinary tumor board and since it could not be determined if this was a primary breast cancer or axillary metastasis, the decision was made to proceed with surgical excision of the two masses with sentinel node biopsy, rather than a full axillary dissection.

During surgery, the masses were clearly identified in the axilla itself, rather than the axillary tail. Five "hot" lymph nodes were identified and removed. Histologic examination of the excision specimen revealed moderately differentiated invasive ductal carcinoma (Nottingham Grade 2), 1.6 cm in greatest dimension with associated extensive intermediate nuclear grade ductal carcinoma *in situ* (DCIS; Figure 4). Benign mammary parenchyma with dense stroma was identified in the periphery of the lesion. All sentinel lymph nodes were negative for metastatic disease. The overall findings were consistent with carcinoma arising in accessory breast tissue and the final pathologic staging was pT1N0(sn). The posterior margin was focally involved with invasive carcinoma and extensively involved with DCIS, which was also located less than 0.1 cm from the anterior, superior, and lateral resection margins. Therefore, the patient was taken back to surgery

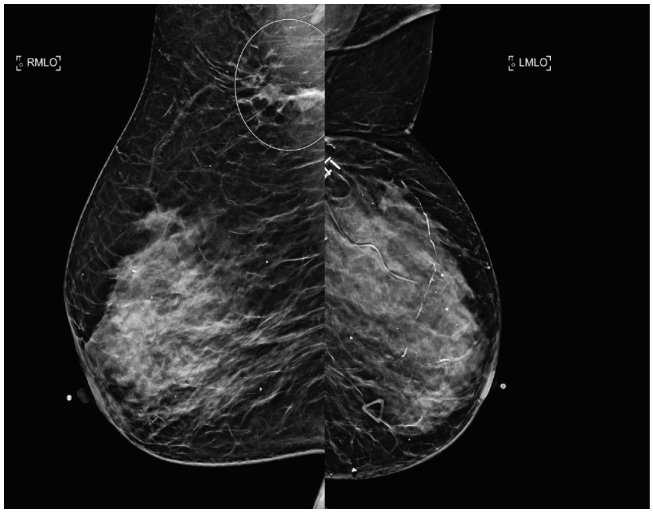

Figure 1. Bilateral mediolateral-view mammography showing right axillary asymmetry (circled)

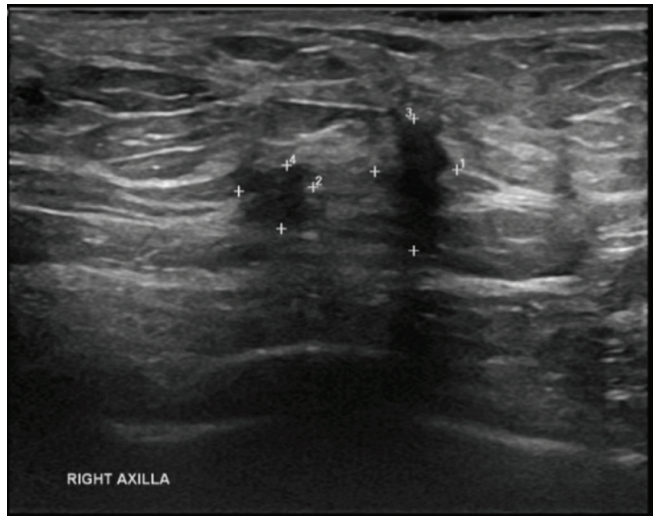

Figure 2. Ultrasonography showing two, ill-defined, hypoechoic, solid masses

for additional margin resection. Since it was clear that this would entail an extensive axillary manipulation, it was decided to add reverse lymphatic mapping to the procedure, in order to identify and protect arm lymphatics, and possibly lower the risk of lymphedema.

Follow-up

The patient was seen three weeks after the second surgery. Final pathology revealed residual DCIS with negative new margins. She healed well and was referred for adjuvant radiotherapy, as well as continued endocrine treatment. Genomic profiling with Oncotype Dx was performed on the surgical specimen and revealed a low recurrence score. Therefore, adjuvant chemotherapy was not recommended. She has no evidence of lymphedema, for which surveillance and monitoring is planned.

Discussion and Conclusion

Ectopic or accessory mammary tissue is most commonly located in the axilla, and development of cancer in it is extremely rare (4, 5). This entity presents unique challenges to breast care providers, ranging from surveillance, through diagnosis to management.

Given the atypical location, escape from screening imaging may occur, as well as low level of clinical suspicion on physical exam, often leading to a delay in diagnosis, a more advanced stage at diagnosis, and eventually worsened outcome for ABT cancer patients (8-9). In addition, due to the relatively small amount of breast tissue in the axilla, direct invasion of carcinoma cells to the skin or underlying axillary fibroadipose tissue is more common (7). Axillary nodal involvement may also occur earlier, due to proximity of cancer cells to axillary nodes (6). These particular issues should be taken into account in the assessment of patients with ABT, and especially on the rare occasions when cancer developed in ABT.

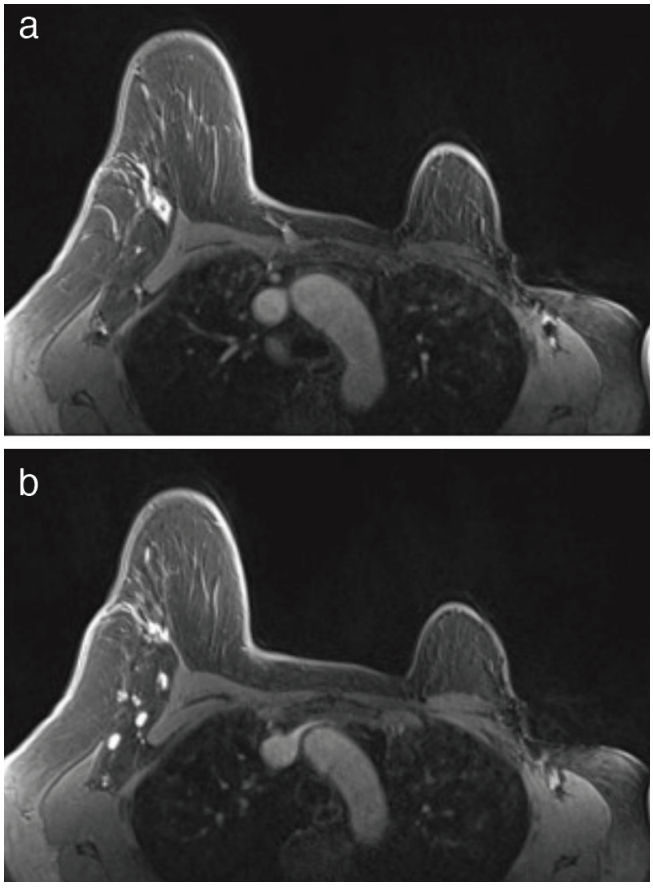

Figure 3. Breast MRI with contrast showing **(a)** right axillary enhancing mass with a biopsy marker, and **(b)** several morphologically abnormal right axillary lymph nodes

MRI: Magnetic resonance imaging

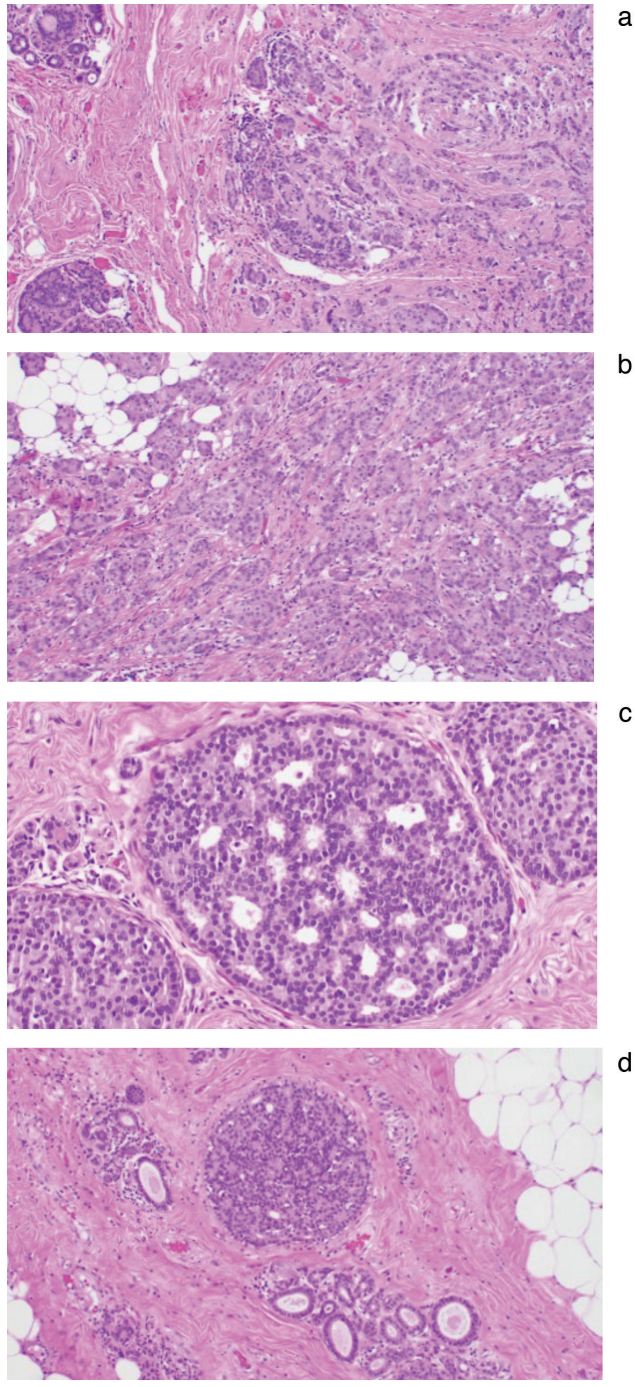

Figure 4. Histologic sections demonstrate moderately differentiated invasive ductal carcinoma (Nottingham Grade 2) [**(a-b)**, Hematoxylin and Eosin (H&E)]. The invasive carcinoma is associated with ductal carcinoma *in situ* (DCIS). High power view of intermediate nuclear grade DCIS with cribriform architectural pattern **(c)**. Benign mammary parenchyma with dense intervening stroma is seen in the periphery of the lesion **(d)**

As previously stated, the management of ABT cancers follows the same principles as pectoral breast cancer guidelines (11) and is largely based on tumor subtype and stage (10-11). Still, there are several issues that are essentially different from pectoral breast cancer and require a unique approach. We chose to focus our literature review on those particular issues.

Axillary staging for cN- patients

Axillary management can be more challenging in ABT cancer patients due to the close proximity of primary tumor to axillary lymph nodes. In some cases, lymph nodes can create a large conglomerate with the mammary cancer tissue, or can be completely replaced by tumor cells (12, 13). Zhang et al. (9) published a case series of 11 patients with ABT cancer and found that more than 80% of the patients presented with stage 2 or higher disease, and 45% of them demonstrated axillary nodal disease. According to Maki et al. (14), ALND is the most common surgical approach and is performed in 64% of cases. Most surgeons advocate routine ALND as part of the primary surgery, due to the higher rate of nodal involvement and the potential for obscuration of sentinel nodes after tracer injection, given their proximity to the tumor (14-17). However, there are reported cases of negative lymph nodes after ALND (16, 18), which raises the concern of overtreatment in these patients. Performing sentinel lymph node biopsy (SLNB) for axillary staging in clinically node negative ABT cancer patients continues to be controversial due to the rarity of cases, insufficient literature, and absence of specific management guidelines (15, 19). There are case reports of successful SLNB for ABT cancers (7, 19-21), but the reliability of localization and the recommended technique to use are largely unknown. Several case reports have shown successful localization using either radioactive tracer, blue dye or both (7, 21). Whether the tracer injection should be located peritumorally in the axilla or in the periareolar region in the breast is another question with no clear answer. Since the embryologic development of ABT occurs independently from that of the breast, it is likely that its lymphatic drainage follows that of the normal anatomy of the armpit, which is towards the ipsilateral axillary nodes and then towards the supraclavicular nodes (2). Therefore it seems more accurate to inject the tracer in the axilla. In several studies, injection was performed peritumorally with good sentinel lymph node identification (21). Preoperative lymphoscintigraphy can sometimes be accompanied with single photon emission computerized tomography (SPECT) for better localization of involved nodes (22).

Adjuvant radiation therapy

Does the adjacent pectoral breast need to be radiated or only the accessory breast? Furthermore, if we indeed consider ABT as a separate organ from the pectoral breast, can radiation be omitted completely since a "mastectomy" of the whole accessory breast is typically performed, thereby lowering the risk of radiation induced lymphedema? Some authors (11, 23) have suggested radiotherapy to the tumor site is indicated if ALND has been avoided to enable local control. However, if sentinel nodes are reliable and negative there should not be a need for this modality, as long as the entire ABT was excised. Those same authors agree that whole breast radiotherapy after surgery is controversial and was not systematically performed. In our opinion, radiation is indicated for partial resection of the ABT and when a sentinel node cannot be localized while no clinically suspicious disease is present in the axillary nodes. In other cases, the role of adjuvant radiation remains controversial and decided by multidisciplinary teams on a case-by-case basis, carefully weighing individual risks and benefits.

Lymphedema rate and prevention

It is unclear how the resection of ABT cancer itself affects the rate of lymphedema, even when ALND is not performed. Factors such as size of excised tissue and number of sentinel nodes removed are important, as well as adjuvant radiation to the axilla (24). Several techniques have been developed to minimize the risk of arm lymphedema among patients undergoing axillary surgery. One of them is the axillary reverse lymphatic mapping (ARM) technique, in which a tracer is injected into the ipsilateral upper extremity, allowing the surgeon to visualize and preserve lymphatic channels and lymph nodes draining the arm, thereby minimizing disruption of lymphatic flow (25). Several studies have reported decreased lymphedema rate when ARM was performed along with ALND (26-28) or even only SLNB (29-30). In the case of ABT cancer surgery it seems reasonable to consider ARM routinely, given the axillary manipulation performed, even if SLNB alone is used. In the event that ALND is necessary, ARM may have a higher impact, and can also serve as the first step to a Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) (31) or S-LYMPHA (Simplified LYMPHA) (32). To the best of our knowledge, this is the first case report describing ARM performance in association with ABT cancer surgery.

In the case presented there was no clinically apparent swelling in the axillae to suggest the presence of ABT, most probably due to the patient's post-menopausal state and her previous axillary surgeries bilaterally (left axillary dissection and right sentinel node biopsy). In retrospect, further anamnesis taken after the right lumpectomy and SLNB revealed episodes of cyclical axillary swelling during her fertility years. The swelling was especially noticeable to her during pregnancy and post-partum.

Learning from this experience, we recommend clinicians to get a full ABT-directed anamnesis for every patient with axillary tail cancer. In addition, raising the clinical suspicion in multi-disciplinary meetings can further assist with meticulous radiologic evaluation of the anatomical localization of the tumor, as well as discussing treatment options that are unique to this condition, especially in relation to extent of surgery, injection site for sentinel node biopsy, adjuvant radiation and lymphedema prevention. Breast care providers must be aware of this entity, and the unique challenges it poses.

In conclusion, cancer arising in axillary ABT is extremely rare and associated with worse outcome due to late diagnosis. It is important to diagnose cancer in ABT before surgery, as it can affect management decisions, such as the extent of axillary surgery, technique of axillary staging, radiation recommendations and reverse lymphatic mapping to prevent lymphedema. Awareness and a high level of suspicion are key.

Ethics Committee Approval: The case report has been exempted by the ethical committee of our institution (EXMPT-26-12-18-01).

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

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Authorship Contributions

Surgical and Medical Practices: O.F.E., S.M., Y.T., E.A.; Concept: O.F.E., S.M., E.A.; Design: O.F.E., E.A.; Data Collection and/or Processing: O.F.E., S.M.,

Y.T., E.A.; Analysis and/or Interpretation: O.F.E., S.M., Y.T., E.A.; Literature Searching: O.F.E., S.M.; Writing: O.F.E., S.M., Y.T., E.A.

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Review

Eur J Breast Health 2022; 18(1): 6-12
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De-Escalation of Breast Cancer Surgery Following Neoadjuvant Systemic Therapy

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ABSTRACT

Breast cancer treatment has seen many advances in recent decades, lessening the morbidity to patients, while improving outcomes. Central to these gains has been the introduction of breast conserving surgery and neoadjuvant systemic therapy (NST). There is a considerable interest in further de-escalation of the treatment of breast cancer, which is being studied in several ongoing randomised trials. We aimed to appraise the current literature regarding the various aspects of de-escalation of surgical treatment of breast cancer after NST, and attempt to prognosticate the future course of breast oncotherapy.

Keywords: Breast cancer, neo-adjuvant therapy, de-escalation

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Key Points

- De-escalation of breast cancer treatment aims to reduce morbidity and improve quality of life without compromising the oncological outcome.
- Patients with triple-negative or HER2 positive breast cancer who achieve an excellent response to NST are suitable candidates for de-escalation of breast cancer surgery.
- Patients with cN1-2 disease before NST who become cN0 after NST can undergo TAD as an alternative to complete ALND if pCR is achieved.
- The elimination of lumpectomy following an excellent response to NST remains the subject of ongoing clinical trials.

Introduction

Currently, over 20% of patients with early breast cancer are treated with neoadjuvant systemic therapy (NST) and this proportion has been increasing over the years (1). Initially, the reason for offering NST was downstaging locally advanced tumours to facilitate breast-conserving surgery (BCS). However, its role has expanded to include other aims such as in vivo drug sensitivity testing and provision of critical prognostic information that can guide and tailor adjuvant treatment for residual disease. The use of adjuvant systemic therapy in patients with residual disease following NST for triple negative breast cancer (TNBC) or human epidermal growth factor receptor 2 (HER2) positive breast cancer has been shown to improve overall survival (2, 3).

Furthermore, advances in NST protocols have increased the rates of observed pathological complete response (pCR). Examples of such refinements in current NST protocols include carboplatin for TNBC (4), the addition of pertuzumab to trastuzumab for HER2 positive breast cancer (5), and more recently, the addition of immunotherapy for TNBC (6).

In addition to the marked improvements in pCR rates, there is a growing body of evidence from randomised controlled trials (RCTs) that omission of surgery for minimal residual disease in the axilla outside the NST does not compromise oncological outcome. Two randomised trials have demonstrated that omission of complete axillary lymph node dissection (ALND) when the sentinel lymph node biopsy (SLNB) is positive for malignancy does not compromise the overall survival. The American College of Surgeons Oncology Group (ACSOG) Z0011 trial showed that patients with clinically node-negative breast cancer with 1-2 positive sentinel lymph nodes achieved equivalent overall (OS) and disease-free survival (DFS) compared to those undergoing ALND (7).

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In the AMAROS trial, patients with positive SLNB undergoing axillary radiation therapy had a similar OS to those undergoing ALND (8). The axillary local recurrence rate was slightly higher in the radiation group and incidence of lymphedema was higher in the ALND arm. The SLNB procedure is known to have a recognised false negative rate (FNR) in patients with cN0 disease of up to 10%. However, the various RCTs comparing the SLNB and ALND in patients with a clinically node-negative breast cancer have shown equivalent oncological outcomes (9). These observations have inspired research into the potential for de-escalating breast cancer surgery following NST. In view of the limited evidence regarding surgery, de-escalation after neoadjuvant endocrine therapy, neoadjuvant chemotherapy +/- immunotherapy will be the focus of this article.

Predictors of pCR

Patients with TNBC or HER2 positive disease are known to have the highest rates of pCR in the breast (10). Other predictors of high pCR include high tumour grade and high proliferation index. Hormone sensitive lobular breast cancer is known to achieve the lowest rate of pCR. Axillary pCR seems to be higher than that of the breast, although breast pCR is the best predictor of axillary pCR (11).

Patients with triple-negative or HER2 positive breast cancer who achieve cCR in the breast would be excellent candidates for de-escalation of breast cancer surgery. Therefore, it is critical that imaging modalities accurately predict pCR so that de-escalation of breast cancer surgery can be accurately planned. However, it should be noted that breast cancer patients who have a partial or complete response in imaging, as well as pCR, are also candidates for de-escalation in surgery.

We have recently reviewed the evidence regarding the potential role of positron emission tomography (PET) in the assessment of axillary disease and concluded that 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (^{18}F-FDG PET/CT) has a low sensitivity but high specificity for axillary nodal disease. Therefore, ultrasound-guided biopsy could be considered in a positive computed tomography/Positron emission tomography (CT/PET). Modest accuracy however prohibits the use of ^{18}FDG-PET/CT alone in axillary staging. Prospective research using standardised protocols and quantitative cut-off points is warranted (12).

Moreover, the diagnostic performance of non-invasive imaging, including PET and magnetic resonance imaging (MRI), for assessment of axillary response after NST in clinically node-positive breast cancer was the focus of a recent systematic review and meta-analysis. The authors concluded that the diagnostic performance of current non-invasive imaging modalities was too limited to accurately assess axillary response after NST in clinically node-positive breast cancer patients (13).

Breast MRI seems to be the most accurate modality for predicting pCR of the primary tumour (Figure 1) and has received the highest rating (rated 9) by the American College of Radiologists (14, 15). A recent meta-analysis has demonstrated that contrast-enhanced breast MRI has performed well in predicting pCR of the primary tumour with a pooled sensitivity of 80% and specificity 84% (16).

Ultrasonography (rated 8) represents the second-best modality for monitoring the primary tumour response in the breast and is valuable in countries with limited MRI resources. In relation to monitoring the nodal response in patients with initially node-positive breast cancer, ultrasonography seems to be the gold standard (Figure 2) (15).

Clinically Node-Negative Breast Cancer (cN0)

SLNB following NST in patients with clinically node-negative (cN0) breast cancer has been shown to be equivalent to SLNB prior to treatment. A recent meta-analysis (17) reported an identification rate of 96% and a false negative rate (FNR) of 6% in post-NST SLNB. There was no significant difference in OS or DFS, thus confirming the oncological safety of this approach (18, 19).

Furthermore, SLNB performed post-NST is more likely to be negative, thus down-staging axillary disease and reducing the rate of ALND. In view of the clear evidence regarding the efficacy of this approach, SLNB after NST has become the gold standard in patients with clinically node-negative breast cancer undergoing NST, as reflected by its incorporation into international guidelines (20). A prospective cancer registry study in Germany recorded that almost 100% of

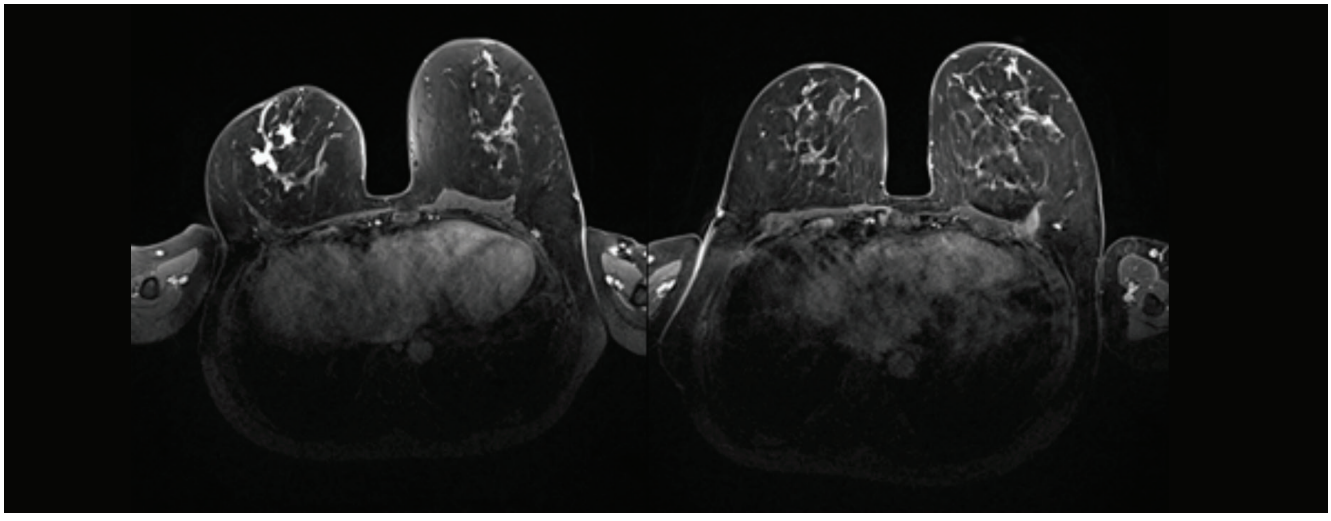

Figure 1. MRI demonstrating clinical complete response (cCR) of recurrent node positive TNBC in the right breast to NST that included Carboplatin and Pembroluzimab in a 50-year old woman (left: before NST; right: after NST. The patient achieved pCR.

MRI: Magnetic resonance imaging, TNBC: Triple negative breast cancer, NST: Neoadjuvant systemic therapy

breast cancer patients underwent complete ALND 2008. However, the number of patients undergoing this radical surgical approach has declined sharply to 24.4% in 2016 (21).

Barron et al. (22) reported that in clinically node-negative, triple-negative or HER2 positive breast cancer who achieve pCR in the breast following NST the incidence of residual nodal disease was less than 2%. The authors reported a nodal pCR of 98.4% in such patients when analysing data spanning more than 4,000 patients in the National Cancer Database. The incidence of positive SLNB was found to be 1.6% which is significantly below the FNR of SLNB in patients undergoing upfront surgery for cN0 breast cancer outside the NST setting. This finding has raised the question whether the SLNB can be safely omitted in this selected group of patients (cN0 triple-negative or HER2 positive breast cancer) who achieve complete clinical response (cCR) in the breast as determined by MRI. This is the basis of a new clinical trial that has just commenced recruitment (23).

Clinically Node-Positive Breast Cancer (cN1-2) and NST

In a previous study, we demonstrated that SLNB alone in patients with initial biopsy proven lymph node involvement undergoing neoadjuvant chemotherapy had a FNR of 13%, which is above the gold standard target of 10% (24). However, the FNR was reduced if a minimum of three lymph nodes were harvested including the marked biopsy-proven lymph node, in addition to the use of immunohistochemistry (IHC) and the dual tracer technique in sentinel node mapping (24).

More recently, we have conducted a pooled analysis of published studies which has shown that harvesting the biopsy proven lymph node that is marked prior to NST is associated with an acceptably low FNR of 6.2% with a successful retrieval rate of 90% (25).

There are currently no RCTs confirming oncological safety of omitting ALND for ypN0 disease following NST in patients presenting initially with cN1. However, a recent large European study demonstrated that there was no difference in OS or DFS between patients presenting with cN1-2 disease who were rendered SLNB negative and patients presenting with cN0. The rate of axillary recurrence was reported to be 1.8% in the former and 1.6% in the latter (26). In this study that included 688 patients, ALND was not performed when the post-NST SLNB was negative. However, some patients received radiation therapy. Furthermore, we have estimated that in the worst-case scenario the probability of compromising OS would be in the region of 1in 4,000 for a FNR of 5% in this setting (27).

Targeted Axillary Dissection (TAD)

Targeted axillary dissection (TAD) refers to the combination of SLNB and marked lymph node biopsy (MLNB), in which lymph nodes are identified and marked radiologically prior the operation and excised during surgery. This has been shown to result in a FNR of 5.2% according to our recent pooled analysis (25). It is, however, worth highlighting that the degree of overlap between the SLNB and MLNB is approximately 75% (26). If histological examination of TAD reveals no evidence of residual disease, then a complete ALND and its associated morbidities could be avoided, thus enhancing quality of life. However, if residual disease is identified in the TAD specimen, then escalation of the treatment in the form of surgery (ALND) or radiation therapy is indicated. This approach of treatment escalation should be considered even if the residual disease is minimal, such as micrometastases or isolated tumour cells (ITCs), for which ALND is not indicated in patients who did not receive NST (27).

This escalation of axillary treatment is important in view of the fact that increased residual disease burden has been associated with worsening overall survival with the 5-year survival being reported as 88.9% for ypN0 compared with 77.6% for ypN1 and 82% for ypN0 (i+) and 79.5% for ypN1 (mi) N2 (28).

TAD is traditionally performed by deploying a marker clip within the biopsy proven lymph node at the time of diagnosis and subsequent localisation by inserting a guidewire under ultrasound control on the day of surgery. In this context, the hydrogel marker (HydroMark) seems to be the best marker in view of the excellent visibility on ultrasonography and sufficiently long half-life (25).

Wire-free techniques have recently been introduced whereby the marker that can be localised by an external detection system is deployed at the

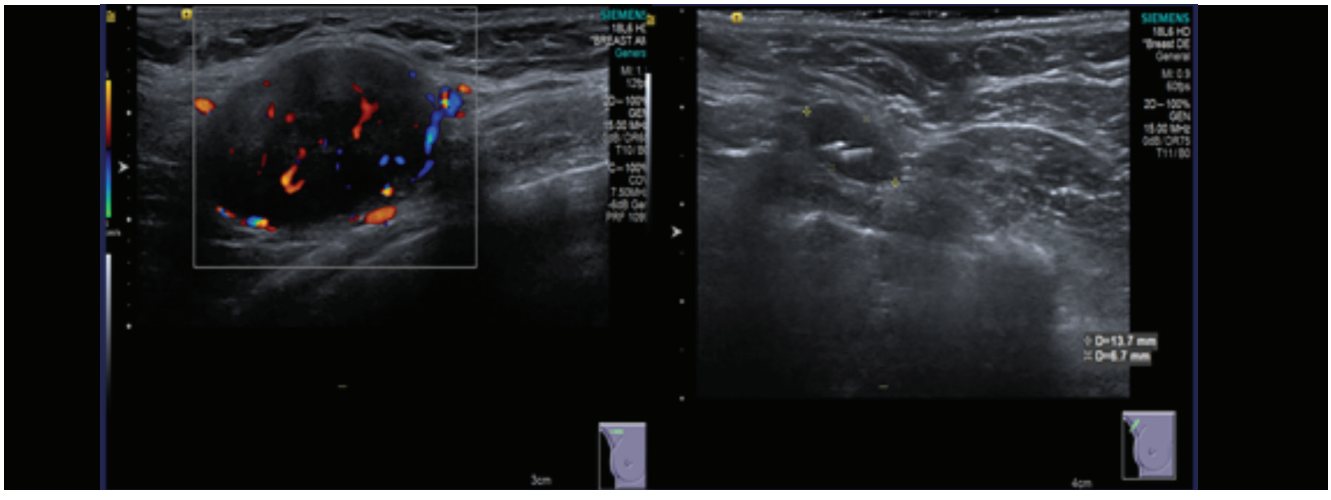

Figure 2. US scan of the right axilla demonstrating a pathological lymph node (cT0N1M0 TNBC) with an increased blood flow (left: before NST) that has responded well to NST (right: after NST). The Savi Scout reflector to facilitate targeted axillary dissection (TAD) is seen within the lymph node (right)

US: Ultrasound, TNBC: Triple negative breast cancer, NST: Neoadjuvant systemic therapy

time of lymph node biopsy, so that a second localisation procedure can be avoided (25). These techniques that allow decoupling of radiology and surgery schedules include the use of radioactive iodine seeds, ferromagnetic seeds (MagSeed; Endomag, London, United Kingdom), radio frequency identification tag (LOCalizer, Hologic Inc., Santa Carla, CA, USA) and infrared reflector combined with radar (SAVI SCOUT, Merit Medical, Aliso Viejo, CA, USA) (25) (Figure 3).

The use of radioactive iodine seeds, also known as MARI technique (Marking the Axillary lymph node with Radioactive Iodine seeds), has been curtailed by the extensive regulatory and administrative requirements due to radiation handling. Unlike magnetic seeds and radiofrequency tags, the SAVI SCOUT system generates minimal MRI-void signals and therefore it can be deployed at the time of biopsy in both the primary tumour and the biopsy-proven lymph node (29).

The optimal management strategy of the axilla in patients with cN1 who achieve a cCR in the axilla (ycN0) is the focus of ongoing AXSANA trial (30). This prospective study is not randomised and includes oncological outcome in its primary endpoints.

Can Breast Lumpectomy Be Safely Omitted?

In patients with occult breast cancer, radiation therapy to the breast has been demonstrated to achieve an OS similar to total mastectomy (31), implying that omission of surgical excision of the occult primary tumour in the breast may not have a detrimental oncological impact. Surgical resection of the primary tumour was not mandatory in some of the trials that compared neoadjuvant and adjuvant chemotherapy. When considering the trials which allowed the omission of primary breast cancer surgery, there is evidence that the distant disease-free survival and OS were not compromised when primary breast cancer surgery is omitted. However, there was a higher incidence of local recurrence (32). A similar observation was reported in a study by Ring et al. (33) where the omission of lumpectomy after NST was associated with a higher risk of local recurrence without a compromise of OS. However, when the ultrasound response was taken into consideration, the local recurrence rate declined from 33% to 8% at five years. These observations raised the possibility of eliminating breast lumpectomy after NST. In order to achieve the optimal outcome, it is logical to consider this form of de-escalation in patients who are most likely to be excellent responders (33).

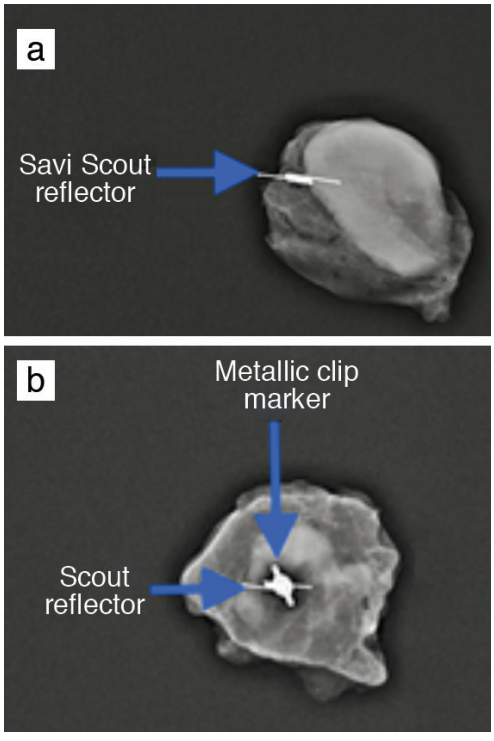

Figure 3. TAD guided by SAVI SCOUT

TAD: Targeted axillary dissection

In this context the molecular subtype plays an important role in patient selection with patients diagnosed with TNBC or HER2 positive disease representing the best candidates. Furthermore, complete radiological response of the primary tumour, as assessed by MRI, would be another important factor to consider in patient selection. For this approach to be effective we should be able to reliably verify pCR without surgery. A meta-analysis of studies evaluating the accuracy of imaging-guided core-biopsy has demonstrated a FNR of 28% which is significantly above the acceptable target of 10%. However, specificity was as expected to be high at 99% (34). When considering patients with triple-negative or HER2 positive breast cancer who achieve a complete or partial response on breast imaging the accuracy improves to 98% with a FNR of 5% with the use of vacuum assisted core biopsy (9-gauge) obtaining 12 cores in addition to fine needle aspiration cytology (35).

These encouraging results have inspired the NCT 02945579 trial at MD Anderson which has completed accrual. In addition to assessing DFS and OS, the trial included quality of life and cost-effectiveness as part of its primary end points. The use of biomarkers of response, such tumour infiltrating lymphocytes (TILs) (36) and circulating tumour DNA (ctDNA), should be included in future studies as a strategy of monitoring response to treatment and predicting pCR. There is a growing body of evidence that ctDNA reflects residual disease burden and disappearance of this marker in the peripheral blood during NST correlates with pCR and an excellent prognosis (37).

De-Escalation of NST

Achieving pCR following NST is associated with significantly better DFS and OS, particularly for triple-negative and HER2+ breast cancer (38). Adjuvant chemotherapy in patients who achieved pCR does not seem to improve outcomes (39). This raises the possibility of de-escalating NST especially in patients with ER-HER2+ breast cancer who are very likely to attain pCR with pertuzumab, trastuzumab, paclitaxel, and carboplatin, thus avoiding the more toxic anthracyclines (40). Patients with cN0-2 disease who achieve cCR, as determined by MRI and ultrasound, can be selected for surgery after a shorter course of NST to verify pCR and avoid the anthracycline phase of treatment (Figure 4).

Conclusion

We know that a certain proportion of, but not all, patients with cCR after NST has pCR and pN0. Patients with triple-negative or HER2 positive breast cancer who achieve a complete clinical response after NST, as determined by breast MRI and/or ultrasound, represent excellent candidates for de-escalation of breast cancer surgery. Patients with the cN1-2 disease before NST and had cN0 after NST can undergo TAD as an alternative to complete ALND if pCR is achieved. TAD has been recently facilitated by the advent of novel wire-free and radiation free technologies.

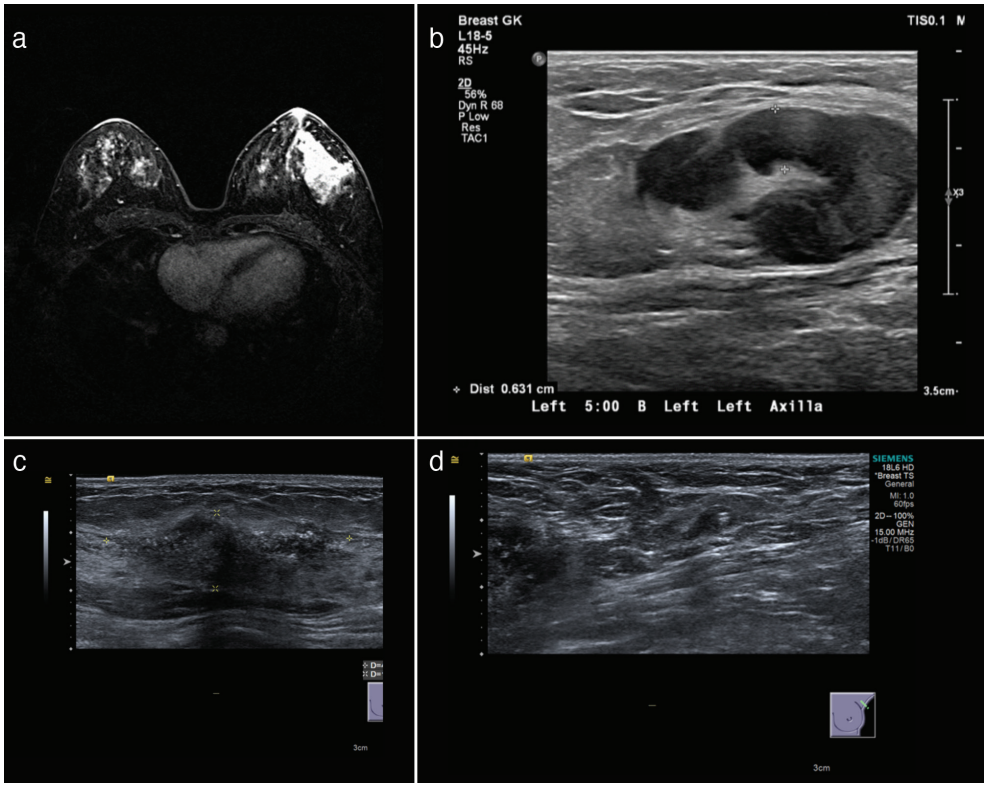

Figure 4. This 45-year-old lady presented with ER-HER2 + T3N1M0 breast cancer. She received 12 weeks of weekly paclitaxel and carboplatin and 3 weekly trastuzumab and pertuzumab followed by surgery that confirmed pCR. **(a)** MRI prior to treatment demonstrating the large primary tumour; **(b)** ultrasound scan of the axilla prior to treatment demonstrating the pathological lymph-node; **(c)** Ultrasound scan of the breast after NST showing non-specific textual change; **(d)** Ultrasound scan of the left axilla after NST showing a normal giraffe note containing the SAVI SCOUT reflector within it that was subsequently used to guide TAD

HER2: Human epidermal growth factor receptor 2, MRI: Magnetic resonance imaging, NST: Neoadjuvant systemic therapy, TAD: Targeted axillary dissection

The elimination of lumpectomy following an excellent response to NST remains the subject of ongoing clinical trials and is likely to become the new standard of care in selected patients in the future.

Informed Consent: Patients provided consent for anonymised specimen radiographs to be used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.W., K.M.; Concept: K.M.; Design: U.W., K.M.; Analysis and/or Interpretation: U.W., K.M.; Literature Searching: U.W.; Writing: U.W., K.M.

Conflict of Interest: K.M. has received honoraria for providing academic and clinical advisory to Merit Medical. U.W. declared no conflict of interest.

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Review

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Lupus Mastitis in a Young Female Mimicking a Breast Carcinoma; a Rare Entity Through a Case Report and Review of the Literature

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ABSTRACT

Lupus mastitis (LM) is a rare presentation of lupus panniculitis (LP) that usually affects women of childbearing age and may mimic malignancy. The condition is recurrent and progresses along with the underlying disease. Breast pathology that may be associated with LM includes fat necrosis, calcification, fibrosis, scarring, and breast atrophy. Therefore, LM should be considered in the differential diagnosis of a suspicious breast mass on mammography or ultrasound, particularly if the patient has a background of systemic lupus erythematosus (SLE) or discoid lupus erythematosus (DLE). Traumatic procedures such as surgery or biopsy may worsen the condition and it is advisable to avoid biopsy if the diagnosis can be established through accurate patient history, with identification of typical clinical and radiological features. Thus, awareness of the radiologic and clinical features of LM is essential to avoid unnecessary interventional procedures that carry the potential for disease exacerbation. The authors present here the imaging findings of LM in a 37-year old female with SLE, which presented as bilateral palpable breast lumps.

Keywords: Lupus mastitis, panniculitis, lupus erythematosus, breast calcification

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Key Points

- Lupus mastitis is a rare presentation of lupus panniculitis that usually affects women of childbearing age.
- Lupus mastitis should be considered in the differential diagnosis of a suspicious breast mass on mammography or ultrasound, particularly if the patient has a background of systemic lupus erythematosus.
- Accurate patient history and knowledge of the typical imaging appearance on ultrasound and mammogram can help the diagnosis.
- It is advisable to avoid biopsy and surgical intervention if the diagnosis of lupus mastitis can be established with the clinical and radiological features.

Introduction

Lupus mastitis (LM) is a rare manifestation of lupus panniculitis (LP), an unusual clinicopathologic variant of systemic lupus erythematosus (SLE) or discoid lupus erythematosus (DLE) that is characterized by an inflammatory process involving subcutaneous fat (1). LM is the term for breast involvement in LP and may often mimic malignancy. The condition is recurrent and progresses along with the underlying disease. Breast pathology that may be associated with LM includes fat necrosis, calcification, fibrosis, scarring, and breast atrophy (2). LM should be considered in the differential diagnosis of a suspicious breast mass on mammography or ultrasound, particularly if the patient has a background of SLE/DLE (3). Diffuse, bilateral calcifications on mammography, mainly related to calcified foci of degenerated or necrotic fat tissue, and sonographic findings of recurrent breast lumps support the diagnosis of LM. In addition, evidence of necrosis in adipose tissue and peri-glandular or perivascular lymphocyte infiltrations on the histological examination, contribute to substantiating the diagnosis (4). Herein, the authors present a rare case of lupus mastitis in a 37-year old female with a known history of SLE, which presented as bilateral palpable breast lumps and diffuse calcification on the mammogram.

Case Presentation

A 37-year-old female presented with palpable nodular masses in her breasts. She had no personal or family history of breast complaints. However, her mother had a diagnosis of familial Mediterranean fever and two cousins were diagnosed with SLE. Around four years earlier the

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index case had joint pain, facial redness, hair loss, and swelling of the eyelids, hands, and feet that had been diagnosed as having a probable connective tissue disease. On physical examination, malar rash, hyperemic lesions around the mouth, and mild eyelid and pretibial edema were noted. There were some local areas of hair loss that also involved the eyebrows. Other findings were unremarkable.

Laboratory results included: hemoglobin (Hb): 10.9 g/dL [normal range (NR): 12–16]; white blood cells (WBC): 2,690/mm3 (NR: 4,500-11,000) with 53.5% neutrophils; platelets 127,000/mm3; urea 17 mg/dL; creatinine 0.58 mg/dL; fasting blood glucose 91 mg/dL; hemoglobin A1c (HbA1c) 5.6%; and 24-hour urine protein 1.36 gr/day. The anti-ribosomal and anti-nucleosome antibodies were positive but other lupus antibodies were negative. Her renal biopsy revealed type-5 lupus nephritis.

On sonographic examination, axillary lymphadenopathy and ill-defined isoechoic masses, with acoustic shadows related to coarse dystrophic calcifications in the breast parenchyma, were observed. These findings were compatible with fat necrosis (Figures 1 and 2). On the mammogram, diffuse calcifications starting under the skin and scattered bilaterally in the whole of the breast parenchyma were observed. These diffuse calcifications had a coarse and curvilinear shape, consistent with the fat necrosis (Figure 3).

The patient was diagnosed with SLE, complicated by lupus nephropathy and LM. She was treated with steroids and antimalarial drugs. She was also advised to undergo ophthalmic examination. Follow-up was arranged as regular outpatient visits.

Discussion and Conclusion

Kaposi first proposed the term "lupus panniculitis" in 1883. It affects both sexes, but 90% of cases occur in women of childbearing age (2). LM is a rare, benign inflammation of the deep subcutaneous adipose tissues of the breast, seen in around 2%–3% of SLE patients and is rarely the initial presentation of SLE (5, 6). LM is part of the presentation of lupus panniculitis but is termed "lupus mastitis" when the breast glands are involved. To date, only 27 cases have been reported. Kinonen et al. (6) reviewed 22 cases and six additional cases have since been reported.

The precise pathophysiology of LP/LM remains unclear, though the predominant theory suggests an autoimmune-related etiology, in keeping with the known mechanisms in SLE and DLE. Supportive evidence for this theory includes the identification of immune complexes, both at the basement membrane of the dermal-epidermal junction and in blood vessels in areas of panniculitis. In addition, there is often a marked improvement of symptoms with immunosuppressive therapy (1).

The manifestations of LM include masses in the breast, axillary lymphadenopathy, fat necrosis, fibrosis, and calcifications (7). Our patient had these typical findings.

LM may mimic breast malignancy (2). Although rare, LM should be considered in the differential diagnosis of a suspicious breast mass on mammography or ultrasound, particularly if the patient has a background of SLE/DLE (3). Common mammographic findings include ill-defined, dense breast tissue with or without associated microcalcifications. Alternatively, there may be coarse, or curvilinear calcifications in the breast tissue, suggesting fat necrosis. Ultrasound may show a similarly ill-defined, isoechoic, or hyperechoic mass.

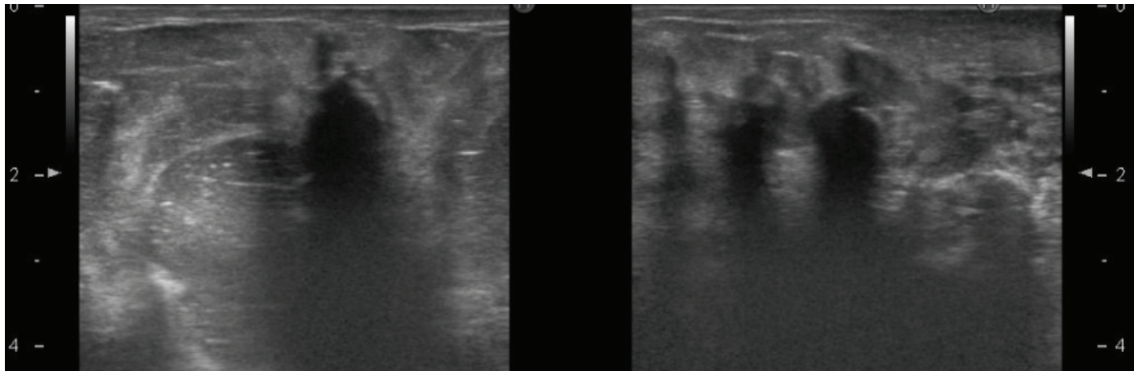

Figure 1. Ultrasound images of both breasts show ill-defined isoechoic masses with posterior acoustic shadow

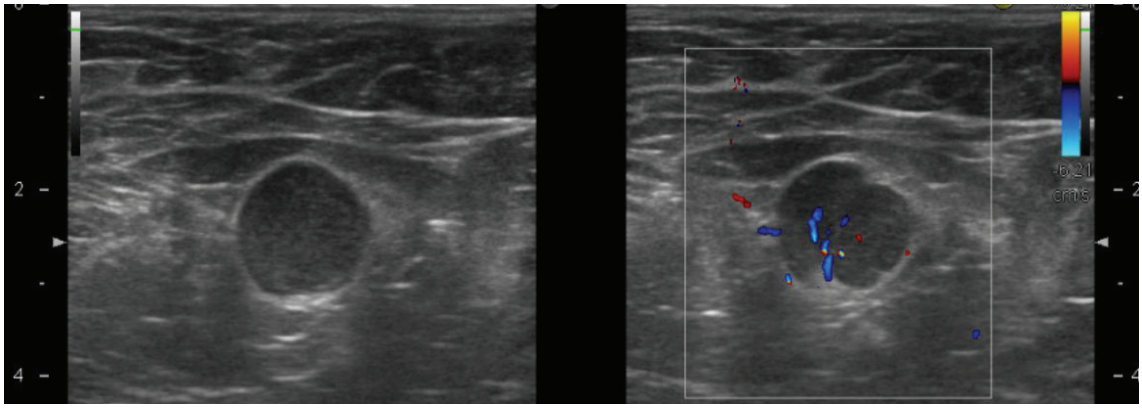

Figure 2. Ultrasound images show axillary lymph nodes enlargement, with a thick cortex

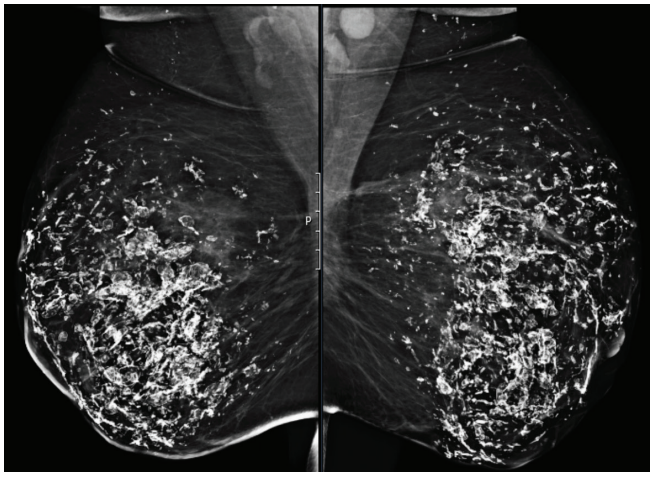

Figure 3. An MLO view of both breasts shows bilateral diffuse, coarse, and curvilinear calcifications, starting under the skin and scattered across the whole parenchyma of the breasts bilaterally

MLO: Mediolateral oblique

It is advisable to avoid biopsy because it may worsen the condition. This is possible if the diagnosis can be established with clinical and radiological features; the unusual mammographic calcification can be particularly helpful for this. However, fine needle aspiration (FNA) biopsy will be helpful if there is a doubt about the diagnosis or when the swelling is localized (1, 5, 8). Accurate patient history and knowledge of the typical imaging appearance of LM may help prevent or minimize biopsy and surgical intervention (8, 9).

Histologically, most LM cases show lymphocyte-predominant inflammation, involving breast ducts, lobules, vessels, and adipose tissue, with hyaline fat necrosis being the most characteristic finding (10).

In our case, there were coarse and curvilinear calcifications on the mammogram and isoechoic masses with axillary lymphadenopathy on ultrasound.

LM should not be confused with breast carcinoma, idiopathic granulomatous mastitis, lymphoma, or other connective tissue diseases. The clinical features and histology help differentiate between these conditions (2, 11). However, LM may be exacerbated by surgical trauma so that needle core biopsy is preferred to open excisional biopsy. Indeed, the latter procedure has been reported to trigger a very painful progression of LM, eventually resulting in obligate mastectomy (4).

Antimalarial drugs are the primary medical treatment option for LM, while corticosteroids may also be used in combination or alone. Surgery should only be considered in patients with ongoing complaints despite appropriate medical treatment, because of the risk of additional exacerbations (3, 12).

In summary, we have reported an unusual case of LM in a female with known SLE. The patient presented with palpable breast masses. The bilateral breast calcification on mammography and isoechoic masses with posterior shadows on sonogram was mimicking a breast carcinoma. However, accurate patient history and knowledge of the typical imaging appearance on ultrasound and mammogram helped obtain a definitive diagnosis. Thus, awareness of the radiologic and clinical features of LM is essential to avoid unnecessary interventions such as biopsy and surgery that carries the potential for disease exacerbation.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O., Ö.A.; Concept: A.O.; Design: A.O., H.A.E.; Data Collection and/or Processing: H.A.E., I.M.; Analysis and/or Interpretation: H.A.E, Ö.A.; Literature Searching: I.M.; Writing: H.A.E.

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

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Original Article

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Genetic Counseling, Screening and Risk-Reducing Surgery in Patients with Primary Breast Cancer and Germline BRCA Mutations: Unmet Needs in Low- and Middle-Income Countries

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ABSTRACT

Objective: Worldwide genetic counseling practices are variable and often not reported in low- and middle-income countries (LMICs). We present the follow-up genetic counseling, breast screening, risk-reducing salpingo-oophorectomy (RRSO) and contralateral prophylactic mastectomy (CPM) in a cohort of study patients with either *BRCA* pathogenic mutations or *BRCA* variant of unknown significance (VUS).

Materials and Methods: Chart review and phone calls for the collection of information. Out of a cohort of 250 patients, 14 had deleterious mutations and 31 had a VUS, of whom 19 had primary early breast cancer. We collected information about genetic counseling, screening, CPM and RRSO.

Results: Fourteen patients with deleterious mutations (7 *BRCA1* and 7 *BRCA2*) and 19 patients with VUS mutations (20 VUS, 4 *BRCA1*, 16 *BRCA2*; 1 patient had both) were surveyed. Of 14 patients with deleterious *BRCA* mutations, 57.14% (8/14 patients) received genetic counseling from their oncologist. Subsequently 85.71% (12/14) are undergoing mammography screening and 35.71% (5/14) breast screening magnetic resonance imaging (MRI). Furthermore, 50% of them underwent CPM and 57.14% underwent RRSO. Of 19 patients with VUS mutations, 10.5% received genetic counseling from their oncologist; 78.9% were undergoing regular screening mammogram and 31.5% were undergoing breast MRI; one patient underwent CPM and two patients RRSO.

Conclusion: Within three years from knowing they have a mutation, 50% of patients with germline *BRCA* mutations had undergone CPM and 60% RRSO, the majority of them had screening mammography surveillance but only 50% had screening MRI. Follow-up of patients with VUS with mammography was 78% but MRI was only 31%. Lack of MRI surveillance reflects both limited resources and insufficient counseling. Genetic counseling was done by medical oncologists, which reflects a trend in LMIC. Our Data shows the importance of the need for professional genetic counselors and optimal surveillance in Lebanon and other LMICs.

Keywords: Hereditary breast cancer, genetic counseling, screening; contralateral prophylactic mastectomy, risk-reducing salpingo-oophorectomy, germline *BRCA* mutation, VUS mutation

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Key Points

- Optimal care, in terms of prevention and early intervention, is provided by identifying women and their family members who are at high risk of carrying mutations.
- Genetic counseling along with appropriate surveillance and interventions for *BRCA* mutations are recommended because of the known benefits from surveillance, chemoprevention and breast/ovarian risk reducing surgeries.
- Worldwide, the practice of genetic counseling among women with deleterious *BRCA* 1 and 2 variants classified as of unknown significance is variable and is limited in most low- and-middle income countries.

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Introduction

Breast cancer is the most common cancer among women, worldwide (1, 2). Hereditary breast cancer accounts for 5 to 10% of cases, 15 to 20% of breast cancer cases are familial and 70 to 80% are sporadic (3). At least 50% of hereditary breast cancer is due to germline autosomal dominant pathogenic *BRCA1* or *BRCA2* mutation (4). Breast cancers in patients with *BRCA1* mutations are usually of high-grade with rates of triple-negative breast cancer (TNBC) as high as 80 to 90% (5). Conversely, the rate of *BRCA* mutation in TNBC ranges between 11 to 35% (4, 6, 7). The risk of developing breast cancer in patients who have a *BRCA* mutation can be as high as 80% (40%–80%) (8), while the chance of having ovarian cancer is between 17 to 44% (9). In terms of prevention and early intervention, breast cancer care is optimized by identifying women and their family members at high-risk of carrying such mutations (10, 11). Individuals identified with a variant of unknown significance (VUS) should be counseled based upon their personal and family history, irrespective of the variant (12, 13). While recent American Cancer Society guidelines for breast cancer screening among average-risk women call for screening starting at the age of 45 years (14), the European Society of Medical Oncology calls for mammography screening for women aged 50–69 years with a Level 1A evidence while leaving it as an option for women in the age groups 40–49 and 70–74 years (15). For early detection in high-risk women and mutation carriers, guidelines call for annual screening with mammogram starting at age 30 years, or 10 years earlier than the first case in the family, along with a yearly breast screening magnetic resonance imaging (MRI), starting at 25 years old (16, 17).

Women who are carriers of *BRCA1/2* mutation and are newly diagnosed with breast cancer have a 17%–37% risk of developing a contralateral breast cancer within 10 years of their initial diagnosis (15, 16). Over 50% of *BRCA* mutation carriers opt for contralateral prophylactic mastectomy (CPM), thus decreasing the risk of breast cancer by 90%. Moreover, women with a *BRCA* variant are also at risk of developing ovarian cancer, ranging from 17% in *BRCA2* to 44% in *BRCA1* carriers, compared to a 2% risk in women without *BRCA* variants (18). Many genetic counseling practices are reported in the literature (19, 20). risk-reducing salpingo-oophorectomy (RRSO) around the age of 40, usually after completion of family plans, is recommended for women who are *BRCA1/2* mutation carriers. This prophylactic surgery reduces the risk of developing breast cancer by 50% and reduces the ovarian cancer risk by 80%–96% (21, 22).

Breast cancer represents 35% of all cancers affecting women in Lebanon and Arab countries, with a median age of diagnosis of 48–52 years (23, 24). We have previously reported the prevalence of *BRCA* mutations in 250 ethnic Lebanese Arab women with a high risk of having hereditary breast cancer and found that 5.6% had either *BRCA1* or *BRCA2* pathogenic mutations (23). Herein, we reported the results of surveillance three years after disclosure of the presence of a mutation to the patients.

Materials and Methods

Patients previously identified as carrying *BRCA* deleterious and VUS mutations were included (23). These patients were investigated in terms of follow-up processes, including genetic counseling, screening recommendations and risk reducing surgeries in patients with early breast cancer. The patients were included in the original study for *BRCA1* and *BRCA2* mutation and considered at high risk of genetic predisposition if: aged <40 years at diagnosis; aged ≤50 years with at least one relative with breast cancer; aged ≤50 years with one relative with ovarian cancer; ≥2 relatives with breast cancer; ≥2 relatives with ovarian cancer; or patient has personal history of breast or ovarian cancer (25, 26). No subjects were male.

The initial study plans included surveillance and follow-up of all patients. There was an additional approval by the Institutional Review Board (IRB) of the American University of Beirut Medical Center (IRB ID: IM.NS.06, date: 17.11.2016 and 29.06.2021) to complete clinical and follow up information via phone calls, when necessary. The content of phone conversations was strictly limited as specified by the IRB. Research Fellows conducted patient interviews and chart reviews. Patients were asked three specific questions about: 1) the screening modality used to detect a second primary breast cancer since they were discovered to have *BRCA* mutation; 2) if any preventive surgical procedure for breast and/or performed during or after treatment for the initial breast cancer; and 3) if they received any advice for genetic counseling for themselves and their families. The data and results were collected and simply analyzed for the processes of genetic counseling, screening, prophylactic CPM and RRSO interventions in this cohort of previously diagnosed patients with breast cancer, with high genetic predisposition according to the inclusion criteria and all of whom harbored either a deleterious or a VUS mutation for *BRCA1/2*.

Results

Study Cohort: In total there were 250 women identified from the earlier study who were at high risk of having hereditary BC. Of these 250, 14 (5.6%) had deleterious *BRCA1* or *BRCA2* mutations and 31 (12.4%) had VUS mutations, of whom 19 had early breast cancer. As reported earlier, 11.2% of patients were TNBC, and 25% of patients with TNBC had a *BRCA1* mutation (25). All patients with a *BRCA1* deletion had triple negative, grade 3, infiltrating ductal breast carcinoma. Of the 19 patients with *BRCA* VUS mutations, four were VUS *BRCA1* and 16 were VUS *BRCA2* while one patient had both *BRCA1* and *BRCA2* VUS detected (24).

Genetic counseling for patients with *BRCA* deleterious mutations: 57.14% of patients with *BRCA* pathogenic mutations said they received genetic counseling. All patients were counseled by their primary oncologist. None received information from a certified genetic counselor.

Genetic counseling for patients with VUS mutations: Only 10.5% reported having genetic counseling, and again this was only by their managing oncologist.

Screening mammography and MRI of the breasts in *BRCA* pathogenic mutation carriers: 85.71% of patients with a *BRCA* pathogenic mutation reported that they were undergoing regular screening mammography. Only 35.71% said they were receiving breast screening MRI in addition to yearly mammograms.

Genetic counseling and screening in family members of *BRCA1/2* pathogenic or VUS mutations: 57.14% reported that they had advised their family members (sisters and daughters) to undergo *BRCA* mutation testing. Furthermore, only 21.0% of the patients with VUS mutations advised their family members to undergo *BRCA* mutation testing.

Mammography and breast MRI in patients with VUS: Regular screening mammograms were consistently and persistently performed in 15 (78.9%) of patients with a VUS. However, only 31.5% had and continued to get regular screening MRI of the breasts (Graph 1).

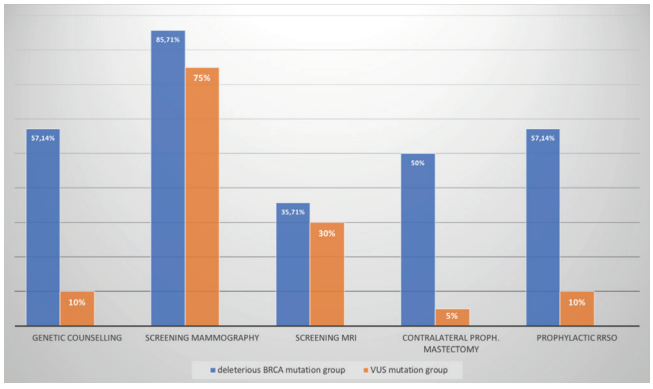
Risk reducing surgery in *BRCA* pathogenic mutation carriers: CPM was done in 50% of patients and RRSO in 57.14% of patients with a pathogenic mutation. 50% of the patients had both CPM and RRSO.

Risk reducing surgery in *BRCA* VUS mutation carriers: Of the patients with *BRCA1/2* VUS mutation, only 5.2% had CPM and 10.5% had RRSO (Graph 1). All patients who underwent these surgeries did so at the recommendation of their private oncologist who initiated discussion and counseling with them.

Chemoprevention: Chemoprevention was given for patients with a *BRCA* mutation in this study. Premenopausal women received tamoxifen, while post-menopausal women had either tamoxifen or aromatase inhibitor (AI). Chemoprevention with tamoxifen was done in 41% of patients. AI was used in 6% of patients. Premenopausal patients on AI also received ovarian function suppression (Goserelin subcutaneous tunnel injection 3.6 mg every 28 days) treatment as part of their adjuvant therapy.

Discussion and Conclusion

This was a follow-up study in a group of patients with pathogenic and VUS mutations in *BRCA*, identified as part of a study of 250 patients at high risk of having a hereditary breast cancer. In the full cohort the mean germline pathogenic mutation rate was 5.6%, with the highest rate (10.6%) in patients below 40 with a positive family history of breast cancer (25). Although the number of patients in the present study is small, we report real world rates of surveillance in patients with *BRCA* pathogenic and VUS mutations. It is notable that half of *BRCA1/2* patients underwent contralateral prophylactic mastectomy, which is consistent with the generally reported rate of prophylactic mastectomy, ranging from 29.9% to 55.4% (28). A meta-analysis had shown that the risk of contralateral breast cancer is 25% for *BRCA1* carriers and 13.5% for *BRCA2* carriers vs. 3.6% for non-carriers (29). There has been a recent trend towards prophylactic contralateral mastectomy or bilateral mastectomy at the time of initial breast cancer surgery (30).



Graph 1. Genetic counseling, screening mammography and MRI, risk reducing surgery in patients with *BRCA* pathogenic and VUS mutations

MRI: Magnetic resonance imaging, VUS: Variant of unknown significance, BRCA: Breast cancer gene

Published literature shows that around 56% of *BRCA1/2* patients undergo prophylactic oophorectomy (31). Prophylactic oophorectomy has been shown to reduce the risks of both breast and ovarian cancer by 50% and 95%, respectively, in women with *BRCA1* or *BRCA2* mutation. If prophylactic oophorectomy is performed by age 40, breast cancer risk can be also reduced by 56% and 43%, for *BRCA1* and *BRCA2* carriers, respectively (32). Once again, our rates of risk reducing prophylactic salpingo-oophorectomy of 57.14% is consistent with the literature.

Surveillance with MRI alternating with mammography is a recommended option in *BRCA1/2* carriers (33-35). In our cohort of patients, more than 80% with either mutation did undergo screening mammography, but only 25%–31% underwent screening MRI. This is likely due to suboptimal counseling and limited resources.

Genetic counseling together with appropriate surveillance and interventions for patients with *BRCA* mutations are recommended because of the known benefits from surveillance, chemoprevention and breast/ovarian risk reducing surgery. Availability of professional genetic counseling is variable and it is generally lacking in most LMICs (36-39), and even in many high income countries (HICs) (10, 12).

Although the National Comprehensive Cancer Network, US Preventive Services Task Force, and American College of Obstetricians and Gynecologists issued specific guidelines for genetic counseling referral, based on personal and family history including screening for hereditary breast and ovarian cancers, women meeting the criteria for genetic counseling and screening are often not referred (12). In the United States only 50% of those identified as high risk for carrying a genetic mutation are offered genetic counseling, highlighting the underuse of this type of recommended health care (10). The few published studies show that physicians have a positive attitude towards genetic counseling but lack sufficient knowledge to counsel adequately (13). In Lebanon, as in many other countries, and especially in LMIC, there is a lack of genetic counselors and there are no national guidelines for genetic screening. In addition, genetic counseling is not generally covered by health insurance companies.

Genetic counseling was documented in only about one third of our cohort of patients, and it was mostly done by the patients' own oncologists because of lack of professional counselors and high-risk breast clinics in the country. The 2015 American Society of Clinical Oncology (ASCO) Policy Statement on Genetic and Genomic Testing for Cancer Susceptibility included quality assurance, informed consent, patient privacy, protection from genetic discrimination, public and provider education, and efforts to identify and reduce disparities in access to clinical genetics services (40). These recommendations are based on studies in countries with robust health systems (41). Genetic counseling should be an integral part of these recommendation, not only for LMICs but also in HICs. In HICs, this is because of the now widely available access to genetic testing when there is a requirement for safe and appropriate counseling concerning prognostic and therapeutic information which is not always available from genetic testing service providers (42, 43).

As for patients with VUS mutations, most of our cohort underwent screening mammography (78.9%), but only 31% had screening MRI. This also reflects both suboptimal counseling and limited resources. As for risk reducing surgery, only one patient had CPM and two had RRSO. This is in line with literature and guidelines, as CPM and

RRSO are not recommended (14, 40, 44) unless the patient has a very strong family history and desires to have CPM and/or RRSO.

Follow up of high-risk patients and mutation-carriers is best done at specialized centers and clinics (45). However, in most parts of the world the majority of patients and carriers are followed by their private oncologists, with the exception of patients attending major cancer centers. Genetic counseling is included in the The European Society for Medical Oncology (ESMO)/ASCO Global Curriculum for training of medical oncologists (45). This issue needs a stepwise implementation. Coordination of care between referral cancer centers and general hospitals and general oncologists would help resolve this unmet need and improve surveillance and risk reducing surgeries (12). Professional genetic counselors are urgently needed in most LMICs and worldwide. Education and awareness of oncologists remains important as most patients are followed up by their primary oncologists. The widespread implementation of telemedicine during the coronavirus disease-2019 (COVID-19) era can be used to help *BRCA* carriers and the high-risk population for breast cancer as online consultations with genetic counselors may become more accessible for patients everywhere including both HICs and LMICs.

In conclusion, in this cohort of women living in the Lebanon, the majority of patients with *BRCA1/2* mutations underwent screening mammography but only a minority had breast screening MRI, despite recommendations. Genetic counseling for both the patients and their families was mostly given by medical oncologists. The requirement for optimal screening and genetic counseling is still not met in this cohort. We therefore believe that there remains a need for greater provision of professional genetic counselors and high-risk breast clinics, not only in our own country but also in other LMICs, and even among HICs, globally.

Ethics Committee Approval: This study approved by the Institutional Review Board (IRB) of the American University of Beirut Medical Center (IRB ID: IM.NS.06, date: 17.11.2016 and 29.06.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.S.E.S.; Design: N.S.E.S.; Data Collection and/or Processing: H.A.M., A.A.M., R.W.A., F.K., L.E.K., R.S., S.D., I.A.D., N.S.E.S.; Writing: H.A.M., A.A.M., R.W.A., F.K., L.E.K., R.S., S.D., I.A.D., N.S.E.S.; Critical Review: H.A.M., A.A.M., R.W.A., F.K., L.E.K., R.S., S.D., I.A.D., N.S.E.S.

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

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Original Article

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PD-1 and PD-L1 Expression in Indian Women with Breast Cancer

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ABSTRACT

Objective: The interaction between programmed cell death protein 1 (PD-1) on activated T-lymphocytes and programmed death-ligand 1 (PD-L1) on tumor cells or antigen-presenting cells sends immunosuppressive signals leading to the escape of tumor cells from the host anti-tumor immune response. Inhibiting this interaction with antibodies against PD-1 or PD-L1 is emerging as a valuable therapeutic strategy. However, tissue distribution patterns for PD-L1 and PD-1 in breast cancer patients from India are not reported, yet many clinical trials are underway. In this study the expression of PD-1 and PD-L1 in breast cancer patient samples from India was characterized.

Materials and Methods: The study included 392 cases of operated breast cancer (2012–2017) from a tertiary cancer care center in Bangalore, Karnataka, India. Paraffin blocks were retrievable and receptor status was known. Immunohistochemistry (IHC) was performed using anti-PD-L1 and anti-PD-1 antibodies. RNA was isolated from 76 fresh tumors and nine adjacent normal tissues (2019). PD-L1 transcript levels were measured by RT-qPCR using *Hypoxanthine-guanine phosphoribosyl transferase (HPRT)* as a reference gene.

Results: Based on IHC, PD-1 expression within tumor-infiltrating immune cells (TIICs) was observed in 55/385 cases (14%) across all breast cancer types. In triple-negative breast cancer (TNBC), 21/132 cases (16%) showed PD-1 staining in TIICs. The overall expression of PD-L1 in breast tumor cells across all breast cancer subtypes and TIICs was 11% (41/378) and 39% (151/385), respectively. A relatively higher proportion of TNBC cases had PD-L1 expression in tumor cells (17/132 cases, 13%) and immune cells (68/132 cases, 52%). We also detected PD-L1 transcript expression by qRT-PCR in freshly isolated tumor samples.

Conclusion: These findings show that around 52% (68/132) of the TNBC cases express PD-L1 in TIICs. Hence, anti-PD-1/PD-L1 therapy alone or combined with chemotherapy may be a promising treatment for TNBC in Indian patients.

Keywords: Triple-negative breast cancer, programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), immunohistochemistry

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Key Points

- PD-1 and PD-L1 expression was studied for the first time in breast cancer patient samples from India.
- 33% of the breast cancer cases were triple negative breast cancer (TNBC).
- 64% of the TNBC cases showed immune response.
- About 13% of the TNBC cases had tumor cells expressing PD-L1.
- Around 52% of TNBC cases had tumor infiltrating immune cells expressing PD-L1.

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Introduction

Breast cancer is the leading cause of death due to cancer among women in the world (1). In India, 14% of the cancer incidence and 11% of cancer mortalities are due to breast cancer (1). Breast cancer is classified into six subtypes, based on gene expression microarray analysis, known as intrinsic subtype classification. The six subtypes are luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), basal-like, normal-like and Claudin-low breast cancer (2). The St. Gallen expert consensus on the primary therapy of breast cancer has released a surrogate classification for breast cancer subtypes to guide adjuvant treatment decisions. These surrogates were defined to distinguish luminal A-like breast cancer from luminal B-like, HER-2/neu, and triple-negative disease, using a combination of estrogen receptor (ER), progesterone receptor (PR), Ki-67%, and HER-2/neu immunohistochemical (IHC) profiles, without a requirement for molecular diagnosis (3).

An effective immune system can identify and eliminate cancerous cells. Innate immune cells produce pro-inflammatory cytokines leading to an inflammatory response and tumor antigen presentation to adaptive immune cells, such as T-lymphocytes. Upon activation, T-lymphocytes eliminate the cancerous cells. Immune checkpoint pathways, such as the programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) axis, regulate T-lymphocyte activity to prevent the destruction of 'self' cells (4).

PD-1 is a co-inhibitory receptor expressed predominantly by cytotoxic T lymphocytes (5). PD-1 interacts with its ligands, PD-L1 and PD-L2, expressed by antigen-presenting cells. PD-L1 is generally expressed by tumor cells and macrophages, whereas PD-L2 is present mainly on dendritic cells (5, 6). On such an interaction, PD-1 signaling results in the attenuation of cytotoxic activity of T lymphocytes and promotes T-regulatory activity, leading to termination of host immune response (5, 7, 8).

Recent studies have shown that cancer cells hijack this immune suppression mechanism by expressing PD-L1 on their surface and evade the host immune response (5, 9). Inhibitors of PD-1/PD-L1 immune checkpoints have been extensively explored in several cancers. The Food and Drug Administration (FDA) has approved anti-PD-1 and anti-PD-L1 immunotherapies for treating nine cancers, including melanoma, head and neck squamous cell carcinoma, urothelial and non-small cell lung carcinoma, among others (10).

Triple negative breast cancers (TNBCs) are more common in younger, premenopausal Indian women and are aggressive, with higher recurrence rates (11). Recent studies of gene expression of the breast cancer stroma have shown increased tumor-infiltrating immune cells and lymphocytic activity, especially in TNBCs (12). Based on the IMpassion130 clinical trial (NCT02425891), the FDA recently granted accelerated approval for Atezolizumab, a monoclonal antibody targeting PD-L1, plus chemotherapy (Abraxane; nabÒ-Paclitaxel) for the treatment of PD-L1-positive, unresectable, locally advanced, or metastatic TNBC (13).

Breast cancer was thought to be less immunogenic when compared to melanoma or non-small cell lung carcinoma. Some studies on PD-1 and PD-L1 levels in breast cancer across the world have reported contradicting correlations between PD-L1 expression and prognosis (14, 15). Furthermore, there is no data on PD-1 and PD-L1 expression in Indian breast cancer patients. The aim of this study was to evaluate the usefulness of anti-PD-L1 immunotherapy in Indian breast cancer patients by elucidating the expression patterns of PD-1 and PD-L1 in tumor and tumor-infiltrating immune cells in breast cancer patients in a regional cancer center in South India.

In clinical practice, immunohistochemistry (IHC) is used to evaluate PD-L1 expression in tumor cells and tumor-infiltrating immune cells (TIICs). In this study an IHC-based assessment of PD-1 and PD-L1 expression in a large-scale evaluation of a breast cancer patient cohort of Indian origin was performed. IHC staining depends on the affinity and avidity of the antibody used and the methodology. Hence, there is no universal cut-off to determine grade positivity (16). There is also inter- and intra-observer variation in the pathological scoring of cells by IHC. Therefore, the effectiveness of PD-L1 mRNA expression by quantitative real-time polymerase chain reaction (qRT-PCR) was also evaluated.

Materials and Methods

Breast Cancer Subtype Scoring System

Hormone receptor positivity (HR+) was defined as either or both estrogen receptor (ER) positivity and progesterone receptor (PR) positivity. This was defined as a nuclear staining of any intensity of ≥1% of the tumor cells or an Allred Score of ≥3.

Human epidermal growth factor receptor 2 positivity (HER-2+) was defined as complete and strong circumferential membranous staining of >10% of tumor cells, scored 3+ with ER and PR being negative.

Triple-negative breast cancers (TNBC) were cases that were negative for all three markers: ER, PR and HER-2.

Reagents Used for IHC and qRT-PCR

Rabbit monoclonal PD-L1 antibody (ACI 3137C) and mouse monoclonal PD-1 antibody (ACI 3162C) were procured from Biocare (Biocare Inc., Concord, CA, USA) and used for IHC at a dilution of 1:150 and 1:80, respectively. PD-L1 and hypoxanthine-guanine phosphoribosyl transferase (HPRT; Control) primers were designed in-house. Primer sequences are as follows: PD-L1 (forward) – 5'-GGCATTTGCTGAACGCAT-3', PD-L1 (reverse) – 5- CAATTAGTGCAGCCAGGT-3', HPRT (forward) – 5'-TGCTCGAGATGTGATGAAGG-3' and HPRT (reverse) – 5'- TCCCCTGTTGACTGGTCATT-3'. RNAlater® (R0901) and TRIzol® (T9424) were procured from Sigma Aldrich (Sigma Aldrich, St Louis, MO, USA). The reverse transcription kit (4368814) was obtained from Applied Biosystems, ThermoFisher, SYBR® green (BIO-98050) was procured from Bioline and ROX reference dye (RR-390Q) was obtained from Takara Biosciences.

Study Population

Indian patients who had undergone modified radical mastectomy for invasive breast carcinoma between 2013 and 2017 were identified from the archives of the associated cancer hospital. Inclusion criteria were: patients with known ER/PR/HER2 status; and paraffin-embedded tissue blocks were available. Exclusion criteria were: 1) a tumor type other than invasive carcinoma; 2) use of preoperative (neoadjuvant) chemotherapy; and 3) human immunodeficiency virus (HIV) seropositivity. Each resected specimen had undergone gross and histological examination by trained surgical pathologists. Paraffin-embedded blocks of retrospective cases were collected from the pathology department of the cancer hospital. All patient data were anonymized before study inclusion.

Ethical Approvals

For prospective samples, patient consent was obtained in a written form before surgery. Both retrospective and prospective arms were approved by the Medical Ethics Committee (no: MEC/001, date: April 30, 2016). The tissue samples for RNA isolation were processed according to the Institute's human ethical clearance (IHEC) protocol of the research institute.

Immunohistochemistry Procedure

Cases of the three breast cancer subtypes (HR+, HER2+ and TNBC) from the years 2013–2017 were retrieved from the archives of the department of pathology. The hematoxylin and eosin (H&E) stained sections were reviewed, and 4 µm thick sections were cut from selected paraffin-embedded tissue blocks. The cut sections were mounted on silane-coated slides. IHC was performed using an automated immunostainer, Benchmark XT (Ventana Medical Systems, Inc., Tucson, Arizona, USA), according to the manufacturer's protocol. Sections were stained with diaminobenzidine and counterstained for the nucleus with hematoxylin for 30 seconds. Slides were then washed under slow-running tap water, air-dried, and mounted with DPX mounting agent. Bright-field images were taken using an Olympus IX71 (Olympus Corporation, Shinjuku-ku, Tokyo, Japan) inverted microscope using Image-Pro software.

Evaluation of TIICs in H&E Sections

The H&E stained sections that had been reviewed for tumor cell content earlier were semi-quantitatively examined to assess the extent of TIICs (Figures 1c–e). These were complete sections from excised specimens and did not include needle core biopsies or tissue microarray samples, given the heterogeneity of TIICs. There was no focus on hot spots. TIICs in tumor zones with crush artifact and necrosis were excluded. TIICs included all mononuclear cells; lymphocytes, macrophages and plasma cells. Granulocytes were excluded.

Only those TIICs within the borders of the invasive tumor were counted. Both intratumoral (immune cells in direct cell-to-cell contact with carcinoma cells with no intervening stroma) and stromal TIICs (immune cells dispersed in the stroma between the carcinoma cells and not directly in contact with carcinoma cells) were counted. Semi-quantitative counting was done by an experienced pathologist. The percentage of TIICs was calculated as the area occupied by TIICs over the total intratumoral stromal area. These values were categorized into percentages: 0%, 1%–10%, 11%–50% and >50%.

Assessment of PD-L1 and PD-1 immunostained sections

After immunostaining, the sections were semi-quantitatively examined for positivity, as described below. The pathologist was blinded to the ER/PR/HER2 status of the cases when scoring.

Tumor cells were labeled positive for PD-L1 if staining at 200x magnification was present in greater than or equal to one percent of tumor cells (≥1%), with partial or complete membrane staining, of any intensity. This method of scoring took into account the general definition of PD-L1-positive (PD-L1+) tumor cells (17). PD-L1

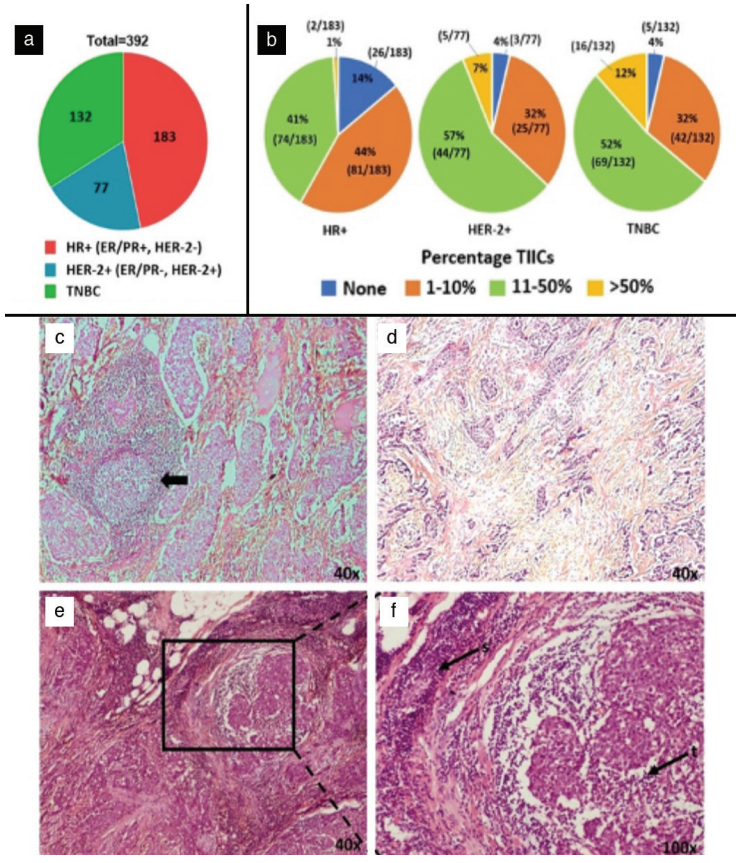

Figure 1. a) Pie chart showing the number of retrospective cases (n = 392) among various subtypes of breast cancer. **b**) Pie charts showing tumor infiltrating immune cells (TIICs) across various breast cancer subtypes. The number of immune cells per field in tumor sections was divided into four categories: 0% cells, 1%–10% cells (mild), 11%–50% cells (moderate), >50% cells (dense). **c)** TIICs as lymphoid follicles (arrow) with germinal centers. Representative images for **d)** mild TIICs (1%–10%), **e)** dense TIICs (>50%). **f)** Magnified image of e. Immune cells infiltrating tumor (t) and stroma (s)

positive tumor cells are those tumor cells that show partial or complete membranous staining for PD-L1 of any intensity. In practice, this would mean staining of ≥1% tumor cells. The magnification of 200x was chosen to assess PD-L1 staining in tumor cells and TIICs, as described by Salgado et al. (18), who assessed tumor-infiltrating lymphocytes (TILs) at the same magnification. Percentage categories were again defined as 0%, <5%, 5%–50%, >50%, although this was later modified to <10% and ≥10%. The Tumor Proportion Score (TPS) was given using the following formula:

TPS = (Number of PD-L1 stained tumor cells/Total number of non-necrotic tumor cells) x 100

TIICs were scored positive for PD-L1 if staining at 200x magnification was present in ≥1% of immune cells, either nuclear or cytoplasmic or both, of any intensity. Percentage categories were again defined: 0%, <5%, 5%–10%, 11%–50%, >50%. The Mononuclear Immune Density Score (MIDS) was calculated using the following equation:

MIDS = (Number of PD-L1 positive immune cells/Total number of non-necrotic tumor cells) x 100

Similarly, TIICs were scored positive for PD-1 if staining at 200x magnification was present in ≥1% of immune cells, either membranous or cytoplasmic or both, of any intensity. The formula for MIDS was again used to calculate results, substituting the count of PD-1 cells for the count of PD-L1 cells used in the formula described above.

Sample Collection and RNA Isolation

Excision specimens were received in the Histopathology laboratory. Regions of the tumor were identified by the pathologist and at least 100 mg samples were taken from the tumor and adjacent grossly normal tissue at least 4 cm away from the tumor. Tissue samples were washed in 1x phosphate-buffered saline containing 1% penicillin and 1% streptomycin to remove surface contaminants and blood. The washed tissue was cut to approximately 1 x 1 x 0.2 cm^3 and was transferred to a sterile 15 mL tube containing RNALater® (Sigma Aldrich, St Louis, MO, USA) and allowed to stand at room temperature overnight. The tubes with samples were then stored frozen at -20 °C until analysis.

Tissue samples were retrieved, thawed on ice, washed with Milli-Q water, and put in a 1.5 mL tube containing TRIzol® reagent (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA). The tissue was homogenized using a handheld homogenizer and RNA was isolated according to TRIzol® reagent's manufacturer's protocol.

cDNA Preparation and qRT-PCR

Two µg of the isolated RNA was used for cDNA synthesis using the reverse transcription kit (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA). cDNA samples were diluted 1:10 by taking 10 µL of cDNA samples into 90 µL of nuclease-free water. For qPCR reaction, one µL of the diluted sample was mixed with one µL of 1X SYBR® Green Master mix (Bioline, Meridian Biosciences, Cincinnati, OH, USA) and 0.2 µL of ROX passive reference dye at a final concentration of 500 nM (Takara Biosciences, Shiga, Japan). Nuclease-free water was added to make up the final volume to 10 µL. Primer concentration was maintained at 10 µM for the qPCR reactions. qPCR was performed in a real-time PCR thermocycler (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) with 40 cycles of denaturation at 95 °C for 30 seconds, annealing at 60 °C for 1 minute, and extension at 72 °C for 1 minute. A final extension at 72 °C for 10 minutes was given for re-annealing of the PCR products into double-stranded DNA. To ensure complete re-annealing, the temperature was then lowered and held at 60 °C for 1 minute. A melting curve analysis was done by increasing temperature stepwise to 95 °C using 1 °C/minute steps.

PD-L1 mRNA levels in the tumor and adjacent normal tissue were evaluated by normalizing the threshold cycle number (Ct) of PD-L1 with the Ct of a housekeeping gene, HPRT. PD-L1 mRNA levels across tumor samples were analyzed by plotting patient code number versus $2^{(-\Delta Ct)}$, where ΔCt was calculated by subtracting Ct of PD-L1 from Ct of HPRT. The fold change in the PD-L1 mRNA in tumors, when compared to matched adjacent normal tissue, was estimated as $2^{(-\Delta\Delta Ct)}$, where ΔΔCt was calculated by subtracting ΔCt of tumor from ΔCt of adjacent normal tissue.

Results

High Triple-Negative Breast Cancer Cases in India

A total of 392 cases were retrieved from the archives of the department of pathology. The distribution of cases based on ER, PR and HER2 status is given in Figure 1a. The majority (48%) of cases were HR+, 19% was HER2+ and 33% was TNBCs (Table 1). Studies from different parts of India have shown a similar trend. One study with a cohort of 5,436 patients had shown a similar trend with 48% HR+, 15% HER2+ and 37% TNBC (19). Another study (n = 123) from a North-Eastern state of India showed a trend of 40.6% HR+, 17.9% HER2+ and 38.2% TNBC while another study (n = 2,062) from the Western part of the country reported 44.6% HR+, 11.1% HER2+ and 26% TNBC (20). Thus, Indian women have a higher proportion of TNBC, whereas TNBCs are less prevalent in European (around 9%) and non-African American females (16%) (21, 22). This is consistent with a study published in 2014 comparing the incidence of breast cancer subtypes among Indian, Hispanic, African-American, Chinese and Non-Hispanic women and it showed that Indian women had a higher incidence of TNBCs than any other race, and it was significantly higher in younger women (23). In this study, all cohorts were divided into two groups, namely a younger group (age <40) and an older group (age >40). The early onset of breast cancer was studied in the younger group. In this group, stage 2 and stage 3 cancers were observed to be highest in the Indian cohort (88%), followed by African American (66%), Chinese (62%), Hispanic (60%), and Non-Hispanic women (36%).

TNBCs and HER2+ Cases Showed the Highest Immune Response

TIICs were counted and categorized by a pathologist. Greater than 10% of stromal TIICs was considered to represent immune responsiveness. Figure 1b and Table 2 show the distribution of cases based on TIICs and breast cancer subtypes. Representative images showing varying densities of TIICs are seen in Figures 1c-f. 85/132 (64.4%) TNBC cases had more than 10% TIICs, followed by 49/77 (63.6%) HER2+ cases and 76/183 (41.5%) HR+ cases (Table 2). TNBCs and HER2+ cases showed the highest immune response.

PD-1 Staining in TIICs

IHC was performed to identify the number of PD-1 positive TIICs within various breast cancer subtypes. The overall staining of tumor-infiltrating immune cells for PD-1 is shown in Table 3 and Figures 2a and 2b. Since seven sections were lost, 385 sections were reviewed. Around 14% of all cases (55/385) showed TIICs stained positively for PD-1 (Table 3), with the positivity rate in the subgroups being: TNBC

21/55 (38.2%); HER2 17/55 (31%); and HR+ 17/55 (30%). The majority (83.6%) of cases across the breast cancer subtypes (46/55) showed staining in ≤10% TIICs. None of the cases showed PD-1 staining in >50% of TIICs. When taken together, the relatively "bad" prognostic groups of TNBC and HER2 positive accounted for 69.1% of cases with PD-1 stained TIICs.

TNBCs Show Higher PD-L1 Positive Tumor Cells

IHC was performed on breast cancer sections to detect PD-L1 positivity in the tumor. Since seven sections were lost and seven more were not suitable for assessment in the tumor area, 378 sections were reviewed. Overall, across all breast cancer subtypes, 41 out of 378 samples (~11%) stained positively for PD-L1 in tumor cells (Figure 3a). IHC showed membranous staining of PD-L1 on tumor cells and varying degrees of staining were observed where some showed partial staining of the cell membrane and others showed complete staining (Figures 3C–F). The results of the overall staining of tumor cells for PD-L1 are shown in Table 4. Of the 41 cases which stained positive for PD-L1, 15 cases (36.6%) showed PD-L1 in more than 10% of cells. Seventeen out of 41 cases that were positive for PD-L1 were TNBCs (41.4%). When taken together, the relatively "bad" prognostic groups, TNBC and HER2+, accounted for (26/41) 63.4% of cases showing PD-L1 positive tumor cells. Amongst all TNBC cases, 12.9% (17 out of 132) of cases were PD-L1 positive (Table 4).

TNBCs show higher PD-L1 expressing TIICs

In the IHC performed for PD-L1 above, the PD-L1 expression in TIICs was assessed. As seven sections were lost, 385 sections were reviewed. Overall, across all breast cancer subtypes, 151/385 (39.2%) cases showed positive staining for PD-L1 in TIICs (Figure 4a). 59/151 (39.0%) positive cases showed PD-L1 staining of >10% and 92/151 (60.9%) positive cases showed staining in ≤10% cells. 68/151 (45.0%) positive cases were TNBC (Figure 4b; Table 5). In absolute numbers, 68/132 (51.5%) of TNBC cases exhibited PD-L1 positive TIICs. When taken together, the relatively "bad" prognostic groups of TNBC and HER2 + accounted for 67.6% of all cases with PD-L1 stained TIICs.

The first study on PD-L1 expression in breast cancer, comprising 44 patients from Saudi Arabia, was published in 2006. In this study, 15 of the 44 (34%) cases had PD-L1 expression in tumor cells and 18 of 44

Table 1. Distribution of estrogen receptor (ER), progesterone receptor (PR) and HER2 in the 392 cases analyzed

	Hormone receptor + (HER-2 +/-): a surrogate for luminal A & B subtypes (HR+)	HER-2 positive, HR-ve: a surrogate for HER-2 overexpressing subtype (HER-2+)	TNBC: a surrogate for basal-like subtypes (ER/PR/HER-2 -ve)	Total
Number of cases	183	77	132	392
Percentage	48%	19%	33%	100%

TNBC: Triple-negative breast cancer, HER2: Human epidermal growth factor receptor 2, HR+: Hormone receptor positivity

Table 2. Distribution of tumor-infiltrating immune cells (TIICs) in the three major breast cancer subtypes

TIICs %	HR+, HER2+/-	HER2+, HR-	TNBC
0%	26	03	05
1%–10%	81	25	42
11%–50%	74	44	69
>50%	02	05	16
Total	183	77	132

p-value <0.0001, chi-squared test, chi-square value = 35.96, degrees of freedom = 6.
HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, HR+: Hormone receptor positivity

Table 3. Percentage of tumor-infiltrating immune cells (TIICs) staining for PD-1

Percentage of TIICs stained for PD-1/100 viable tumor cells	HR+, HER2+/-	HER2+ HR-	TNBC
1%–4%	6	5	10
5%–10%	11	9	5
11%–50%	0	3	6
>50	0	0	0
Total = 55/385 (14.3%)	17/55 (30.9%)	17/55 (30.9%)	21/55 (38.18%)

p-value >0.05, chi-squared tests are not valid for contingency tables with values of 0, hence 5%–10%, 11%–50% and >50% were merged for statistical analysis, chi-squared value = 1.406, degrees of freedom = 2.
HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, HR+: Hormone receptor positivity

(41%) had tumor-infiltrating lymphocytes (TILs) expressing PD-L1 (24). A study with 650 cases from Switzerland had shown a higher PD-L1 expression in tumor cells (23.4% of the cases) and a small subset of cases (9.2%) showed PD-L1 positive TILs (14). A large retrospective study involving 5,763 patients from METABRIC genomic study, SEARCH observational study and NEAT randomized controlled trial from the United Kingdom showed that TIICs expressed PD-L1 in only 6% of the cases and by tumor cells in 1.7% cases. 19% of TNBCs had PD-L1 positive immune cells in their study (25). In contrast, our study showed 11% of the cases expressing PD-L1 in tumor cells and 39% of the cases expressing PD-L1 in TIICs, which is relatively higher. We also observed as high as 51.5% of TNBCs with PD-L1 positive TIICs.

Discussion and Conclusion

RT-qPCR for Detecting PD-L1 Expression

We undertook a pilot study to assess if qPCR can be used to detect PD-L1 transcript expression. Fresh tissue samples (76) were collected and quantitative PCR was conducted successfully for 29 samples. The PD-L1 expression levels determined by RT-qPCR were scored based on ΔCt values. RT-qPCR could detect PD-L1 transcripts in all 29 samples. The data showed that PD-L1 has a heterogeneous expression (Figure 5a). Fifteen samples showed lower expression relative to the housekeeping gene HPRT, while 14 samples showed higher expression than HPRT. Of the 29 tumor samples, for nine samples, we additionally procured adjacent normal samples. When compared to adjacent normal tissues, 6/9 tumors had higher expression of PD-L1 and 3/9 had lower expression of PD-L1 compared to respective adjacent normal tissue (Figure 5b). Thus, RT-qPCR could detect the mRNA of PD-L1. However, use of qPCR for diagnostic purposes should be assessed further in experiments with larger sample size and should also be correlated with the pathologist's IHC scoring.

Limitations of the Study

Research-use antibodies were used instead of IVD clones, as the latter are expensive and were not supported by the funding agency. Further, the intention of this study was to check only the expression of PD-L1 protein and not for any therapeutic intervention. Comparison of PCR with IHC could not be made because of the limited number of good quality RNA samples from resected tumors owing to technical/procedural issues.

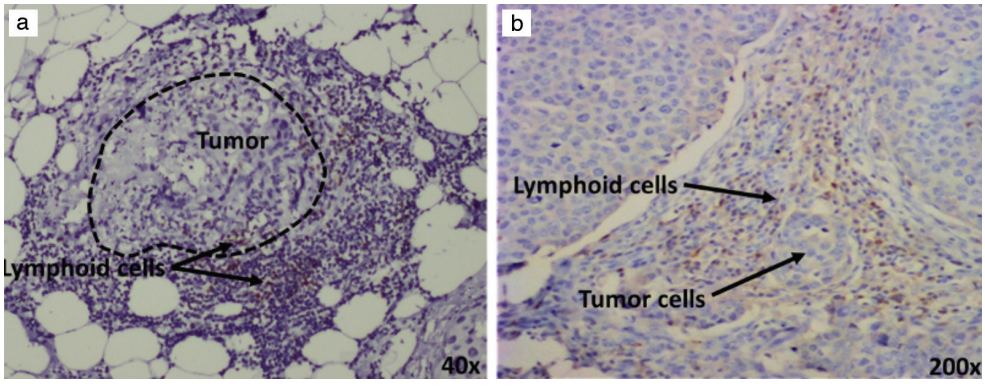

Figure 2. a) Lymphoid cells with PD-1 around a focus of tumor cells. **b)** PD-1 positive immune cells around unstained tumor cells

PD-1: Programmed cell death protein 1

Table 4. Percentage of tumor cells showing PD-L1 positivity in breast cancer subtypes

Percentage of tumour cells stained/100 viable tumour cells	HR+, HER2+/-	HER2+, HR-	TNBC
1%–9%	9	7	10
10% and above	6	2	7
Total = 41/378 (10.85%)	15/41 (36.6%)	9/41 (21.9%)	17/41 (41.46%)

p-value >0.05, chi-squared test, chi-square value = 1.03, degrees of freedom = 2.
HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, HR+: Hormone receptor positivity

Table 5. Staining of TIICs for PD-L1

Percentage of TIICs stained/100 viable tumor cells	HR+, HER-2+/-	HER-2+, HR-	TNBC
1%–10%	34	24	34
>10%	15	10	34
Total = 151/385 (39.2%)	49/151 (32.5%)	34/151 (22.5%)	68/151 (45%)

p-value >0.05, statistically not significant, chi-squared tests are not valid for contingency tables with values of 0, hence 11%–50% and >50% were merged for statistical analysis, chi-squared value = 7.475, degrees of freedom = 4.
HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, HR+: Hormone receptor positivity

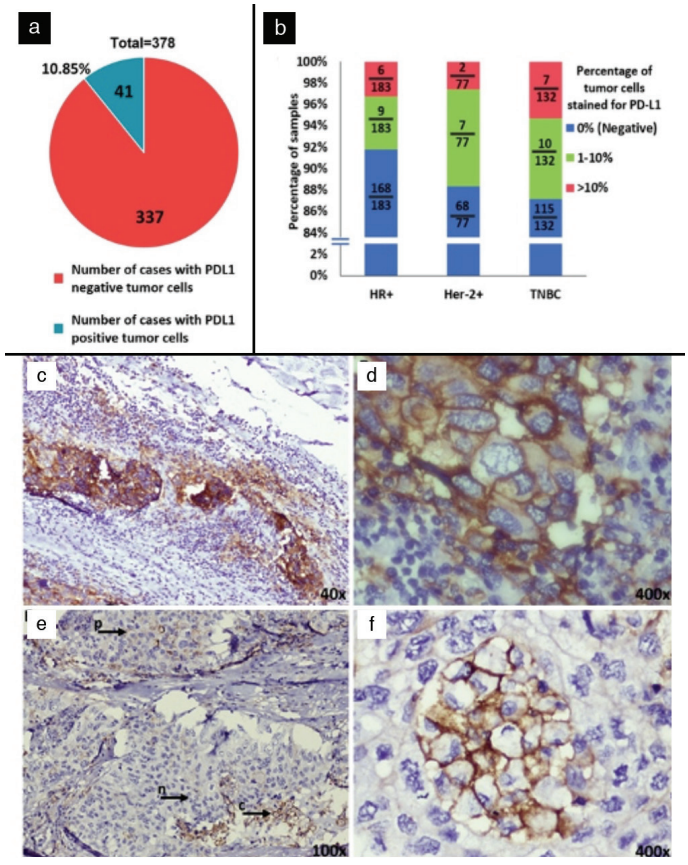

Figure 3. a) Pie chart representing breast cancer cases (n = 378, after eliminating 14 cases in which IHC failed) with tumor cells expressing PD-L1 (41/378). **b)** Stacked column graph depicting he percentage of cases expressing PD-L1 on tumor cells. Representative image of immunohistochemistry (IHC) of PD-L1 **c)** with dense staining on tumor cells. **d)** with strong membranous staining of PD-L1 **e)** arrows indicate tumor cells with nil (n), partial (p) and complete (c) membranous staining in the same field of view. **f)** PD-L1 expression observed in tumor cells and not the adjacent lymphoid cells.

PD-L1: Programmed cell death ligand 1

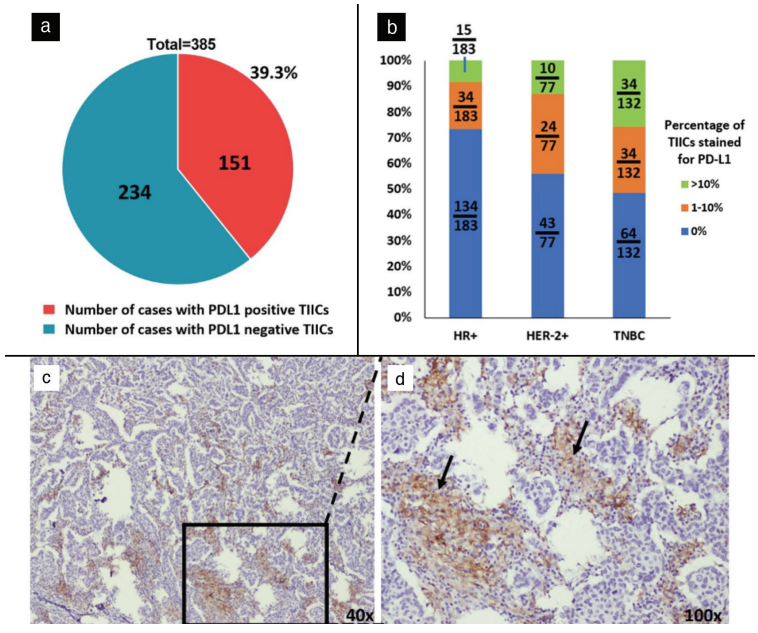

Figure 4. a) Pie chart representing breast cancer cases (n = 385, after eliminating seven cases in which IHC failed) which had tumor infiltrating immune cells (TIICs) expressing PD-L1 (151/385). **b)** Column graph depicting the distribution of cases with TIICs stained for PD-L1 (categorized by breast cancer subtypes). **c)** Lymphoid cells with PD-L1 around tumor cells. **d)** Magnified image of c showing the infiltration of PD-L1 positive immune cells.

IHC: Immunohistochemistry, PD-L1: Programmed cell death ligand 1

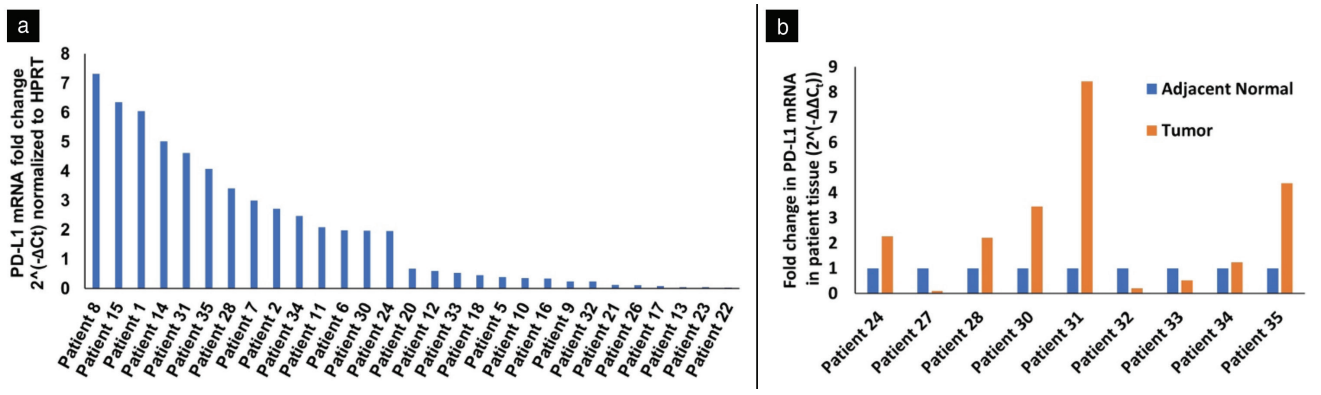

Figure 5. a) PD-L1 mRNA expression normalized to HPRT in 33 tumor tissue samples. Seventeen of the samples showed PD-L1 mRNA levels lower than HPRT while 16 of them showed higher than HPRT **b)** PD-L1 mRNA expression in tumor and adjacent normal tissue from nine patients.

HPRT: Hypoxanthine-guanine phosphoribosyl transferase, PD-L1: Programmed cell death ligand 1

In conclusion, we had quantified the PD-L1 levels in breast cancer for the first time in an Indian cohort. Around 92% of cases had TIICs and about 39% of cases showed PD-L1 staining in TIICs. Further, 52% (68/132) of TNBC cases had PD-L1-expressing TIICs. Although breast cancers are immunogenic, this immune response may be suppressed by the PD-L1 expressing TIICs. This has opened an opportunity to explore anti-PD-L1 therapy to treat the most aggressive TNBCs in the Indian population.

PD-L1 is regulated mainly by interferon I and II pathways. Interferons signal through multiple pathways via JAK-STAT transcription factors to up-regulate the expression of PD-L1. Signals from the ERK pathway converge on STAT1, while signals from PI3K/Akt pathway converge on STAT3 and induce PD-L1 expression (26). Recent studies have shown AMP-activated protein kinase (AMPK) to phosphorylate PD-L1 at S195, which leads to abnormal glycosylation leading to degradation of PD-L1 (27). Interestingly, we observed that AMPK inhibition with pharmacological inhibitor Compound C led to an increase in PD-L1 expression in the MDA-MB-231 (TNBC) cell line while reduced PD-L1 expression in MCF7 (HR+) (Supplementary Figure 1). AMPK activators, such as the anti-diabetic drug metformin, and inhibitors can be used as an immunomodulator. Our lab is currently investigating the role of AMPK in the regulation of PD-L1 in various stages of cancer. Understanding the molecular mechanisms involved in the PD-1/PD-L1 axis is likely to unveil other pharmacological targets in the future.

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Ethics Committee Approval: This study was approved by the Medical Ethics Committee (No: MEC/001, date: April 30, 2016).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: A.R., R.V.K.; Design: A.R., R.V.K.; Supervision: S.M.N., S.M.C.B., A.R., R.V.K.; Data Analysis and/or Interpretation: K.R.B., R.V.K.; Data Acquisition: K.D., Statistical Analysis: K.R.B.; Literature Search: K.R.B.; Manuscript Review: S.M.N., R.C., S.M.C.B., A.R., R.V.K.; Writing: K.R.B., K.D., S.M.N., R.C., S.M.C.B., A.R., R.V.K.

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

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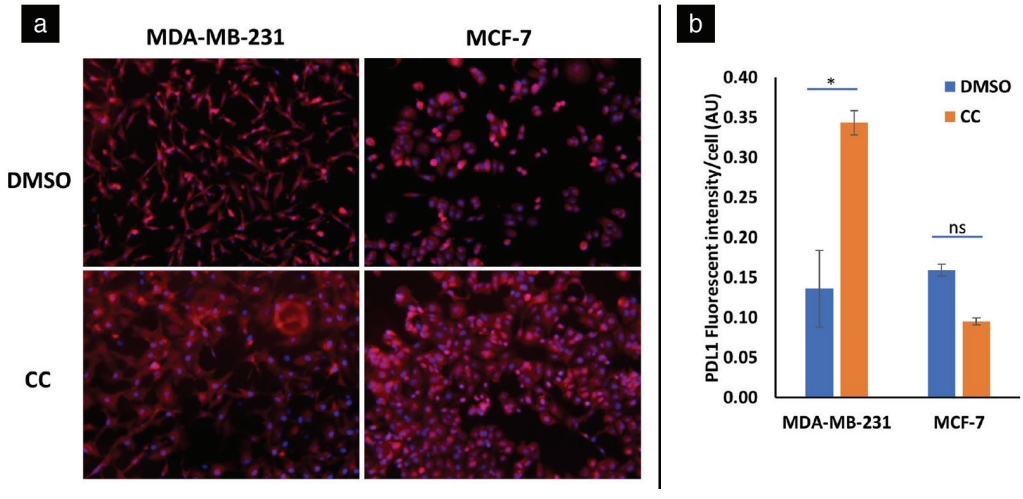
Supplementary data



Supplementary Figure 1. a) Immunocytochemistry showing PD-L1 expression in MDA-MB-231 and MCF7 cell lines. DMSO – vehicle control, CC – Compound C – a pharmacological inhibitor of AMPK. **b)** Quantification of PD-L1 fluorescence intensity in immunocytochemistry. MDA-MB-231 showed increased PD-L1 expression on CC treatment while MCF7 showed reduced PD-L1 expression on CC treatment, AU – arbitrary units, mean fluorescence intensity was calculated from at least 100 cells, n=4, *p-value <0.05

PD-1: Programmed cell death protein 1, DMSO: Dimethylsulfoxide, CC: Compound, ns: Not significant

Original Article

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Neuroendocrine Tumors of the Breast: Single-Center Experience

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ABSTRACT

Objective: Breast carcinomas with neuroendocrine (NE) differentiation are extremely rare. The aim was to discuss breast cancer cases with NE differentiation in the light of World Health Organization 2019 classification and literature information.

Material and Methods: The pathology records of 56 cases diagnosed as neuroendocrine tumor (NET) and/or breast cancers with NE differentiation presenting to a single center between January 2010 and June 2020 were evaluated. The patients were evaluated in terms of age, tumor size, location, histological grade, hormone profiles (ER, PR, HER2), guideline American Joint Committee on Cancer, lymph node status, stage, metastases, progression, survival, radiological features, surgery type and therapy modality.

Results: The age of the patients ranged from 34 to 81 years. Average tumor size was 2.3 cm. Median (range) follow up time was 31.5 (1–73 month). Metastatic lymph nodes were found in 20 cases. In our series, NE differentiation mostly accompanied invasive carcinoma of no special type, less frequently solid papillary carcinoma, and mucinous carcinoma.

Four patients had a history of neoadjuvant chemotherapy. Response to treatment was very poor in all four cases. Synaptophysin and chromogranin were positive in 38 cases. No correlation was found among tumor size, grade, age, lymph node status, and presence of distant metastasis in our series.

Conclusion: Clinical features and morphology may not help to distinguish NET from other subtypes of breast cancer. Therefore, the morphologic findings of a nested or trabecular architecture, nuclear or cytoplasmic features of NE differentiation, mucin production, or solid papillary growth pattern should prompt a pathologist to order NE markers.

Keywords: Neuroendocrine, breast, solid papillary, mucinous

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Key Points

- NE markers should be added when morphologically suspected or in SPC and MC cases to determine the actual rate of NE tumors of the breast.
- As these tumors are rare; diagnosis requires exclusion of metastasis from an extra-mammary site.

Introduction

Primary breast carcinoma with neuroendocrine (NE) features is a rare subtype of breast cancer. NE differentiation in breast carcinomas was first described by Feyrter and Hartmann in 1963 (1-5). In 1977, Cubilla and Woodruff (6) published the first case series and coined the term "primary carcinoid of the breast" (1-3, 6). Sapino et al. (7) in 2001 proposed the first diagnostic criteria for neuroendocrine tumors (NETs) of the breast, suggesting that tumors with more than 50% of the expression of NE markers, specifically synaptophysin (SNP) and chromogranin, should be classified as primary NE breast carcinomas (1, 7, 8). In 2003, the World Health Organization (WHO) divided neuroendocrine carcinomas (NECs) into solid, small cell, and large-cell NECs (1, 2, 9). The term "NEC of the breast" was revised to "carcinomas with NE features" in the 2012 WHO Classification of Tumours of the Breast (10). In 2012, the WHO classification was revised, and minimum percentage of cells exhibiting positive immunostaining for NE markers was removed (2-4, 10). Carcinomas with NE features are subclassified into three groups: well-differentiated NET, poorly differentiated NEC/small-cell carcinoma, and invasive breast carcinoma with NE differentiation (1, 2, 10).

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According to the 2019 WHO classification, most NE neoplasms of the breast presumably represent mixed NETs, with most cases showing a component of classic-type mammary carcinoma. Similarly, the majority of primary small-cell NEC (SCNEC) of the breast show a component of classic-type mammary carcinoma. Therefore, if SCNEC makes up 10%–90% of the tumour area, the terminology of mixed invasive carcinoma (NST or other special type) and SCNEC may be used, and the NEC percentage should be reported. Cancers with <10% NET pattern should be classified as invasive carcinoma-non-spesific type (IC-NST) or other types, with an option to describe the focal specialized NE pattern in the report comment. Cancers with >90% NE neoplasm pattern should be classified as NET or NEC (11).

NETs in other sites, such as the lungs and gastrointestinal tract, could easily be recognised by their classical growth patterns (solid, alveolar, ribbons, cords, nested and rosette formation) and cytonuclear features (salt and pepper chromatin distrubition) (2). NET/well-differentiated subgroup and the poorly differentiated/small-cell carcinoma are easy to distinguish because they exhibit NE features. Invasive breast carcinoma eith NE differentiation is usually overlooked because they lack the typical morphological features of NE tumors. Recognation of this group by pathologists would help determine the actual frequency of this tumor and its effect on prognosis.

As well as primary NETs of the breast, metastatic NE tumors have also been reported. Clinical and radiological examinations are essential to differentiate a primary invasive breast carcinoma with NE features from a metastatic NE carcinoma. The presence of ductal carcinoma *in situ* (DCIS) components and extensive positive immunstaining for estrogen receptor/progesterone receptor (ER/PR) within the tumor suggest the primary origin to be the breast (4, 10, 12).

The most common form of NE breast tumor-solid papillary carcinoma (SPC) and mucinous carcinoma (MC) is a suitable example of diagnostic and conceptual challenges with NET (8, 13, 14). However, SPC is a distinctive clinico-pathological entity that often expresses NE markers.

The prognostic relevance of the NE differentiation of breast tumors is still debated. The present study aimed to evaluate breast carcinomas showing NE differentiation in terms of histopathological features, hormone receptor status, radiological features, and treatment modalities.

Material and Methods

The pathology archive of our hospital between January 2010 and June 2020 were evaluated and found cases diagnosed as NETs and/or breast cancers with NE differentiation were identified. Clinical follow-up was obtained from the electronic data system and record archive of our center. A 10-year electronic data search was performed with the laboratory information system using the keywords "breast" and "neuroendocrine tumor/NE differentiation" for diagnosis. In addition, MC cases without NE differentiation were compored with MC cases showing NE differentiation. SNP, chromogranin, ER, PR, human epidermal growth factor receptor 2 (HER2), and Ki-67 were studied in the cases with histopathological NETs. If NE differentiation areas were suspected in primary breast tumor, SNP and chromogranin were studied first. When both were negative, neuron-specific enolase (NSE) and CD56 were added. When one or two of them were found to be positive by 10% or more with immunohistochemistry, invasive breast carcinoma (mucinous, solid, IC-NST, lobular), showing NE differentiation was diagnosed. NET or NEC was diagnosed when 90% or more positivity was observed to accompany histological features.

For each cases; age, location, tumor size, histologic grade, the presence of associated DCIS, lymphovascular invasion, perineural invasion, microcalcification, nodal metastasis, hormone receptors, tumor type, follow-up duration and outcome (dead or alive, presence or absence of local recurrence or metastasis), and treatment modalities were also documented.

In accordance with the American Society of Clinical Oncology-College of American Pathologists (ASC0-CAP) guidelines, the tumor was defined as positive for ER and PR if positive nuclear staining was noted for ≥1% of the invasive tumor cells (15). HER2 immunhistochemical expression was scored in accordance with ASC0-CAP guidelines (16): 0, no staining or weak-moderate incomplete stainig in ≤10% of cells; 1, weak and incomplete staining in >10% of cells; 2, weak-moderate staining in >10% of cells or strong staining in less than 10% of cells; and 3, strong complete membranous staining in 10% of cells. Cases suspicious for HER2 overexpression (Score 2) underwent further fluorescence *in situ* hybridization (FISH) analysis. When the ratio of Cerb2/chromosome 17 was <2 and ≥2, it was accepted as negative and positive for gene amplification, respectively.

Statistical analysis was performed using the SPSS software, version 17.0 (IBM, Inc., Chicago, IL, USA). The normality of each continuous variable was checked by Shapiro-Wilk tests and by histograms. All numerical data were expressed as median values (minimum-maximum) or as proportions. The Kaplan-Meier method was used for the survival analysis.

Ethics committee approval was obtained from Başkent University Medicine and Health Sciences Research Board (decision no: KA21/399, date: 08.10.2021).

Written consent was not obtained from the patients since the study was designed retrospectively and needed no consent.

Results

Results showed that 59 patients had undergone biopsy, including 56 primary breast NETs. Three of the 59 tumor cases were excluded because of metastases to the breast. Thus, 56 patients were included in the study (Table 1). Microcalcifications were observed in nine (16.1%) of the cases. SNP (Figure 1) was positive in 50 (89.3%), and negative in six (10.7%) cases, whereas chromogranin (Figure 2) showed positive staining in 41 (73.2%), and negative staining in 17 (30.4%) cases. SNP and chromogranin were both positive in 38 (67.9%) cases. NSE was positive in eight (14.3%) cases. The mean Ki-67 proliferation index was 14.9% (range: 2–70). Regarding the molecular subtypes of NET, 34 (78.6%) were ER +/Her2- (Luminal A), and 12 (21.4%) were ER+/HER2+ /- and Ki67 >14% (luminal B).

The mean age at diagnosis was 57.2 years, with a median of 60 years (34–81). Fifteen cases were premenopausal (age <50, 26.8%), and 41 cases were postmenopausal (age >50, 73.2%). Average tumor size was 2.3 cm (0.3–7 cm). In addition, 26 (46.4%) of the cases were located in the right breast and 30 (53.6%) were in the left breast. Multifocality was noted in six of the 56 cases (10.7%). The patients mostly presented because of a complaint of a palpable mass. In addition, 53 (96.4%) of the cases were women and 3 (5.4%) were men. Of the 56 cases, two

(3.6%) were dead, 54 (96.4%) were alive. Bilateral breast carcinoma was present in three of the cases. Morever, 10 (17.9%) patients had a family history of breast cancer. Median follow-up time was 31.5 (1–73) months. The estimated mean life expectancy of all patients was 41±18.9 months.

Twenty-one patients underwent mastectomy with sentinel lymph node biopsy (SLNB), 31 patients underwent breast conserving surgery with SLNB. Two cases were those evaluated with consultation blocks. Another two cases were diagnosed with core biopsies. Metastatic lymph nodes were observed in 20 (38.5%) of 52 cases with lymph node sampling, whereas lymph nodes were reactive in the remaining 32 cases. In terms of N staging, 32 cases were pN0 (57.2%), 15 cases were pN1 (26.8%), one case was pN2 (1.8%), four cases pN3 (7.1%) and four cases pNx. The pNx stage consisted of two consultation cases, and the two patients were diagnosed with core biopsy.

In accordance with the Modified Bloom and Richardson score, five cases were Grade 1 (8.9%), 23 cases Grade 2 (41.1%), and 28 cases Grade 3 (50%). When evaluated in terms of pT: one (1.8%) case was pT *in situ*, 21 (37.5 %) cases pT1, 26 (46.4%) cases pT2, three (5.4%) cases pT3, one (1.8%) case pT4 and four cases (7.1%) pTx. The pTx stage consisted of two consultation cases, and two patients were diagnosed with core biopsy. Our archive records contained 81 MC cases (33 pure MCs and 48 MCs with mixed carcinomas) without NE differentiation. We did not find any significant difference between these two groups in terms of pT (p=0.081), pN (p=0.118), DCIS (p=0.719), grade (p=0.595), hormone receptor positivity (p=0.414), age (p=0.022), follow-up time (p=0.043) and Ki-67 score (p=0.417).

Radiotherapy (RT) only was performed in seven (12.5%) patients and chemotherapy (CT) only was also performed in seven patients. CT and RT were performed in 28 (50%) patients. Eight (7.1%) patients received hormone therapy alone. Tamoxifen was added in the treatment of ER positive patients, and Trastuzumab in HER2 positive patients. Of the 56 patients, six (10.7%) were lost to follow-up, and the follow-up period for the remaining 50 patients ranged from 1 to 73 months (31.5). Among these 56 patients, one patient died of the disease after 24 months. The other case who was dead was a patient diagnosed by core biopsy and was not followed up. Clinico-pathological characteristics of 56 patients are summarized in Table 2.

Four (7.1%) patients had a history of neoadjuvant CT. Two of these were IC-NST with NE differentiation, and two were invasive MC with NE differentiation. Response to treatment was very poor in all four cases. Four of the patients had a second primary carcinoma accompanying breast carcinoma. Two of them were non-Hodgkin's lymphoma, one was oncocytoma and one was endometrium carcinoma.

Table 1. Original diagnosis of 56 cases showing neuroendocrine features

Diagnosis and number of cases with NE differentiation n (%)	
IC-NST	32 (57.1%)
Solid papillary carcinoma with invasion	13 (23.2%)
With invasive mucinous carcinoma	5
With IC-NST	5
Mixed IC-NST + mucinous carcinoma	3
Mucinous carcinoma	5 (8.9%)
Solid papillary carcinoma	2 (3.6%)
Mixed IC-NST + mucinous carcinoma	2 (3.6%)
Mixed IC-NST + lobular carcinoma	1 (1.8%)
IC-NST + Poorly differentiation NET	1 (1.8%)
Totally	56 (100%)

NE: Neuroendocrine; IC-NST: Invasive carcinoma-carcinoma of no special type; n: Number

Discussion and Conclusion

Primary NE carcinoma of the breast includes a heterogeneous group of tumors with different biological behavior and prognosis (3). The incidence has been reported to range from <1%–5% of breast cancers. In contrast, some authors reported NE differentiation in up to 20% of breast carcinomas (3). However, the exact incidence of this disease is difficult to assess because immunohistochemical NE markers are not routinely used in breast tumors (3, 10).

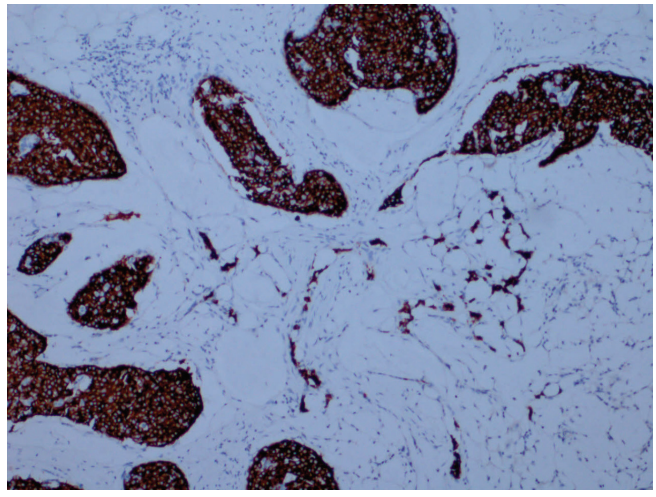

Figure 1. Immunohistochemically, SNP positivity in tumor cells (IHK ×200)

SNP: Synaptophysin; IHK: Immunohistochemistry

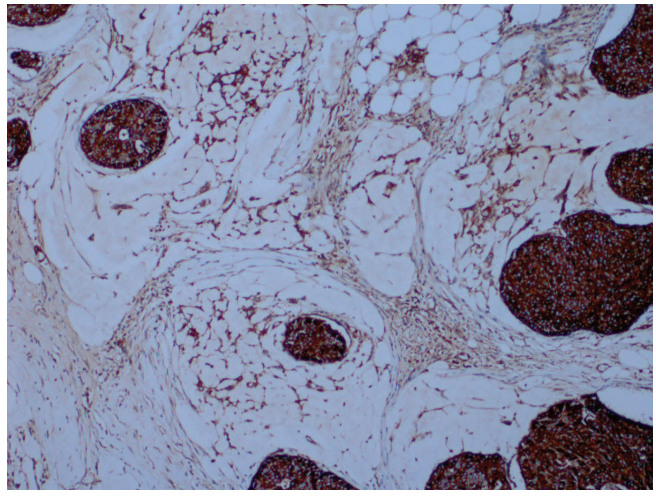

Figure 2. Immunohistochemically, chromogranin positivity in tumor cells (IHK ×200)

IHK: Immunohistochemistry

Table 2. Clinico-pathological characteristics of 56 patients

	n	(%)
Age group		
Mean age	57.2	-
Median (range) age	60 (34-81)	-
Age <50	15	26.8
Age >50	41	73.2
Tumor location		
Right	26	46.4
Left	30	53.6
DCIS		
Present	41	73.2
Absent	15	26.8
Estrogen receptor (ER)		
Positive	56	100
Negative	0	0
Progesterone receptor (PR)		
Positive	48	85.7
Negative	8	14.3
HER2/neu		
Positive	8	14.3
Negative	48	85.7
Tumor size		
Mean size	2.3 cm (0.3–7)	-
Median size	1.8 cm	-
Histologic grade		
G1	5	8.9
G2	23	41.1
G3	28	50
PN		
pN0	32	57.2
pN1	15	26.8
pN2	1	1.8
pN3	4	7.1
pNx	4	7.1
LN		
Present	5	8.9
Absent	51	91.1

Table 2. Continued

	n	(%)
pT		
pT *in situ*	1	1.8
pT1	21	37.5
pT2	26	46.4
pT3	3	5.4
pT4	1	1.8
Unknown	4	7.1
Metastasis		
Bone	2	3.6
Liver	1	1.8
No metastasis	53	94.6
LVI		
Present	39	69.6
Absent	17	30.4
PNI		
Present	21	37.5
Absent	35	62.5
Surgery		
M and SLND	21	37.5
SM and SLND	31	55.4
Unknown	4	7.1
Systemic therapy		
CT + RT	28	50
CT	7	12.5
RT	7	12.5
TMX	8	14.3
Unknown	6	10.7
Final status		
Alive	54	96.4
Dead	2	3.6

SLND: Sentinel lymph node dissection; M: Mastectomy; SM: Segmented mastectomy; CT: Chemotherapy; RT: Radiotherapy; pT: Pathologic tumor stage; pN: Pathologic nodal stage; DCIS: Ductal carcinoma *in situ*; IC-NST: Invasive carcinoma-carcinoma of no special type; TMX: Tamoxifen; LVI: Lymphovascular invasion; PNI: Perineural invasion; LN: Lobular neoplasia; n: Number

NETs of the breast occur predominantly in postmenopausal women during the sixth to seventh decade of life, although rare cases have been reported in males (1, 3). In this study, most of the cases (73.6%) were in the postmenopausal period, with a median (range) age 60 (34–81) years. This situation is similar to the literature. Three of our cases were male. The tumor size of NETs of the breast ranges from 0.8 to 13.5 cm with a mean of 2.7 cm (1, 17). Similarly, average tumor size was 2.3 cm (0.3–7 cm) in our series. Tumors may be grossly infiltrative or expansile, and those with mucin production are soft and gelatinous (1, 10). Microcalcification was identified in a small number of cases in our series (n=9, 16%) which is consistent with that reported in the literature (10% and 25%).

Two main theories exist on the histogenesis of primary NETs of the breast. The first theory is that these tumors evolve from neoplastic transformation of native NE cells. The second and more accepted theory is that NE differentiation arises from divergent differentiation of neoplastic stem cells into epithelial and endocrine cell lines during early carcinogenesis. This theory is supported by the lack of benign NETs of the breast and evidence that NE cells are clonally related to malignant epithelial cells (1, 3).

NE differentiation is frequently found in MC, particularly the hypercellular variant, and SPC (1). However, the expression of NE markers is not unique to MC of the breast (18). This phenomenon has been described in other breast carcinomas, including infiltrating lobular carcinoma, IC-NST (18). Invasive lobular carcinoma, particularly the alveolar variant, can also demonsrate NE differentiation (19). In our series, mostly IC-NST, less frequently SPC and MC were observed. These histopathological subtypes with similar frequencies were reported in previous studies (2). In our series, NE differentiation areas were found in 44 IC-NST carcinoma cases. Meanwhile 32 of these cases were pure IC-NST, and 11 had mixed breast carcinoma (five cases SPC + IC-NST, two cases MC + IC-NST, one case invasive lobular carcinoma + IC-NST, one case SPC + MC + IC –NST (Figure 3), and 1 case IC-NST + poorly differentiation / small-cell carcinoma NET).

MC is histologically characterized by nests of tumor cells floating in mucin lakes with fine fibrovascular septae (10). NE differentiation is more frequently observed with the hypercellular variant of MC, characterized by large clusters of tumor cells (1). In our series, NE differentiation was observed in 15 cases with MC. The significance of NE differentiation in MC has been controversial. Some authors reported a difference in the age and prognosis of patients, whereas others found no such difference (18). Our archive records contained 81 MC cases without NE differentiation. No significant difference was found between these MC cases and the NET/NE differentiation group in terms of classification of pT and pN rate of DCIS, grade, hormone receptor positivity, age, follow-up time and Ki-67 score.

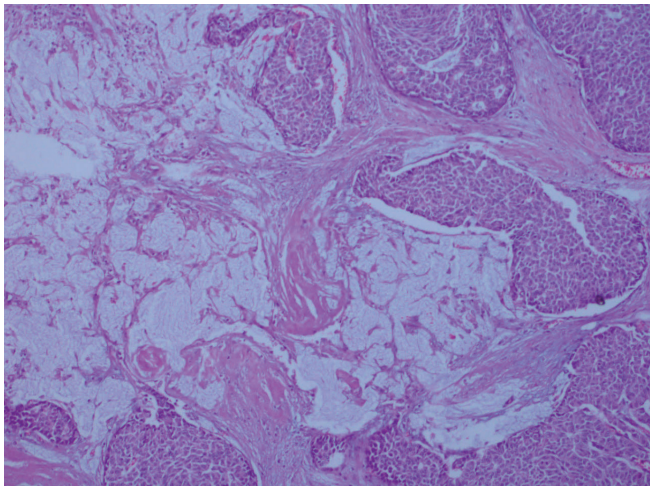

Figure 3. Mucinous carcinoma developed on the basis of solid papillary carcinoma, showing neuroendocrine differentiation (H&E ×200)

H&E: Hematoxylin and eosin stain

SPC is a rare form of breast carcinoma composed of large circumscribed nests of small monotonous polygonal to spindled cells, fine fibrovascular cores, and a round to elongated nucleus, plus finely granular eosinophilic cytoplasm (1, 13, 14). NE differentiation is present in up to 50% of cases. Our archive contained 17 cases of SPC, 15 of which had NE differentiation areas. Two of the SPC cases with NE differentiation in our series were pure SPC, and 13 cases with invasive breast carcinoma (five cases MC, five cases IC-NST, three cases IC-NST + MC) developed on an SPC backround. SPC usually arises in the seventh or eighth decade and has a better prognosis than other breast cancers (13, 14). Concordantly, the mean age of patients with SPC in our series was 62.

DCIS can also display NE differentiation, especially in solid-type DCIS. Endocrine DCIS is often of low nuclear grade, with eccentric nuclei and open chromatin (1, 20). In our series, 41 (73.2%) patients had DCIS, with the most frequent patterns being solid, cribriform, comedo, NE, and papillary. SNP was positive in 37 patients, and chromogranin was positive in 27 patients.

Although morphological features may suggest NE differentiation, the diagnosis of NET requires expression of NE markers. The most sensitive and spesific immunohistochemical markers are SNP and chromogranin A (1, 20). NSE and CD56 may show positivity but are less sensitive and specific (1). Ki-67 is a prognostic indicator of NETs (21). In our series, SNP was positive in 50 cases and negative in six cases, whereas chromogranin was positive in 41 cases and negative in 17 cases. SNP and chromogranin were positive in 38 cases. NSE was positive in eight cases.

The series reported in the literature were mostly of the ER+/Her2 - luminal A molecular subtype. (1-3, 8). Studies have shown that NETs are more likely to be ER and PR positive than IC-NST (1). Wei et al. (22) demonstrated that 95% of NETs are ER positive, 80% are PR positive and 91% are HER2 negative. In our series, all cases were ER positive, and 85% were PR positive while 14% HER2 amplified. Regarding the molecular subtypes of NETs, more than three quarters were ER +/Her2 - (Luminal A), and while a fifth were ER+/HER2+ /- and Ki-67 >14% (luminal B). Six of the Her2 positive cases were IC-NST, one was IC-NST + invasive lobular carcinoma, and the other was invasive MC.

The differential diagnosis of NET of the breast is broad and includes benign and malignant entities. The most important differential diagnosis is metastatic NET from an extramammary site, as well as lymphoma and malignant melanoma (1). Metastatic NETs account for 1%–2% of metastases to the breast. Few cases of metastatic NE carcinoma to breast were noted in the review of literature. The majority of these were from the small intestine and the pancreas (23). The distinction of primary from metastatic NET is critical to avoid

misdiagnosis and unnecessary surgical and medical therapy in the latter (1). Approximately 68% of primary NETs are associated with DCIS, which is the most convincing evidence of a primary breast tumor (1, 2). A panel of immunohistochemical stains can prove useful in distinguishing these two entities. As both primary and metastatic tumors show NE differention, neither NE markers nor ER and PR, which can also show positivity in metastasis, are useful in distinguishing the diagnosis (24). The most specific markers for a breast primary tumor are GATA3, mammaglobin, and GCDFP15, for which secondary tumors are consistently negative (2, 24). TTF1 shows positivity in approximately 70% of metastases from the lung and CDX2 shows positivity in 100% of metastases from the gastrointestinal tract (2, 24). TTF1 may be strongly positive in poorly differentiated NETs of the breast (1). Therefore, especially when ruling out lung NET metastasis, attention should be paid to hormone receptors in breast tumors, GATA3 and GCDFP15 positivity, and the presence of DCIS. Moreover, obtaining detailed past medical history of patients is important because those with known history of carcinoid tumors may present with metastatic lesions many years after their initial diagnosis.

A spesific guideline for the grading, staging, or treatment of primary NETs of the breast is lacking (10). Similar to conventional breast cancers, NETs of the breast must be staged and treated (22). Surgical management is based on tumor location and stage as with conventional breast cancers (22). Well-differentiated NET and invasive breast carcinoma with NE differentiation receive cytotoxic therapy similar to conventional breast cancer, and those with poorly differentiated NETs receive cytotoxic therapy with protocols similar to that of pulmonary small-cell carcinoma. The use of hormone therapy should be based on receptor status.

Tumor size and nodal metastases are the main prognostic factors for evaluating risk of relapse for NET of the breast, as for other types of breast cancers (3). NET of the breast can metastasize to multiple sites several years after the treatment for primary tumor. Therefore, a long-term follow-up is advisable. Metastatic sites include liver, bones, lungs, pancreas and brain (3). In our series, two cases had metastasized to the bone and one case to the liver. Although no consensus has been reached on the clinical or prognostic significance of this entity, many large studies that used updated criteria suggest poor prognosis. In our series, no statistically significant relation was observed in terms of tumor size, nodal metastasis, grade, survival, age, and prognostic terms.

Breast carcinoma with NE differentiation is a heterogeneous disease composed of many different subtypes with varying clinical characteristics. As these tumors are rare, diagnosis requires exclusion of metastasis from an extra-mammary site. Clinical features and morphology may not be helpful to distinguish NET from other subtypes of breast cancer. Therefore, the morphologic findings of a nested or trabecular architecture, nuclear or cytoplasmic features of NE differentiation, mucin production, or a solid papillary growth pattern should prompt a pathologist to order markers specific SNP and chromogranin. Similar regimens to conventional breast carcinoma are used in terms of treatment; but neoadjuvant CT response was poor in the small number of cases in our series. However, larger series are needed to predict the need for different treatment protocols or to decide on prognosis. As NE markers are not used routinely, the exact frequency of this tumor type remains unknown. Therefore, NE markers should be added when morphologically suspected, or in SPC and MC cases to determine the true rate of NE tumors of the breast.

Ethics Committee Approval: This study was approved by Başkent University Medicine and Health Sciences Research Board (decision no: KA21/399, date: 08.10.2021).

Informed Consent: Retrospective archive research.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: B.H., F.A.B.; Design: B.H.; Supervision: H.Ö.A., F.A.B.; Materials: B.H., H.Ö.A., F.A.B.; Analysis and/or Interpretation: B.H., F.A.B.; Writing: B.H., H.Ö.A.

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Original Article

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Diagnostic Value of Axillary Ultrasound, MRI, and ^{18}F-FDG-PET/CT in Determining Axillary Lymph Node Status in Breast Cancer Patients

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ABSTRACT

Objective: Knowing axillary lymph node (ALN) status before surgery affects decisions about treatment modalities. Therefore, reliable, noninvasive diagnostic methods are important for determining ALN metastases. We aimed to accurately evaluate the patient's ALN status with noninvasive imaging modalities while making treatment decisions.

Materials and Methods: Patients who received the axillary ultrasound (AUS), magnetic resonance imaging (MRI), or ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) imaging modalities and whose ALNs were confirmed histopathologically by fine needle aspiration cytology (FNAC), sentinel lymph node biopsy (SLNB), or ALN dissection (ALND) were included in the study.

Results: The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of AUS for the detection of ALN metastases were 83%, 62%, 59.2%, 54.8%, and 79.1%, respectively. For MRI they were 86.1%, 75%, 68.5%, 51.6%, and 85.3%, respectively, and for ^{18}F-FDG-PET/CT they were 78%, 53%, 56.2%, 51.4%, and 72.5%, respectively. ALNs were found to be metastatic in all patients who were reported positive in all three imaging modalities. ALN metastases were detected in 19 of 132 patients (false negativity, 14.3%) in whom AUS, MRI, and ^{18}F-FDG-PET/CT images were all reported as negative.

Conclusion: In our study, we found that the diagnostic performance of MRI was slightly better than AUS and ^{18}F-FDG-PET/CT. When we used imaging modalities together, our accuracy rate was better than when we used them alone. For accurate evaluation of axillary lymph nodes, imaging modalities should be complementary rather than competitive.

Keywords: ^{18}F-FDG-PET/CT, Axillary lymph node metastases, axillary ultrasound, diagnostic performance, MRI, Sentinel lymph node biopsy

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Key Points

- The status of the axillary lymph nodes is one of the most important prognostic factors in patients with breast cancer.
- Axillary lymph node evaluation is the crucial step for treatment decision in newly diagnosed breast cancer.
- Imaging modalities can be used to accurately determine the status of axillary lymph nodes.
- False negativity rates are the most important deficiency of imaging modalities such as axillary ultrasound, MRI, ^{18}F-FDG-PET/CT.

Introduction

Despite advances in breast cancer management, axillary lymph node (ALN) status remains the most important prognostic factor in terms of staging, treatment, prognosis, recurrence, and survival. In a 10-year follow-up, ALN metastasis at the time of diagnosis in breast cancer increased the risk of recurrence (1, 2). Until recently, axillary lymph node dissection (ALND) was standard in breast cancer patients with clinically suspected ALNs, or cytologically proven axillary metastasis following ultrasound-guided guided fine needle aspiration cytology (FNAC) at the time of diagnosis or after neoadjuvant chemotherapy (NAC) (3, 4).

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ALND gives precise information about the nodal burden, but due to the associated morbidities, particularly seroma and lymphedema, the less invasive method of sentinel lymph node biopsy (SLNB) is now standard in patients with clinically negative ALNs (3, 5). In addition, the International Breast Cancer Study Group (IBCSG) 23-01 study, which included patients with micrometastatic SLNB, found no significant difference in disease-free survival at 5-years of follow-up (5, 6). Similarly, in the American College of Surgeons Oncology Group (ACOSOG) Z0011 study in patients for whom only breast conservative surgery (BCS) and whole breast radiotherapy (RT) were performed, and ≤2 macrometastatic SLNB patients with or without ALND were compared, no significant differences were found in terms of disease-free survival during approximately 5 years of follow-up (7). In the AMAROS study, initiated by the European Organization for Research and Treatment of Cancer (EORTC), patients with clinically negative ALN, T1 or T2 stage breast cancer, and micro- or macrometastatic SLNB, no difference was found between the groups treated with ALND or axillary radiotherapy during five years of follow-up in terms of local recurrence and survival. In addition, less morbidity was found in the axillary radiotherapy group (5, 8).

However, SLNB is also invasive, and may have undesirable consequences. Therefore, the requirement for SLNB in the radiologically negative axilla in breast cancer has been investigated in many studies (Sentinel node vs. Observation after axillary UltrasouND (SOUND) and Intergroup-Sentinel-Mamma (INSEMA)-Trial-GBG 75) (9-11). This has encouraged reassessment of the role of imaging modalities for ALN staging (4).

Knowing ALN status before surgery affects decisions about treatment modalities. Therefore, reliable, non-invasive diagnostic methods are important for determining ALN metastases (1, 2). The aim of our study was to evaluate the diagnostic value of axillary ultrasound (AUS), magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) in determining ALN status in breast cancer patients with and without NAC compared to the gold standard of pathohistological or cytologic findings.

Materials and Methods

Study Design

Patients diagnosed with breast cancer and treated at the University of Health Sciences, Turkey, İstanbul Haydarpaşa Numune Training and Research Hospital, between January 2015 and December 2019, were retrospectively evaluated. In the daily practice of our clinic, AUS is routinely performed in the evaluation of axillary metastasis in patients with breast cancer. MRI is used to evaluate whether breast cancer is multicentric or not, and, notably, ^{18}F-FDG-PET/CT is used in the evaluation of distant metastasis. Of the 528 patients, a total of 336 patients who underwent AUS, MRI, and ^{18}F-FDG-PET/CT imaging were included. Patients who did not receive the AUS, MRI, or ^{18}F-FDG-PET/CT imaging modalities and whose ALNs were not confirmed histopathologically or cytopathologically by FNAC, SLNB, or ALND were not included in the study. Patients with distant metastases at the time of diagnosis were also excluded. Since the axillae of these 336 patients were evaluated retrospectively, AUS, MRI, and ^{18}F-FDG-PET/CT evaluations were reviewed, blinded to the other findings and investigators had no information about the final pathological ALN status.

Since axillary metastases may be eradicated with chemotherapy, and hence lack reference standard for axillary surgery, patients who received NAC were not included in the surgery group. The patients were categorized into two groups: patients who received NAC (NAC group, 100 patients) and those who underwent surgery after diagnosis (upfront surgery group, 236 patients). In the upfront surgery group, the axilla was evaluated according to the SLNB/ALND results, and in the NAC group, the axilla was evaluated according to the FNAC results. Primary tumor and ALN sizes were determined according to the largest radiological size in the NAC group and were evaluated according to the results of the surgical specimens in the upfront surgery group. With the results of SLNB or ALND in 236 patients in the upfront surgery group, patients with metastatic ALNs were grouped as 'metastatic', and patients with benign ALNs were grouped as 'benign'. According to the surgical specimen results of the upfront surgery group, ALN metastasis diameter and number were recorded. Micrometastatic nodes were defined as 0.2–2 mm as per the seventh edition of the American Joint Committee on Cancer breast cancer stage classification, published in 2010. In addition, isolated tumor cells in a sentinel node (<0.2 mm) were defined as node negative (12). Of 117 patients with FNAC results, there were 100 patients in the NAC group and 17 in the upfront surgery group. In the upfront surgery group, the FNAC results were compared to the SLNB and ALND results. According to FNAC results, patients with metastatic ALNs were grouped as 'metastatic', and patients with benign ALNs were grouped as 'benign'. Insufficient samples were not included in the FNAC results.

This study was approved by the local ethics committee (decision no: TUEK-771/04/2020).

AUS Protocol

Different US systems were used for the axillary US examinations by radiologists with variable years of experience. AUS was performed using a linear array transducer, in the supine oblique position, with the patient's hand above her head, with the arm abducted and externally rotated. ALNs were considered metastatic on US in the presence of any of the following criteria: loss or disruption of the central fatty hilum; loss or compression of the hyperechoic medullary region; parenchymal cortical thickness >3 mm; asymmetric cortical thickening; left-to-right asymmetry; round morphology (Solbiati Index <2); loss of the pericapsular fat line or irregular outer margins; the relationship with neighboring lymph nodes; and presence of increased peripheral blood flow. In the absence of these criteria, ALNs were considered negative for metastasis (Figure 1).

MRI Protocol

Breast MRI was performed on a 1.5T scanner using a dedicated 16-channel double-breast coil covering both breasts in the prone position (GE Optima 360 Bamboo: General Electric, Milwaukee, WI, USA). Gadobutrol (Gadovist®, Bayer Health Care, Germany) was automatically injected as contrast agent through a catheter in the antecubital vein at 0.1 mmol/kg, followed by a saline flush. In the axial plane, T1-weighted FSE images (TR/TE, 677/5.6; matrix, 352 × 192; slice thickness, 5 mm) and T2-weighted FSE images (TR/TE, 6682/104; matrix, 256 × 256; slice thickness, 5 mm) were obtained. Dynamic, contrast-enhanced MRI examination included one pre- and five post-contrast images with bilateral axial acquisition using fat-suppressed T1-weighted imaging. Subtraction images and three-dimensional maximum intensity projection images were generated

for all studies. Diffusion-weighted imaging was also performed. MRI findings indicating lymph node metastases included the following: a short-axis diameter >5 mm; a maximal cortical thickness >3 mm; round shape; eccentric cortical thickening; and loss or compression of the fatty hilum. Both axillae were evaluated at the same time, and the ALNs ipsilateral to the breast cancer were compared to the contralateral nodes. If there were no differences in number, size, or shape between the ipsilateral and contralateral ALNs, they were recorded as negative. ALN was considered positive when one or more suspicious MRI findings were noted. Radiologists with varying years of experience evaluated the pretreatment MRI findings (Figure 2).

^{18}F-FDG-PET/CT Protocol

All patients fasted for at least four hours before ^{18}F-FDG administration. When the blood glucose was <11 mmol/L, 5–6 MBq ^{18}F-FDG per kilogram of body weight was intravenously administered. ^{18}F-FDG-PET/CT scans were carried out approximately 60 minutes after ^{18}F-FDG administration using an integrated Philips Gemini TF model PET/CT scanner system (Philips Medical Systems, Cleveland, Ohio, USA). No additional contrast agent containing iodine was used for CT. PET/CT images were obtained from the head to the proximal thighs. Prior to PET acquisition, helical CT was performed under shallow breathing conditions using a low-dose CT protocol for attenuation map. PET images were reconstructed using CT for attenuation correction with an ordered subset expectation maximization iterative reconstruction algorithm (Figure 3). We considered a ≥1.2 maximum standardized uptake value (SUV_{max}) a positive ALN (as used in the clinic), and an SUV_{max} value <1.2 and reactive designation were accepted as negative.

Statistical Analysis

Analyses of the data were performed using the statistical software package SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as numbers and percentages for categorical variables, and mean, standard deviation, minimum, and maximum for numerical variables. The Student's t-test was used to compare demographic parameters. The Kruskal-Wallis test was used to compare quantitative variables that did not show a normal distribution. A Bonferroni correction and Tukey test were used to compare quantitative variables that did not show a normal distribution between more than two groups. The Pearson correlation coefficient method was used for correlations. Diagnostic screening tests including sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV), and kappa compliance tests were used to determine the compatibility between qualitative data. The statistical significance level was at 95% confidence intervals, and $p<0.05$ was considered significant.

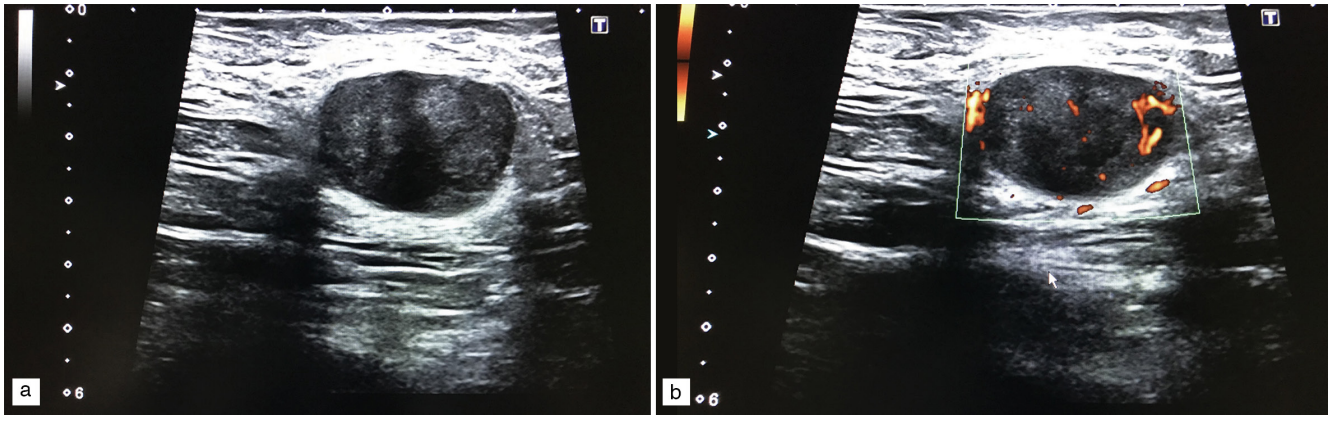

Figure 1. Human epidermal growth factor receptor 2 (+), Invasive ductal carcinoma in a 45-year-old woman with ipsilateral axillary lymph node metastasis. (a) B-mode sonogram shows an enlarged, round shaped lymph node with loss of the central fatty hilum in the left axillary fossa. (b) Power Doppler Sonogram reveals increased peripheral blood flow signals

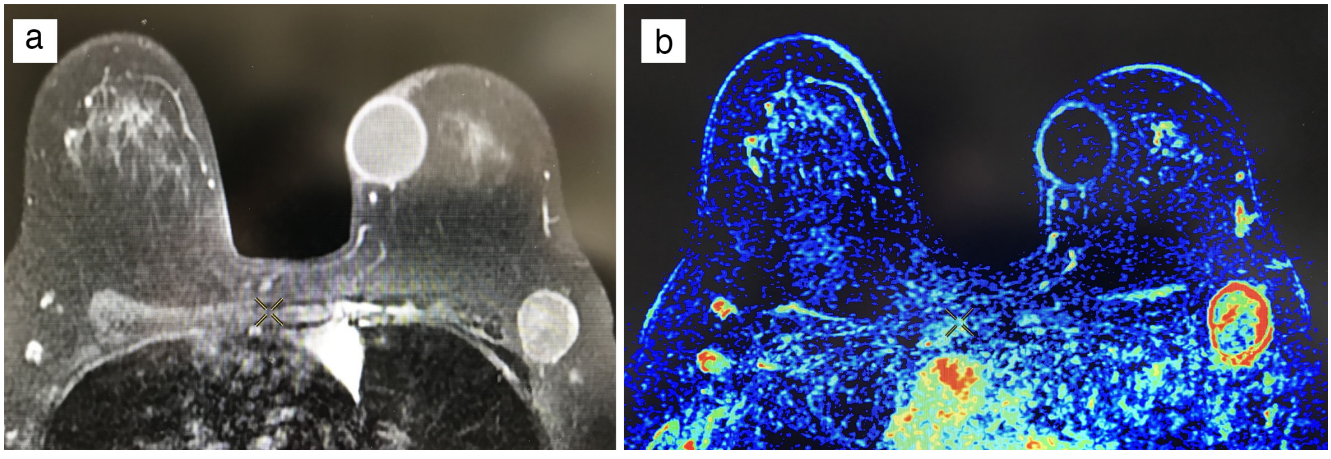

Figure 2. Dynamic contrast-enhanced magnetic resonance imaging examination of the same patient mentioned in Figure 1. (a) Contrast enhanced fat-suppressed T1-weighted axial image shows peripherally enhanced, round shaped left axillary lymph node with diameter of 38 × 22 mm. (b) Postcontrast subtracted axial image emphasizes rim-like contrast enhancement

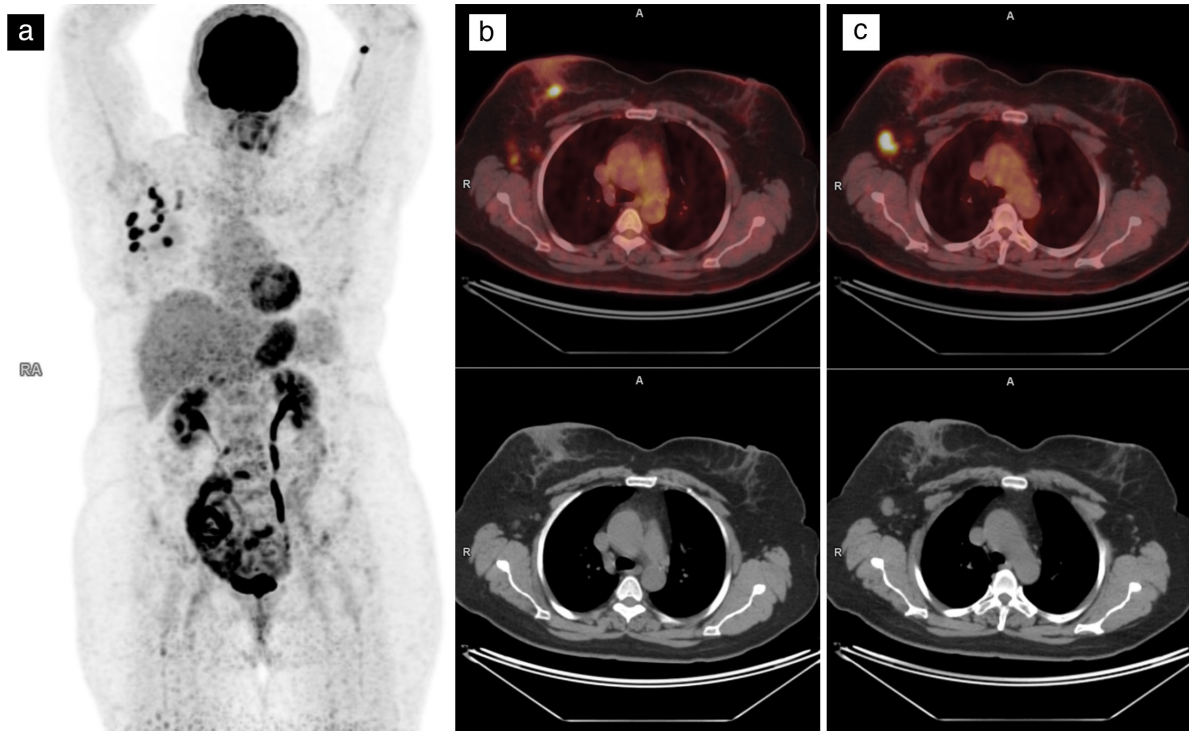

Figure 3. Invasive ductal carcinoma in a 49-year-old woman. (a) Maximum intensity projection positron emission tomography (PET) image demonstrates invasive ductal carcinoma in the right breast and multiple metastases in the right axillary lymph nodes. (b) Axial fused positron emission tomography-computed tomography (PET/CT), and CT show an intensely hypermetabolic focus [maximum standardized uptake value (SUV_{max}), 9.4] in the right retroareolar region with diameter of 12 x 11 mm, corresponding to the breast tumor. (c) Axial fused PET/CT, and CT reveal a metastatic axillary lymph node with high fluorodeoxyglucose (FDG) uptake (SUV_{max}: 10.7)

Results

The patients were categorized into two groups: patients who received NAC, and those who underwent surgery after diagnosis. Of the 336 patients, there were 100 in the NAC group and 236 in the upfront surgery group. The mean ± standard deviation (SD) age was 50.1±11.8 years (range: 18–84). The mean ± SD primary tumor size was 26.1 ± 12.7 mm (range: 6–80 mm), and the mean ± SD ALN size was 14.2±6.5 mm (range: 5–46 mm) (Table 1). When the two groups were compared, age was significantly younger in the NAC group (p = 0.047). There was no significant difference between tumor size and ALN size (p = 0.187, p = 0.113, respectively) (Table 1). A total of 172 tumors (51.1%) were located in the left breast. Tumor sizes were clinically categorized into four groups: cT1: <20 mm; cT2: 20–50 mm; cT3: >50 mm; cT4: invasion. Of these, 173 cases (51.4%) were cT2. ALN clinical findings on physical examinations of the patients were divided into three groups: cN0: non-palpable, cN1: mobile, and cN2: fixed. Of them, 165 cases (49.1%) were cN1. According to the results of histopathological evaluation, most patients (75%, 252 patients) had invasive ductal breast cancer (IDC), and 26 patients (7.7%) had invasive lobular carcinoma (ILC) in breast. On immunohistochemical profiling, out of 336 patients, 89 patients (26.4%) were Luminal A, 144 patients (42.8%) were Luminal B, HER2 (-), 42 patients (12.5%) were Luminal B, HER2 (+), 30 patients (8.9%) were HER2 (+), and 31 patients (9.2%) were TN (Table 2). When FNAC, SLNB, and ALND specimen results were evaluated histo- or cyto-pathologically, ALNs were metastatic in 188 patients (55.9%). Clinical and pathological characteristics of the patients in the upfront surgery group and NAC group are given separately in Table 2. In the NAC group, evaluated by FNAC, 90 of 100 patients had metastatic and 10 had benign ALNs. Upfront surgery patients were categorized into four groups according to the diameter of ALN metastases: no metastasis or isolated tumor cells, ≤2 mm, 3–9 mm, and ≥10 mm, respectively. In these 236 patients, the mean ± SD ALN metastasis diameter was 3.84 ± 5.94 mm (median: 0 mm, range: 0–40 mm), and no metastases were detected in 138 patients (58.5%). The mean ± SD positive ALN metastasis diameter was 9.06 ± 6.16 mm (median: 9 mm, range: 0.2–40 mm) in 98 patients. Metastases were ≤2 mm in 13 patients (5.5%), 3–9 mm in 44 patients (18.6%), and ≥10 mm in 41 patients (17.3%). Again, in the upfront surgery group, when the pathological ALN number (pN) was evaluated, it was categorized into four groups: pN0, benign; pN1, 1–3; pN2, 4–9; and pN3, ≥10 metastatic ALNs. In the upfront surgery group, 98 patients (41.5%) had metastatic ALNs. In all, 66 patients (27.9%) were pN1, 23 patients (9.7%) were pN2, and nine patients (3.8%) were pN3 (Table 2). In breast surgery, 149/236 patients (63.2%) underwent BCS, and 87/236 patients (36.8%) underwent mastectomy. In the upfront surgery group, direct ALND was performed on 35 patients (13.5%) in the evaluation of the axilla for staging. There were 138 patients (58.4%) who received SLNB/ALND and were reported as benign. SLNB followed by ALND was performed in 14.8% of patients (35 patients) and ≤2 metastatic ALNs were detected. In 3.8% of patients (n=9), ALND was performed following SLNB and ≥3 metastatic ALNs were detected. As in the ACOSOG Z0011 study, there were 22 patients (9.3%) who underwent BCS alone, had scheduled radiotherapy, and had ≤2 macrometastatic SLNs, and no further ALND.

In AUS, ALNs were determined to be positive in 181 cases (53.9%), and negative in 155 cases (46.1%). On histopathological examination, ALN metastases were found in 188 cases (56%), with

benign ALNs in 148 cases (44%). The accuracy of AUS in showing ALN status was 79.1%. ALNs were positive in 155 cases (46.1%) on MRI and ^{18}F-FDG-PET/CT, while ALNs were determined to be negative in 181 cases (53.9%). The accuracy of MRI and ^{18}F-FDG-PET/CT in showing ALN status was 85.3% and 72.5%, respectively (Table 3). When evaluated by receiver operating characteristics curve analyses, the area under the curve (AUC) was 0.851 for ALN SUV_{max}.

In cases where AUS, MRI and ^{18}F-FDG-PET/CT were false negative in the upfront surgery group, the mean ALN metastasis diameters were 3.73 (range: 0.2–9) mm, 3.54 (range: 0.2–10) mm, and 4.56 (range: 0.2–12) mm, respectively (Table 4). ALNs of the patients in whom AUS, MRI, and ^{18}F-FDG-PET/CT images concordantly were reported as positive were also found to be metastatic according to the FNAC, SLNB, and ALND results. ALN metastases were detected in 19 of 132 patients (all upfront surgery group) (14.3%) in whom AUS, MRI, and ^{18}F-FDG-PET/CT images concordantly were reported as negative. Mean ALN metastasis diameter was 3.27 (range: 0.2–9) mm (Table 5), and only one patient was pN2 (Table 6).

The sensitivity, specificity, PPV, NPV, and accuracy of AUS for the detection of ALN metastases were 83%, 62%, 59.2%, 54.8%, and 79.1%, respectively. For MRI these values were 86.1%, 75%, 68.5%, 51.6%, and 85.3%, respectively, and for ^{18}F-FDG-PET/CT they were 78%, 53%, 56.2%, 51.4%, and 72.5%, respectively. Kappa correlation levels between ALN positivity and AUS, MRI, and ^{18}F-FDG-PET/CT results were 67.3%, 77.5%, and 60.5%, respectively (Table 3).

Discussion and Conclusion

ALN staging is an important step in the evaluation of newly diagnosed breast cancer patients. Knowing the presence of metastatic ALN involvement in clinically node-negative or node-positive patients is important in their treatment (12).

Radiological staging of ALN is performed with AUS, MRI, and ^{18}F-FDG-PET/CT. AUS is widely used in the evaluation of ALN status in breast cancer because it is easy to perform, inexpensive, does not involve radiation, and is noninvasive (1). AUS is an operator-dependent modality for ALN metastases, so that reported sensitivity and specificity are variable and controversial (13). However, its accuracy for evaluating ALN metastases depends on the size of the ALNs. In the case of cN0, small ALN or metastasis diameter, the overall sensitivity of AUS is 56%–75%, and specificity is 70%–90% (14). In the upfront surgery group, the mean ALN metastasis diameter of our false-negative patients on AUS was 3.73 mm. In addition, AUS allows image-directed needle biopsy. In morphological evaluations, AUS alone has insufficient sensitivity and low PPV, and if ALN metastasis is suspected, AUS-guided FNAC is recommended and enables ALNs to be evaluated more accurately (15, 16).

Table 1. Comparison of means of patients' variables with and without NAC and ALN metastases

	ALN	n	Mean ± SD	Min-max	p-value
Age (year)		336	50.1±11.8	18–84	
	Metastatic	188	29.6±13.8	8–80	
Tumor size (mm)	**Benign**	148	21.6±9.5	6–53	**0.007**
	Total	336	26.1±12.7	6–80	
	Metastatic	188	16.5±7	7–46	
ALN size (mm)	**Benign**	148	11.4±4.4	5–30	**0.001**
	Total	336	14.2±6.5	5–46	
	Metastatic	188	4.54±4.9	0–24.9	
ALN SUV_{max}	**Benign**	148	0.2±0.7	0–4	**0.037**
	Total	336	2.6±4.3	0–24.9	
	Metastatic	188	31.4±19.5	2–90	
Ki-67 level	**Benign**	148	25.5±20.5	2–90	**0.008**
	Total	336	28.8±20.2	2–90	

	NAC group (n=100)		Upfront surgery group (n=236)		p-value
	Mean ± SD	Min-max	Mean ± SD	Min-max	
Age (year)	43.4±8.7	18–66	52.8±11.8	24–84	**0.047**
Tumor size (mm)	33.2±13.4	9–80	23.2±11.2	6–72	0.187
ALN size (mm)	18.2±7.5	8–41	12.6±5.3	5–46	0.113
ALN SUV_{max}	5.5±4.9	0–22.4	1.4±3.3	0–24.9	**0.042**
Ki-67 level	35.3±19.8	2–90	26.1±19.7	2–90	**0.031**

NAC: Neoadjuvant chemotherapy, ALN: Axillary lymph nodes, SD: Standard deviation, Min: Minimum, Max: Maximum, mm: Millimeter, ALN SUV_{max}: Axillary lymph nodes maximum standardized uptake value, n: Number

Table 2. Clinical and pathological characteristics of the patients

		Upfront surgery group (n=236)		NAC group (n=100)		p-value	Total (n=336)	
		n	%	n	%		n	%
ALN	**Metastatic**	98	41.5	90	90	**0.052**	188	55.9
	Benign	138	58.5	10	10		148	44.1
cT	**cT1: ≤20 mm**	110	46.6	16	16		126	37.5
	cT2: 20–50 mm	115	48.7	58	58	0.769	173	51.4
	cT3: >50 mm	9	3.8	8	8		17	5.1
	cT4: invasion	2	0.8	18	18		20	5.9
cN	**cN0: non-palpable**	149	63.1	8	8		157	46.7
	cN1: mobile	81	34.3	84	84	**0.049**	165	49.1
	cN2: fixed	6	2.5	8	8		14	4.2
Histopathological types	**IDC**	170	72	82	82		252	75
	ILC	18	7.6	8	8	0.882	26	7.7
	IDC + ILC	5	2.1	0	0		5	1.4
	Others	43	18.2	10	10		53	15.7
Luminal subtypes	**A**	80	33.9	9	9		89	26.4
	B, HER2 (-)	101	42.8	43	43		144	42.8
	B, HER2 (+)	21	8.9	21	21	**0.031**	42	12.5
	HER2 (+)	18	7.6	12	12		30	8.9
	TN	16	6.8	15	15		31	9.2
AUS	**Positive**	81	34.3	100	100	**0.001**	181	53.8
	Negative	155	65.6	0	0		155	46.1
MRI	**Positive**	70	29.7	85	85	**0.038**	155	46.1
	Negative	166	70.3	15	15		181	53.8
^{18}F-FDG-PET/CT	**Positive**	70	29.7	85	85	0.127	155	46.1
	Negative	166	70.3	15	15		181	53.8
pN	**pN0: benign**	138	58.4					
	pN1: 1–3	66	27.9					
	pN2: 4–9	23	9.7					
	pN3: ≥10	9	3.8					
ALN metastasis diameter (mm)	**1: 0**	138	58.4					
	2: ≤2 mm	13	5.5					
	3: 3–9 mm	44	18.6					
	4: ≥10 mm	41	17.3					
Breast surgery	**BCS**	149	63.2					
	Mastectomy	87	36.8					
Axillary surgery	**BCS + ALND**	35	14.8					
	BCS + SLNB	114	48.3					
	Mastectomy +ALND	44	18.6					
	Mastectomy + SLNB	43	18.2					

NAC: Neoadjuvant chemotherapy, ALN: Axillary lymph nodes, cT: Clinical tumor, mm: Millimeter, cN: Clinical node, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, HER2: Human epidermal growth factor receptor 2, TN: Triple negative, AUS: Axillary ultrasound, MRI: Magnetic resonance imaging, ^{18}F-FDG-PET/CT: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography, pN: Pathological node, BCS: Breast conserving surgery, ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy, n: Number

Table 3. Diagnostic performance of imaging modalities in detecting the axillary lymph nodes metastases

		AUS		MRI		^{18}F-FDG-PET/CT	
		n	%	n	%	n	%
ALN (+), radiological (+) (true positive)	Upfront surgery group	67	19.9	67	19.9	57	16.9
	NAC group	90	26.7	85	25.2	81	24.1
	Total	157	46.7	152	45.2	138	41.1
ALN (-), radiological (+) (false positive)	Upfront surgery group	14	4.1	3	0.8	13	3.8
	NAC group	10	2.9	0	0	4	1.1
	Total	24	7.1	3	0.8	17	5.1
ALN (-), radiological (-) (true negative)	Upfront surgery group	124	36.9	135	40.1	125	37.2
	NAC group	0	0	10	2.9	6	1.7
	Total	124	36.9	145	43.1	131	38.9
ALN (+), radiological (-) (false negative)	Upfront surgery group	31	9.2	31	9.2	41	12.2
	NAC group	0	0	5	1.4	9	2.6
	Total	31	9.2	36	10.7	50	14.8
Sensitivity		83		86.1		78	
Specificity		62		75		53	
PPV		59.2		68.5		56.2	
NPV		54.8		51.6		51.4	
Accuracy		79.1		85.3		72.5	
Kappa		67.3		77.5		60.5	

AUS: Axillary ultrasound, MRI: Magnetic resonance imaging, ^{18}F-FDG-PET/CT: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography, ALN: Axillary lymph nodes, NAC: Neoadjuvant chemotherapy, PPV: Positive predicted value, NPV: Negative predicted value, n: Number

Breast MRI is frequently used because, like AUS, it is non-invasive and does not use radiation (17). The main advantage of MRI is that it provides anatomical information about the breast and axilla. It is used to evaluate the distance of the primary tumor to the skin, pectoral muscle, and areola, the local regional areas, and the contralateral breast (3, 18, 19). In addition, it has high sensitivity for detecting additional lesions that cannot be detected by ultrasound or mammography (17, 20). The role of MRI in determining ALN metastases has shown moderate sensitivity and low-medium specificity (16). In our study, sensitivity and specificity were 86.1%, and 75%, respectively.

^{18}F-FDG-PET/CT is expensive, involves isotopic radiation, and has high false-positive rates in inflammatory processes. In addition, ^{18}F-FDG-PET/CT has low sensitivity for detecting micrometastases in ALNs (1, 3). The mean ALN metastasis diameter of 41 patients in the upfront surgery group, considered false negatives in ^{18}F-FDG-PET/CT results, was 4.56 mm. Micrometastases (0.2–2 mm) were detected in 13 of these patients. Its main advantage is that it is a functional imaging method that enables early detection of distant metastases (21, 22).

The mean pathologic ALN metastasis diameter was 3.73 mm in false negative AUS, 3.54 mm in false negative MRI, and 4.56 mm in false negative ^{18}F-FDG-PET/CT in the upfront surgery group, respectively. In our and other imaging-pathologic comparative studies the mean diameter of metastatic ALNs was smaller in false negative cases of AUS, MRI, or ^{18}F-FDG-PET/CT than the diameter of metastases that were visible in these modalities. One study reported that the prognostic information obtained from MRI has a certain advantage over AUS, particularly when considering axillary surgery, and that MRI provides a more accurate prediction of axillary nodal burden than AUS (12). When nodal burden and false negative AUS, MRI, and ^{18}F-FDG-PET/CT were evaluated in upfront surgery patients, two patients were pN2 on AUS, one was pN2 on MRI, and three were pN2 and two were pN3 on ^{18}F-FDG-PET/CT. MRI and AUS were found to provide a more accurate prediction compared to ^{18}F-FDG-PET/CT. In an earlier study, we found that the nodal burden is predictable according to the ALN SUV_{max} results, which is important when deciding between surgical or NAC treatment (23).

In a previous study, histopathologically confirmed ALN metastases were detected in 13 of 82 patients. ALN SUV_{max} showed an AUC value of 0.916, and the cut-off value of 1.1 was appropriate (24). The overall accuracy, sensitivity, and specificity of the ALN SUV_{max} cut-off value of 0.72 for the detection of ALN metastasis were approximately 65.3%, 85.8%, and 77.8 %, respectively, and its positive and negative predictive values were 74.7% and 79.4%, respectively (25). In the present study, the AUC was 0.851. Riegger et al. (26) found that ^{18}F-FDG-PET/CT was significantly more accurate than AUS for the detection of ALN metastases ($p = 0.019$). The sensitivity, specificity, PPV, NPV, and accuracy of ^{18}F-FDG-PET/CT for the detection of ALN metastases in that study were 54%, 89%, 77%, 74%, and 75%, respectively. For AUS they were 38%, 78%, 54%, 65%, and 62%, respectively (26). In our study,

Table 4. Mean metastasis diameter, pN, histopathological types and luminal subtypes data of imaging modalities

			ALN (+), radiological (+) (true positive)		ALN (-), radiological (+) (false positive)		ALN (-), radiological (-) (true negative)		ALN (+), radiological (-) (false negative)	
AUS	**Mean metastasis diameter, (mm) (n=236)**		11.18	n=67	0	n=14	0	n=124	3.73	n=31
	pN, (n) (n=236)	**pN0: benign**	0	n=67	14	n=14	124	n=124	0	n=31
		pN1: 1–3	37		0		0		29	
		pN2: 4–9	21		0		0		2	
		pN3: ≥10	9		0		0		0	
	Luminal subtypes, (n) (n=336)	**A**	20	n=157	4	n=24	54	n=124	10	n=31
		B, HER2 (-)	79		10		41		14	
		B, HER2 (+)	28		2		11		1	
		HER2 (+)	14		3		8		5	
		TN	16		5		10		1	
	Histopathological types, (n) (n=336)	**IDC**	130	n=157	20	n=24	79	n=124	24	n=31
		ILC	13		2		9		2	
		IDC + ILC	1		1		2		1	
		Others	13		1		34		4	
MRI	**Metastasis diameter, (mm) (n=236)**		11.52	n=67	0	n=3	0	n=135	3.54	n=31
	pN, (n) (n=236)	**pN0: benign**	0	n=67	3	n=3	135	n=135	0	n=31
		pN1: 1–3	37		0		0		29	
		pN2: 4–9	21		0		0		2	
		pN3: ≥10	9		0		0		0	
	Luminal subtypes, (n) (n=336)	**A**	20	n=152	2	n=3	56	n=145	11	n=36
		B, HER2 (-)	77		0		51		16	
		B, HER2 (+)	26		1		12		3	
		HER2 (+)	13		0		11		6	
		TN	16		0		15		0	
	Histopathological types, (n) (n=336)	**IDC**	124	n=152	2	n=3	97	n=145	29	n=36
		ILC	12		1		10		3	
		IDC + ILC	2		0		3		0	
		Others	14		0		35		4	
^{18}F-FDG-PET/CT	**Mean metastasis diameter, (mm) (n=236)**		12.18	n=57	0	n=13	0	n=125	4.56	n=41
	pN, (n) (n=236)	**pN0: benign**	0	n=57	13	n=13	125	n=125	0	n=41
		pN1: 1–3	30		0		0		36	
		pN2: 4–9	20		0		0		3	
		pN3: ≥10	7		0		0		2	
	Luminal subtypes, (n) (n=336)	**A**	17	n=138	4	n=17	54	n=131	14	n=50
		B, HER2 (-)	67		5		46		26	
		B, HER2 (+)	26		3		10		3	
		HER2 (+)	12		3		8		7	
		TN	16		2		13		0	
	Histopathological types, (n) (n=336)	**IDC**	116	n=138	12	n=17	87	n=131	37	n=50
		ILC	9		3		8		6	
		IDC + ILC	0		0		3		2	
		Others	13		2		33		5	

pN: Pathological Node, ALN: Axillary lymph nodes, AUS: Axillary ultrasound, mm: Millimeter, HER2: Human epidermal growth factor receptor 2, TN: Triple negative, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, MRI: Magnetic resonance imaging, ^{18}F-FDG-PET/CT: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography, n: Number

Table 5. Comparison of imaging modalities and ALN status

	Upfront surgery group (n=236)			NAC group (n=100)		Total (n=336)	
	n	ALN (+) (n)	Mean ALN metastasis diameter (mm)	n	ALN (+) (n)	n	ALN (+) (n)
AUS (+), MRI (+), ^{18}F-FDG-PET/CT (+)	48	48	12.74	84	84	132	132
AUS (+), MRI (+), ^{18}F-FDG-PET/CT (-)	16	13	6.6	6	3	22	16
AUS (+), MRI (-), ^{18}F-FDG-PET/CT (-)	15	6	4.16	5	1	20	7
AUS (+), MRI (-), ^{18}F-FDG-PET/CT (+)	2	0	0	5	2	7	2
AUS (-), MRI (+), ^{18}F-FDG-PET/CT (+)	3	3	6	0	0	3	3
AUS (-), MRI (+), ^{18}F-FDG-PET/CT (-)	3	3	5.16	0	0	3	3
AUS (-), MRI (-), ^{18}F-FDG-PET/CT (+)	17	6	4.2	0	0	17	6
AUS (-), MRI (-), ^{18}F-FDG-PET/CT (-)	132	19	3.27	0	0	132	19

ALN: Axillary lymph nodes, NAC: Neoadjuvant chemotherapy, mm: Millimeter, AUS: Axillary ultrasound, MRI: Magnetic resonance imaging, ^{18}F-FDG-PET/CT: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography, n: Number

Table 6. Data of luminal subtypes and histopathological types of false negative patients

		AUS (-), MRI (-), ^{18}F-FDG-PET/CT (-) (n=132)		ALN (+) (false negative)	
Upfront surgery group (n=236)				**n=19 (0.2-9mm) (14.3%)** 1: 4 metastases (pN2) 1: 2 metastases (pN1) 17: 1 metastasis (pN1) (5: pN1mic)	
Luminal subtypes (n/%)	**A**	55	41.6	6	31.5
	B, HER2 (-)	49	37.1	9	47.3
	B, HER2 (+)	8	6.1	0	0
	HER2 (+)	11	8.3	4	21.1
	TN	9	6.8	0	0
Histopathological types (n/%)	**IDC**	88	66.6	14	73.6
	ILC	8	6.1	2	10.5
	IDC + ILC	2	1.5	0	0
	Others	34	25.7	3	15.7

AUS: Axillary ultrasound, MRI: Magnetic resonance imaging, ^{18}F-FDG-PET/CT: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography, ALN: Axillary lymph nodes, mm: Millimeter, pN: Pathological node, HER2: Human epidermal growth factor receptor 2, TN: Triple negative, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, n: Number

MRI and AUS had higher accuracy for showing ALN metastases compared to ^{18}F-FDG-PET/CT (MRI, AUS, ^{18}F-FDG-PET/CT; 85.3%, 79.1%, and 72.5%, respectively). In another study, there were no statistically significant differences between MRI and AUS for the evaluation of ALNs (27). However, with MRI alone or AUS combined with MRI, that study found a statistically significant difference in specificity and PPV. Among the 21 MRI or ^{18}F-FDG-PET/CT studies included in a meta-analysis, the pooled sensitivities

of MRI and ^{18}F-FDG-PET/CT were 0.82 and 0.64, respectively, suggesting that MRI has a higher sensitivity than ^{18}F-FDG-PET/CT for an ALN metastasis diagnosis in breast cancer patients (21). It has been reported that MRI is better at diagnosing ALN metastases in breast cancer than ^{18}F-FDG-PET/CT, and MRI combined with US can lead to a more precise diagnosis (28). In our study, MRI was found to have higher sensitivity and specificity for showing ALN metastases compared to ^{18}F-FDG-PET/CT (86.1%, 75% and 78%, 53%, respectively). An et al. (29) found that ^{18}F-FDG-PET/CT for detection of ALN metastasis was not significantly different from AUS or MRI in breast cancer patients. They concluded that combining ^{18}F-FDG-PET/CT with AUS or MRI could improve the diagnostic performance compared to ^{18}F-FDG-PET/CT alone (29). In our study, ALNs were found to be metastatic in all patients who were reported positive in all three imaging modalities. Using multiple imaging modalities improved overall imaging diagnostic performance and increased accuracy. However, it should be noted that although all three imaging modalities were negative, we found 14.3% false negativity.

Our study had some limitations. First, we evaluated the cases retrospectively. In addition, imaging data was obtained from different imaging centers, and thus lack of standardization was inevitable. Also, AUS is an operator-dependent modality, which has poor interobserver agreement. So, it is important that an experienced breast radiologist should interpret the imaging findings using this modality. We could not show a one-to-one correspondence between histopathology and AUS, MRI, and ^{18}F-FDG-PET/CT images. In addition, ALN status at the time of diagnosis of patients scheduled for NAC was evaluated with FNAC.

In conclusion, evaluation of ALNs with imaging modalities in a patient with newly diagnosed breast cancer is crucial. In most studies, the accuracy of AUS, MRI, and ^{18}F-FDG-PET/CT in demonstrating ALN metastasis have been compared with each other and no clear conclusion has been reached. In our study, we found that the diagnostic performance of MRI was slightly better than AUS and ^{18}F-FDG-PET/CT. When we used imaging modalities together, our accuracy rate was better than when we used them alone. Thus, we suggest that for accurate evaluation of ALNs, imaging modalities should be complementary rather than competitive.

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul Haydarpaşa Numune Training and Research Hospital (no: TUEK- 771/04/2020, date: 04/05/2020).

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Original Article

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The Importance of Superb Microvascular Imaging for the Differentiation of Malignant Breast Lesions from Benign Lesions

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ABSTRACT

Objective: In this prospective study, the diagnostic performance of the new version of superb microvascular imaging (SMI) in differentiating malignant from benign lesions was evaluated.

Material and Methods: Ninety breast lesions were included. During color SMI examination, both free-hand region of interest (ROI) and box ROI were used. Vascular index (VI) values were obtained from the lesion using both types of ROI and from normal breast tissue via box ROI. VI values, monochrome SMI grading and histopathological results were compared. The efficacy of color SMI and monochrome SMI was investigated in differentiating between benign and malignant breast lesions.

Results: The cut-off value, in the differentiation of benign and malignant lesions with color SMI was 0.50 for box ROI, while it was 0.30 for free-hand ROI. The specificity of VI values obtained with box ROI was higher than that of free-hand ROI when differentiating malignant lesions from benign. Comparison of VI values from a lesion and from normal breast tissue showed that VI values in malignant lesions were significantly higher ($p<0.05$). The VI values of benign lesions and VI values of normal breast tissue were similar. There was a statistically significant relationship between monochrome SMI grading and the malignancy or benign status of the lesion ($p<0.001$).

Conclusion: Drawing the lesion circumference free-hand using a free-shape ROI did not enhance the sensitivity and specificity. Contrary to popular belief, a more easy and practical measurement method may be more suitable for SMI examination. It is hoped that this will be one of the earliest studies to assess the clinical performance of the latest version of SMI.

Keywords: Superb microvascular imaging, new version, breast lesions, women's health, ultrasonography

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Key Points

- SMI is a promising development to improve the differentiation of malignant and benign breast lesions because of its superiority in imaging microvascular structures in breast lesions.
- The qualitative and quantitative values obtained from the detailed display of the blood supply in the tumoral tissue can be used as an indirect indicator of abnormal vascularity.
- The vascular index has only been used in a few recent current SMI studies and only a few of these.
- Lesions with a high risk for breast cancer can be easily detected with the contribution of SMI and can also serve as a guide for indeterminant lesions.

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Introduction

Breast cancer is the most common type of cancer in women and among the most common causes of death (1, 2). Advances in tools for early diagnosis contributed significantly to a decrease in the death rate due to breast cancer. It is sometimes challenging to distinguish malignant lesions from benign lesions using radiological imaging methods because of the wide spectrum of imaging and pathological features of breast lesions (3). Malignant breast lesions express high metabolic activity and require newly developed microvascular structures to invade the basement membrane (4). Thus malignant breast lesions exhibit greater vascularity compared to benign lesions and develop irregular vascular structures within the tumor, termed neovascularization (5). To be able to identify this irregular vascularity may increase the diagnostic effectiveness of conventional methods.

Superb microvascular imaging (SMI), an alternative Doppler ultrasonography (US) method developed in recent years using a new adaptive algorithm, separates tissue movements from the slow flow of small vessels and provides novel additional information compared to conventional imaging methods (3, 6). In the latest version of SMI, used in the present study, quantitative values for vascularity, known as the vascular index (VI) can be obtained. Thus, it is possible to objectively evaluate the presence of microvascular structures in a selected area of the diagnostic images (7). Given the neovascularity of malignant lesions, we hypothesized that SMI would aid in breast cancer diagnosis.

The aim of this study was to evaluate the vascularity of breast lesions using SMI, and to compare and correlate the findings with histopathological results. In contrast to previous studies, with this newly developed version of SMI, an additional aim was to investigate whether there is an objective quantitative value of VI that can distinguish malignant breast lesions from benign lesions. Thus, it was hoped that this study would be one of the first to provide numerical values obtained with SMI for distinguishing malignant from benign lesions.

Materials and Methods

Female patients who attended Outpatient Clinic between 01.01.2019–01.09.2019 and had suspicious breast lesions on US were examined prospectively. Oral and written consent were obtained from all patients who participated in our study. Ethics committee approval was obtained from the Scientific Research Ethics Committee of Selçuk University Faculty of Medicine.

Solid lesions classified as Breast Imaging Reporting and Data Systems (BI-RADS) categories 4a, 4b, 4c and 5 in breast US were eligible for inclusion in the study. Exclusion criteria were: patients with a history of mastectomy; patients with severe organ failure; patients who underwent chemo-radiotherapy; and those without histopathological results reported by our own histopathologists.

US and SMI were performed in the supine position in all patients, with 7–14 MHz high-frequency probes using a US device, the Aplio 300 (Toshiba, Tokyo, Japan). On grayscale US examination, the size of the lesions, contour features, location in relation to the skin, echo pattern and posterior acoustic properties were evaluated. The sonographically detected morphological features of the lesion were categorized according to the BI-RADS categorization, proposed by the American College of Radiology (8).

After sonographic examination, SMI was performed. During the SMI examination, the scale was 1.5–2.5 cm/s, mechanical index, wall filter, and frame rate were 1.5, 1.5, 50–100 Hz, and >50 Hz, respectively. SMI has two different modes, color SMI (cSMI) and monochrome SMI (mSMI). Initial examination was performed with cSMI, during which the "box" region of interest (ROI), a built-in feature of the program, and free-hand ROI, marked by manually drawing around the lesion, were used. VI values were measured using both ROI types. The number of vascular codes was divided by the area of the ROI, and thus VI was calculated automatically by the device. VI values were measured in the range from 0 to 100. Box ROI and VI values were obtained for normal tissue from the same quadrant of the contralateral breast without lesions. After completing cSMI, mSMI was performed. The skeletal structure of the microvascular vessels was visually evaluated using mSMI. We created a grading system to visually score the vascularity of the lesions for mSMI. Accordingly, Grade 1 was defined as a normal background with punctate blood supply and minimal vascularity. In Grade 2, vascularity was observed in lesions in the absence of anarchic vascular structures and no more than two linear microvascular signals were detected. Lesions with an anarchic blood supply or more than two vascular structures were classified as Grade 3. Observation of distorted, irregularly shaped and curved microvascular structures in the center and periphery of the lesion on mSMI was accepted as an anarchic blood supply. In three cases recommended by the clinician or requested by the patient, and patients with BI-RADS category 4a, 4b, 4c and 5 lesions, tru-cut biopsy was performed after SMI and histopathological results were obtained. In patients whose tru-cut biopsy results were benign, no further surgery was performed and final results were those reported for the tru-cut biopsy. All lesions that were found to be malignant or indeterminate on biopsy were surgically removed (lumpectomy or mastectomy). These lesions were thus definitive surgical results.

Statistical Analysis

All statistical analysis was performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). was used for statistical analysis. Continuous data are presented as mean ± standard deviation (SD) or median (interquartile range), and categorical data are presented as the number (n) and percentage (%). The normality of the data was assessed using the Anderson-Darling normality test. Homogeneity of variances was tested using Levene's test. Mann-Whitney U test was used to compare the VI values obtained with cSMI in malignant and benign lesions. A $p<0.05$ was assumed to indicate significance. The diagnostic performance of the VI values obtained by box and free-hand ROIs in distinguishing malignant and benign lesions was calculated. The cut-off values for distinguishing malignant and benign lesions were determined using receiver operating characteristic (ROC) curves, and performance was evaluated. For the cut-off value, sensitivity, specificity, positive and negative predictive values, and accuracy were calculated at a 95% confidence level. Interactive point charts were created to determine the threshold values. The relationship between VI values of benign or malignant lesions and VI values of normal tissue was tested using Spearman's rho correlation coefficient. The relationship between mSMI grading and pathological findings was evaluated using the chi-square test.

Results

Eighty-six women with lesions assessed bu US imaging to be at risk of malignancy were included in the study. Lesions in four patients were

bilateral. The mean ± SD diameter of 90 lesions detected on US was 21.89 ± 17.12 mm, and 49 lesions were located in the right breast. The majority of lesions were BI-RADS category 4b and numbered 32 (35.6%). There were a further 19 (21.1%) of lesions classified as BI-RADS category 5 (Table 1).

Thirty breast lesions were malignant, and 60 were benign on histopathological examination. The majority of malignant lesions were invasive ductal carcinomas (n = 28, 93.3%). One patient had invasive lobular carcinoma, and one patient had ductal carcinoma *in situ*. Fibroadenomas constituted the majority of benign lesions.

For benign lesions, the mean VI value was 1.68 for the box ROI and 0.81 for free-hand ROI (Table 2). While the mean VI value measured using box ROI in malignant lesions was 4.30, the mean free-shaped ROI was found to be 3.23 (Table 2). The VI values of benign and malignant lesions measured by SMI were statistically significant for the both ROI type (p<0.001).

The cut-off VI value for cSMI, was 0.50 and above for box ROI, while it was 0.30 and above for free-hand ROI. While the sensitivity of VI value measured by box ROI to differentiate benign lesions from malignant lesions was 89% and the specificity was 56%, these values for free-hand ROI were 89% and 49%, respectively. The NPV was 92% for the box ROI and 91% for free-hand ROI while the PPV for box ROI was 46% and 43% for free-hand ROI (Table 3; Figures 1 and 2).

The area under the ROC curve showed that SMI gave significant results in distinguishing between malignant and benign lesions (Graph 1). Differential and interactive point charts were drawn for box and free-hand cSMI VI values, which were used to distinguish between benign and malignant lesions (Graph 2, Table 4).

In the comparison of VI values of the lesion and normal breast tissue, box and free ROI VI values detected in malignant lesions were significantly higher than those in normal breast tissue (p<0.05). There was no statistically significant difference between the VI values found in benign lesions and VI values obtained from normal breast tissue (p>0.05) (Table 4).

Table 1. Descriptive Features

Parameters	Number of lesions (n=90)
Age (year), mean, (min-max)	49 (27–86)
US diameter (mm), mean, (min-max)	21 (5–100)
Side	
Left breast, n	41
Right breast, n	49
US BIRADS	
BI-RADS 3, n	8
BI-RADS 4a, n	22
BI-RADS 4b, n	32
BI-RADS 4c, n	9
BI-RADS 5, n	19

US: Ultrasonography, BI-RADS: Breast Imaging Reporting and Data Systems, min: Minimum, max: Maximum, n: number

There was a statistically significant correlation between the mSMI grading and whether the lesion was malignant or benign (pathological finding) (p<0.001). While 94.4% of the lesions with Grade 1 vascularity were benign, 76.0% of the Grade 3 lesions were malignant. As the severity (grade) of vascularity detected with mSMI increased, the rate of malignancy increased. However, 5.6% of the lesions with Grade 1 vascularity were malignant, and 24.0% of the Grade 3 lesions were benign (Table 5).

Discussion and Conclusion

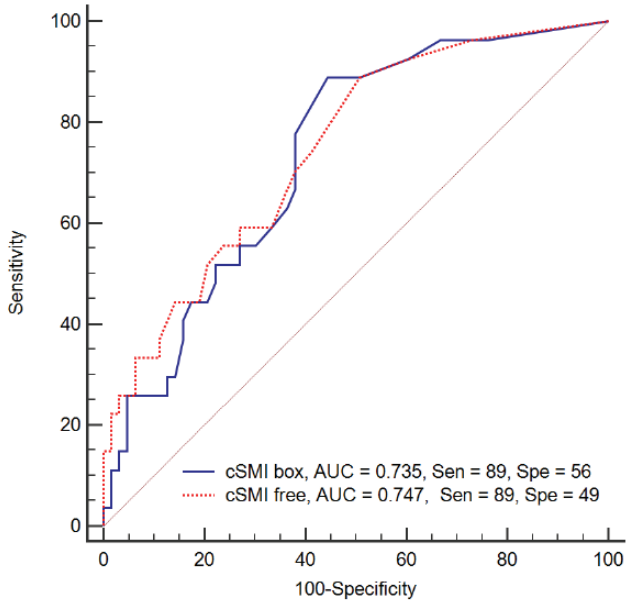
US is the basic imaging modality used for examination of dense breasts with a high degree of fibroglandular tissue components (9). However, descriptive morphological features, such as margin, shape or echo pattern of the lesion do not always provide clear

Table 2. Comparison of vascular index (VI) values of benign and malignant lesions measured by SMI using two modes for defining regions of interest (ROI), box ROI and free-hand ROI

	VI value	
	cSMI box	**cSMI free**
Benign (n=63)		
mean ± SD	1.68 ± 3.21	0.81 ± 1.44
Malign (n=27)		
mean ± SD	4.30 ± 5.51	3.23 ± 4.41
***p-value**	<0.001	<0.001

ROI: region of interest, n: Number of lesions, cSMI box: Box shape ROI. cSMG free: free-hand ROI. SD: Standard deviation

*p<0.05 was considered as statistically significant. Mann Whitney-U was used.



Graph 1. ROC curve for box and free cSMI VI value used in differentiation of benign and malignant lesions

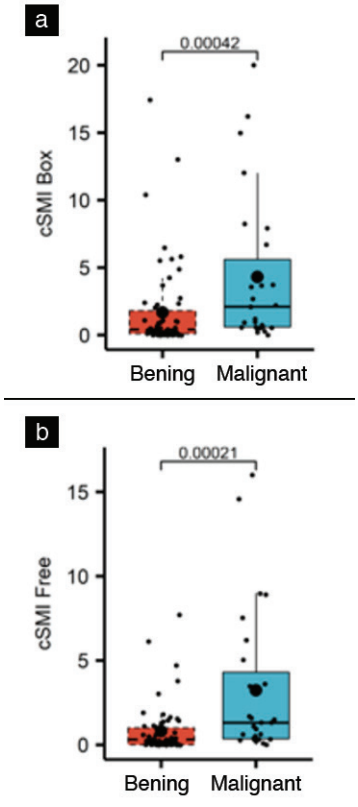
cSMI: Color superb microvascular imaging, cSMI box: Box shaped ROI, cSMI free: Free shaped ROI, ROC: Receiver operating characteristics, Sen: Sensitivity. Spe: Specificity

Table 3. Diagnostic effectiveness of box and free cSMI in differentiating benign and malignant lesions

	cSMI VI value	
	Box	**Free-hand**
Diagnostic measurements (%)		
Cut-off value	≥0.50	≥0.30
TP-FP-FN-TN (subsquently)	24-28-3-35	24-32-3-31
Sensitivity	89	89
Specificity	56	49
NPV	92	91
PPV	46	43
ROC statistics		
AUC	0.735	0.747
*p-value	<0.001	<0.001

cSMI: Color superb microvascular imaging, VI: Vascularity index, ROI: region of interest, Box: Box shaped ROI, Free-hand: Free-hand drawn ROI, TP: True positive value, FP: False positive value, FN: False negative, TN: True negative, NPV: Negative predictive value; PPV: Positive predictive value, ROC: Receiver operating characteristics curve, AUC: Area under the ROC curve

*p<0.05 was considered statistically significant. Mann-Whitney U test was used.



Graph 2. Difference and interactive point graphic for VI value detected by cSMI in benign and malignant lesions

cSMI: Color superb microvascular imaging, VI: Vascular index, cSMI box: box shaped ROI, cSMIfree: Free-hand drawn ROI

information about whether the lesion is malignant or benign. In particular, granulomatous mastitis, atypical hamartoma and some fibroadenomas do not exhibit the characteristics of typical BI-RADS category 3 (10). DM is the most important radiological screening and diagnostic tool that has been proven to increase survival in breast cancer (11). While DM has great sensitivity in fatty breasts, it decreases to 30% in dense breasts. Especially in young patients, DM cannot provide very detailed information and when these patient groups are considered, alternative methods are needed to increase the effectiveness of US (12). Breast MRI has the highest sensitivity for distinguishing breast cancer among the available modern imaging modalities (13). However, performing MRI on every patient is time-consuming and not cost-effective.

Conventional sonographic methods, such as color and power Doppler do not provide the necessary additional information in such breast lesions. Thus, unnecessary biopsies and surgical procedures may be performed. In breast cancer, angiogenic factors and abnormal neovascular vessels develop within the tumoral tissue. For this reason, distorted, folded and deeply penetrating vascular structures are observed around tumoral lesions. Regularly shaped microvessels are observed in benign lesions (14). Thus, attempts have been made to reveal irregular neovascular vessels using complementary methods in addition to US. Conventionally, color Doppler imaging and power Doppler imaging are used to show tissue vascularity. Unfortunately, classical Doppler methods identify the slow flow of microvascular structures as artifacts and therefore erase them (14, 15).

Table 4. Relationship between VI values of benign and malignant lesions and VI values of normal tissue

	Comparison of benign lesion and normal breast tissue		**Comparison of malignant lesion and normal breast tissue**	
	ρ	**p**	**ρ**	**p**
cSMI box	0.095	0.458	0.478*	0.012
cSMI free	0.210	0.098	0.468*	0.014

cSMI: Color superb microvascular imaging, VI: Vascularity index, ρ: Spearman's rho correlation coefficient

*p<0.05 was considered as statistically significant

Table 5. The relationship between monochrome SMI grading and pathological finding

mSMI Grade	**Pathological finding**		**Total lesion (n)**	**p-value**
	Benign	**Malign**		
Grade 1, n	51	3	54	
Grade 2, n	6	5	11	
Grade 3, n	6	19	25	<0.001*
Total lesion, n	63	27	90	

SMI: Superb microvascular imaging, n: Number of lesions

*p<0.05 was considered statistically significant. Chi-square test was used

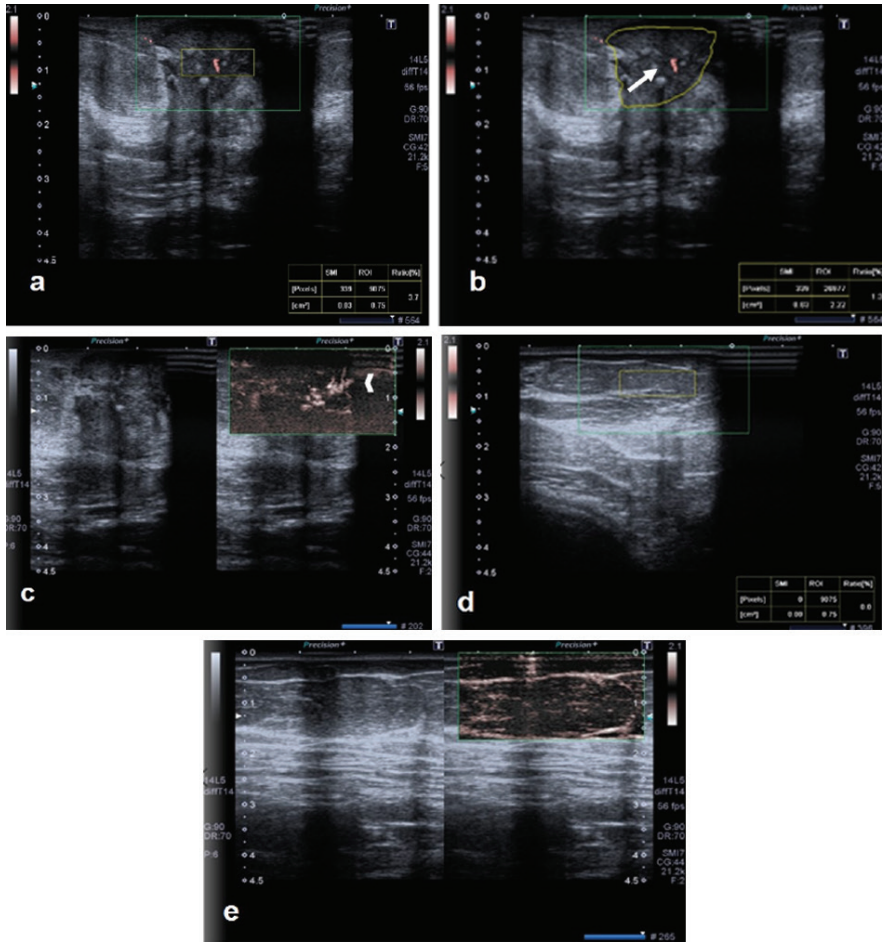


Figure 1. A lesion on the left breast at the 3 o'clock position, vertically located in relation to the skin and with irregular contours, and subsequently, histopathologically proven as invasive ductal carcinoma, is shown. On cSMG examination: **a)** the VI value obtained from inside the lesion using box ROI was 3.7; **b)** the value obtained by using free ROI was 1.3. (arrow); **c)** on mSMG examination, both peripherally and centrally located, irregularly-shaped, microvascular structures are observed (arrowhead). **d)** For normal breast tissue; **e)** the VI values taken with the box ROI are zero

SMG: scintimammography, VI: Vascular index, SMI: Superb microvascular imaging, ROI: region of interest

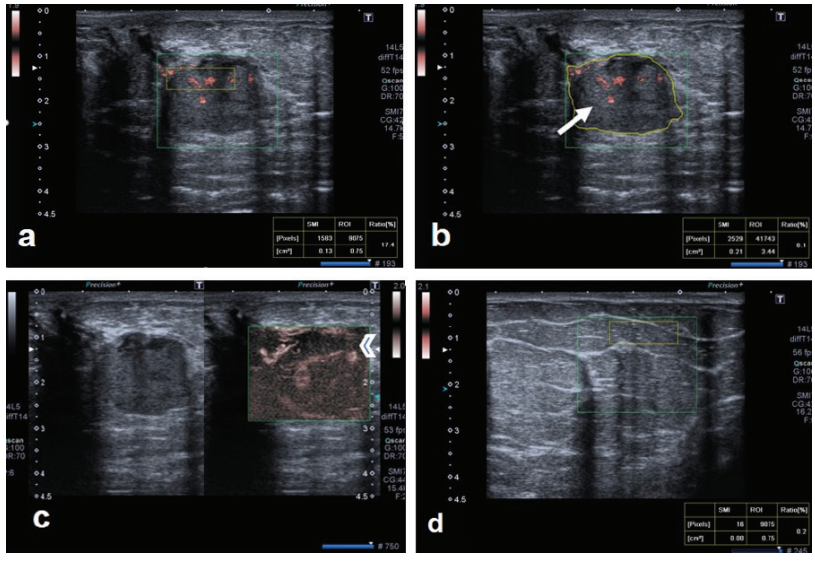


Figure 2. A round-shaped breast lesion, diagnosed as papillary neoplasia after biopsy, at the 9 o'clock position in the left breast. On cSMG examination: **a)** the VI value obtained from inside the lesion using box ROI was 17.4; **b)** the value obtained by using free ROI was 6.1 (arrow). **c)** On mSMI examination, both peripheral and centrally located, irregularly-shaped, microvascular structures were observed (arrowhead). **d)** Box ROI VI value for normal tissue from the same quadrant of the contralateral breast was 0.2.

SMG: scintimammography, VI: Vascular index, SMI: Superb microvascular imaging, ROI: region of interest

While traditional Doppler methods are successful in showing strong flows with high velocity, they are insufficient for showing the slow flow of small vessels (16). The macrovascular structure of the lesion is evident with color Doppler US, while the microvascular structures, found histopathologically, are not visible. Many recent studies have shown that blood supply within the lesion, detected by color and power Doppler US, cannot distinguish benign from malignant lesions (17). It has been shown that the highest diagnostic accuracy is obtained by combining SMI examination with gray-scale US to identify tumor microvasculature (18). Unlike other conventional Doppler methods, the addition of adaptive software in SMI distinguishes the slow flow of microvascular structures from artifact created by tissue movement. However, VI has only been used in a small number of recent SMI studies and in only a few of these the new version of VI, which gives a quantitative value, was used (19-21). In the present study, VI per unit area was measured using SMI, which is superior to conventional Doppler in showing the slow blood flow of microvessels and demonstrated vascularization in tumoral tissue. In a recent study, cSMI values in malignant lesions were reported to be two-fold higher than those in benign lesions (22). In our study, cSMI values were more than two-and-a-half times greater in malignant compared to benign lesions ($p<0.001$). In the present study, specificity for identification of malignant lesions through evidence of irregular vascularity using box ROI was greater than for free-hand ROI and that drawing the lesion circumference by hand using a free-shape ROI did not contribute to determining the vascularity of the lesion. A recent study used a free-hand ROI and the latest version of VI (23). However, in light of our results, drawing lesion contours manually does not appear to contribute any additional data about the nature of the lesion and is more time-consuming. Thus, simply adopting the built-in box ROI feature of the SMI software may be easier and more practical for SMI examination.

A recent study reported that SMI distinguishes benign breast lesions from malignant lesions with 78% sensitivity and 75% specificity (17). Bakdık et al. (5) determined the sensitivity and specificity of SMI to be 66.6% and 80.7%, in a prospective study respectively, in distinguishing malignant intraductal breast lesions. They evaluated a total of 54 intraductal breast lesions and vascularity grading, distribution of microvessels, and penetrating vessels were investigated. Du et al. (18) found that the sensitivity, specificity, and true positivity rates were 93.8%, 86.2%, and 90.2%, respectively. In our study, while the sensitivity was 89% for both ROI types, the specificity was only 56% for box ROI and 49% for free-hand ROI, indicating that SMI has a low ability to discriminate benign lesions in our cohort. In contrast to the limited number of published studies, the specificity of SMI was low in our study, and larger-scale prospective studies are needed to elucidate this issue. Based on SMI findings, Bakdık et al. (5) classified the vascularity of the lesions as low, medium and high. They argued that when distinguishing benign and malignant breast lesions with SMI, the highest success is achieved when vascularity is classified as low or high. Bakdık et al. (5) determined the VI cut-off value to be 0.80 to categorize a breast lesion as hypervascular. In our study with a higher number of patients, the VI cut-off value was 0.73 for box ROI and 0.74 for free-hand ROI. Zhan et al. (24) reported that a VI cut-off value of 0.91 was reliable in distinguishing malignant breast lesions. In our study, the VI value of malignant lesions was higher than that of both benign lesions and normal breast tissue, while, interestingly, the VI values of benign lesions and the VI values of normal breast tissue were similar. Our results show that the cut-off value, which demonstrates the diagnostic efficiency of cSMI in the differentiation of benign and malignant lesions was ≥0.50 for box ROI, while it was ≥0.30 and for free-hand ROI. We believe that these differences suggest that the cutoff values should be calculated for each ROI type.

SMI has two different modes, cSMI and mSMI. Similar to existing studies (16), in our study, while quantitative values of intralesional vascularity were obtained with cSMI, more detailed information was obtained about the morphology of microvascular structures with mSMI. Park et al. (25) reported that detailed examination of microvascular structures with mSMI without contrast agent injection increased the diagnostic performance of US. Another study emphasized that most published studies were based on quantitative measurements using cSMI, and few studies have examined microvascular structures with mSMI (18). In our study, including both qualitative and quantitative evaluations, a relationship was found between the irregular vascularity detected on mSMI and the malignancy of the lesion. We found that as the grade of vascularity detected with mSMI increased, the rate of malignancy increased. However, there was still a degree of false negativity with 5% of the lesions with Grade 1 vascularity being malignant, and 24% of Grade 3 lesions being benign. Studies have shown that microvessels in malignant lesions are tortuous and show irregular and chaotic vascularity (18, 26). Raza et al. (26) reported that small vascular structures in malignant lesions mostly progressed to penetrate deep into the lesion. Moreover, they emphasized the importance of penetrating small vascular structures by stating that they may be the most important clue for malignancy (26). In a recent study, showing penetration of small vessels were more accurate on SMI compared toclassical Doppler methods (24). In addition, it has been reported that there is a decrease in inter-observer variability compared to classical Doppler methods in the detection of penetrating distorted small vessel structures and vascularity assessment. Park et al. (22, 25) reported that if SMI is integrated into the US, SMI decreases the risk level of BI-RADS categories in a significant number of patients and protects patients from unnecessary invasive procedures. As malignant lesions are growing rapidly, necrotic areas may occur within the lesion if the tumoral microvasculature cannot develop sufficiently to feed it. Recent studies have reported that false-negative results can also be obtained in malignant lesions because signals cannot be received with Doppler and SMI from necrotic areas (18). In our study, the false negativity rate of SMI in detecting malignant lesions was found to be 3%.

Our study has some limitations. First, the number of patients included in the study was relatively small. Another limitation was that all patients were evaluated with SMI by a single radiologist and interobserver variability could not be evaluated. In addition, a further significant limitation was the lack of inclusion of MG data and different imaging modalities. Future prospective studies should seek to negate these limitations in their design.

In conclusion, SMI is a promising development to improve the differentiation of malignant and benign breast lesions because of its superiority in imaging microvascular structures in breast lesions. The qualitative and quantitative values obtained from the detailed display of the blood supply in the tumoral tissue can be used as an indirect indicator of abnormal vascularity. Thus, lesions with a high risk for breast cancer can be easily detected with the contribution of SMI and can also serve as a guide for indeterminant lesions. However, prospective studies with larger sample sizes and including comparison

with different modalities are needed to evaluate the effectiveness of SMI in diagnosis of breast lesions.

Ethics Committee Approval: Ethics committee approval was obtained from the Scientific Research Ethics Committee of Selçuk University Faculty of Medicine (decision number: 2018/400, date: 21.11.2018, number of meetings: 2018/22).

Informed Consent: Informed, written consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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Can Skin Sparing Mastectomy and Immediate Submuscular Implant-Based Reconstruction Be a Better Choice in Treatment of Early-Stage Breast Cancer?

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ABSTRACT

Objective: To discuss if skin sparing mastectomy (SSM) with immediate submuscular implant-based reconstruction (IBR) can be the preferred treatment in early-stage breast cancer.

Materials and Methods: Patients treated for clinical *in situ* or early-stage invasive breast cancer with SSM and immediate submuscular IBR between October 2016 and October 2018 were retrospectively evaluated.

Results: Twenty-one cases were reviewed, of whom18 had two-stage and three had one-stage IBR. Median (range) follow-up period was 42 (32–61) months. Five underwent axillary dissection and 1–2 metastatic nodes were found in three (60%). Eight patients (38.09%) with two-stage IBR had radiotherapy because of upstaging and three (37.5%) experienced radiotherapy-linked complications. Rate of complications and mean number of events recorded per patient were higher with radiotherapy. Four patients (44%) had unwanted events after secondary surgery. The mean number of surgeries was higher after two-stage IBR. Mean duration increased in those with chemo-radiotherapy. Six with two-stage and two with one-stage IBR discontinued secondary surgeries.

Conclusion: SSM with immediate submuscular IBR is not suitable in all patients with early-breast cancer. It takes long to have aesthetically pleasing, symmetrical breasts after primary operation because of additional corrective/matching surgeries. Radiotherapy may still be required because of upstaging. Expectation and tolerability of the patient to the process should be evaluated as well as tumor biology and the status of the axilla.

Keywords: breast cancer surgery, immediate breast reconstruction, implant-based reconstruction, direct-to-implant reconstruction, two-stage implant-based reconstructions, breast-conserving therapy

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Key Points

- In early-stage invasive breast cancer, mastectomy protects the patient from radiotherapy and its unwanted effects, if upstaging after surgery is not required.
- SSM with immediate submuscular IBR is oncologically safe, but minor and major complications requiring medical and surgical therapies may result. Two-stage IBR is safer but requires at least two operations and several hospital visits for expander inflations.
- To have esthetically pleasing, soft and symmetrical breasts, several ipsilateral and contralateral secondary surgeries are required, which may also cause unwanted events.
- The long duration to reach a satisfying result, extra payments for surgery and devices, extra operations and multiple hospital visits, together with the stress of the main disease can be stressful. Expectations and tolerability of the patient to the process should be evaluated.

Introduction

In early-stage breast cancer, breast-conserving therapy (BCT), which includes breast-conserving surgery (BCS) and adjuvant radiotherapy, has been preferred to mastectomy as local recurrence rate and overall survival are equivalent. Most patients are pleased to have retained their own breasts but the esthetic outcome is not always satisfying, even after oncoplastic surgery. Fear of recurrence may increase patient stress and exposure of normal tissues to radiation sometimes results in morbidities.

The decision to choose mastectomy has increased in patients with *in situ* and early-stage breast cancer due to increased use of magnetic resonance imaging (MRI) and genetic testing. Skin sparing mastectomy (SSM) with immediate submuscular implant-based reconstruction (IBR) is an oncologically safe alternative (1).

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In this study, in patients requiring mastectomy because of disease- or patient-characteristics for clinical *in situ* and early-stage breast cancer, the outcome of those who were treated with SSM and immediate submuscular IBR were retrospectively evaluated. The aim was to assess if SSM with immediate submuscular IBR was superior to BCT in the treatment of early-stage breast cancer by providing psychosocial and esthetic benefits and by negating the need for radiotherapy for a small mass.

Materials and Methods

Patients operated for clinical *in situ* and early-stage invasive breast cancer between October 2016 and October 2018 were eligible for inclusion. Inclusion criteria were:

1. Clinical *in situ* or early-stage invasive breast cancer with preoperative stages of 0 (TisN0), I (T1N0) and IIA (T0N1, T1N1, T2N0)

2. Treatment with SSM, sentinel lymph node biopsy with or without completion axillary lymph node dissection (ALND) and immediate submuscular IBR using a one-stage or two-stage technique.

3. No systemic metastasis, no neoadjuvant therapy.

All patients were re-examined in the breast clinic in May, 2021.

The clinical staging was performed through physical examination, mammography and ultrasonography. Preoperative MRI for the contralateral breast and positron emission tomography scan were performed in all. Tissue diagnoses were performed through core biopsy, fine needle aspiration biopsy or excisional biopsy in cases with a mass and through stereotactic excision in cases with microcalcifications or occult masses.

The choice of mastectomy instead of BCT was made in conjunction with the patient, taking into account lesion characteristics, presence of family or personal history, patient's fear of recurrence and/or in order to avoid radiotherapy. None of the patients had a preoperative genetic test. SSM was performed with removal of the nipple-areolar complex (NAC). Removal of the NAC was decided by the patient to eliminate the risk of recurrence and the need for adjuvant radiotherapy. Nipple-sparing mastectomy (NSM) was performed when prophylactic removal of the contralateral breast was performed and there was minimal risk of malignancy or the need for radiotherapy.

Mastectomy was conducted with the pectoral fascia through the subcutaneous adipose tissue. In NSM, the NAC was spared with a thickness of about 2 cm. Sentinel node biopsy was performed through subareolar injection of methylene blue dye. The sentinel nodes were removed through an axillary incision and examined by both intraoperative imprint and postoperative immunohistochemistry. Levels 1–2 completion ALND was added in all cases with any macrometastasis in sentinel nodes and a suction drain was positioned in the axilla. Thoracodorsal vessels were spared if possible.

IBR and all esthetic surgery was performed by the reconstructive surgeon. Two-stage reconstruction was preferred when the surface area was insufficient or when postoperative radiotherapy was expected. A subpectoral pocket was prepared in the avascular plane between the pectoralis major and minor muscles. The lower pole was covered by the elevated serratus anterior muscle or its lower slips. In patients with ptotic breasts, skin reduction was added and inferior dermal-adipose flap was also prepared by deepithelization of the inferior skin. Non-autologous materials to cover the prosthesis were not used in the diseased side, because of the risk of complications delaying adjuvant therapies. The costs of the initial reconstruction and the prosthetic devices were paid for by the Social Insurance Institution (SGK).

Two suction drains were placed, one in the surgical pocket and the other above the muscle, which were removed when the drainage decreased to less than 30 mL/24 hours. In-patient follow-up occurred in the plastic surgery department for 3–5 days. Antibiotic prophylaxis was started half an hour before the induction of anesthesia and was continued up to the removal of the drains. Supportive brassieres were worn in the operation room and continued through the first two months postoperatively. The tissue expander (TE) was filled with saline once a week after the first fill in the operation room. Inflations were carried on during chemotherapy. Exchange to a permanent implant (PI) was performed after adequate size was achieved by multiple inflations. The PI was postponed until completion of chemotherapy and, when radiotherapy was planned, 4–6 months after completion of radiotherapy.

The necessity and timing of the other esthetic procedures were decided on a per patient-basis by the reconstructive surgeon. Autologous fat grafting was performed under general anesthesia (UGA) to the subcutaneous plane to correct breast contours and deformities. NAC reconstruction included C-V flap for the nipple and tattooing to the nipple/areola. Contralateral matching surgery was performed to correct asymmetry. In contralateral NSM, the PI was placed into the subcutaneous area and covered with biological matrix, which was derived from acellular bovine pericardium.

The requirement for and type of adjuvant therapies were determined by the institutional oncology council. Postmastectomy radiotherapy (PMRT) was applied as intensity-modulated radiotherapy (IMRT) after completion of chemotherapy. Hormone therapy was given when estrogen and/or progesterone receptors were positive. Patients were followed by an oncologist every three months, by the surgeon every six months and, when on hormone therapy, by the gynecologist every six months. The reconstructive surgeon determined appropriate intervals for follow-ups.

This study was approved by the institutional Ethics Committee for Clinical Researches (HNEAH-KAEK 2020/168).

Results

In total, 21 cases were included in the retrospective analysis. The median (range) age and follow-up period were 48 (37–67) years and 42 (32–61) months, respectively. Six patients (28.57%) had a previous history of breast cancer. One had a personal history of contralateral breast cancer. Contralateral mastectomy was added in two cases, one for contralateral widespread microcalcifications and the other for contralateral fibroadenomatosis with ipsilaretal invasive lobular carcinoma (Table 1).

Completion ALND was performed in five (23.8%) cases. Total numbers of metastatic lymph nodes found were 5/13, 3/15, 2/17, 1/11 and 1/16 (Table 2). Upstaging after surgery was necessary in eight cases (38.09%), four in the nodal stage, one in the tumor stage and three for both nodal and tumor staging (Table 3).

All had SSM for the tumor side with submuscular IBR (18 two-stage IBR and 3 one-stage IBR). Two women requiring contralateral

mastectomies underwent SSM in Case 1 and NSM in Case 7 with submuscular two-stage IBR.

Thirteen patients with TE had adjuvant chemotherapy (61.90%) and eight (38.09%) also had adjuvant radiotherapy. Adjuvant chemotherapies were not delayed beyond 1.5 months after the tumor operation (Table 4). Hormone therapy was given to 19 (90.47%) patients. In the remaining two patients, one was hormone-negative and the other had received anti-estrogen therapy previously. At the time of writing, all 21 patients are alive and disease free.

Mean implant size was 346.66 mL (between 300 mL and 390 mL) in one-stage and 519.70 mL (between 375 mL and 700 mL) in two-stage cases. Median mean intraoperative fill volume was 141.76 mL (between 20 mL and 350 mL) and mean number of fills to complete expansion was 7.85 (between 3 and 14). Replacement of the TE with a PI was performed successfully in 14 out of 18 cases. Case 4 is scheduled to have a third PI after removal of the preceding two. Two patients needed removal of the TE because of rupture and one refused the exchange of the inflated TE with a PI.

Complications after primary and secondary surgeries are shown in Table 5.

Seven events were detected in 3/8 (37.5%) patients who had adjuvant radiotherapy over the subpectoral TE. Case 2 had placement of a new TE and scoring of the capsule. Case 13 had capsulotomy. In Case 4, exposure of the PI was detected four months after placement and fat grafting. The latissimus dorsi muscle was atrophic and a new PI was placed, which was removed one month later due to wound dehiscence, infection and abscess.

In 6/18 (33.3%) patients with two-stage reconstruction, complications unrelated to radiation were observed. Dermatitis concurrent with cellulitis was treated with long-term medical therapies. Skin flap ischemia was treated by excision. Ruptured TE was exchanged with a PI in one and removed in two cases. Capsulotomy was performed for capsular contracture. Among the three patients with one-stage reconstruction, two (66.6%) had skin flap ischemia and one (33.3%) progressed to wound dehiscence. None of the patients had grade IV capsular contracture. Mild to moderate contractures were managed during operations performed for other reasons.

Ipsilateral fat grafting was performed in 12 patients; more than once in three. Dermatitis detected after nipple reconstruction occurred in Case 5 and lasted one month; skin biopsy revealed no malignancy.

Breast-matching surgery was required in 19 cases with unilateral operation. Contralateral NSM and subcutaneous one-stage IBR with acellular matrix was performed 10 months after mastopexy in Case 2, to eliminate the deformities produced by macrocysts, and in Case 16, to relieve the patient's anxiety about contralateral recurrence. Postoperative infection was managed by medical therapy

Table 1. Patient characteristics and co-morbidities with breast signs

Case number	Age of diagnosis (year)	Pre-menopausal	Cancer History	Co-morbidities	Breast sign
1	62	No	Family	DM	Mass Calcifications
2	47	Yes	-	-	Mass
3	65	No	-	-	Mass
4	37	Yes	-	Smoking	Mass
5	46	Yes	-	-	Mass
6	48	Yes	-	-	Calcifications
7	43	Yes	-	-	Mass Mass
8	56	No	Personal	-	Calcifications
9	51	Yes	Family	-	Mass
10	43	Yes	-	DM	Mass
11	41	Yes	-	HT	Mass
12	46	Yes	-	Smoking	Mass
13	48	Yes	-	-	Mass
14	67	No	Family	DM, HT, HF	Mass
15	54	No	-	-	Mass
16	48	Yes	-	-	Mass
17	52	No	-	HT	Calcifications
18	45	Yes	-	-	Mass
19	45	No	Family	-	Mass
20	45	Yes	Family	DM	Mass
21	48	Yes	-	-	Mass

DM: Diabetes mellitus, HT: Hypertension, HF: Heart failure

and debridement on three occasions in one. However, in the other case, removal of the PI was required followed by placement of a TE. Capsulorrhaphy was performed for exposition of the contralateral implant placed during augmentation mammoplasty.

In total 6/18 (33.3%) who had two-stage reconstruction declined to have the complementary and/or corrective surgery. Among the three patients who refused the second stage, one continued with the expanded TE, and the other two opted for no prosthesis. Two of three (66.6%) patients with one-stage reconstruction refused all secondary surgery (Table 6).

In patients who completed all the surgery, the mean number of operations UGA and the mean duration are detailed below. One patient with one-stage IBR had four operations UGA within 19 months. The mean (range) number of operations UGA in nine patients with two-stage procedure was 3.5 (2–8). The mean (range) duration in these was 17.5 (11–24) months in two patients who did not receive chemo-radiotherapy, 18 (12–23) months in four patients requiring chemotherapy and 29.3 (24–39) months in three patients requiring chemo-radiotherapy. The mean (range) number of operations performed UGA in the three patients who have not yet completed because of complications is 4.6 (3–7).

Discussion and Conclusion

SSM with immediate IBR has a local recurrence rate ranging between 0% and 8.3%. Recurrence occurs in the subcutaneous tissue at the tumor location in 82%. Survival and local recurrence rates are not worse after NSM, although some glandular tissue is left *in situ* with the NAC to prevent ischemia (2). The inferolateral pole of the subpectoral implant may be covered with biological matrices or synthetic meshes

Table 2. Clinical and pathological stages with tumor characteristics

Case number	Clinical stage	Pathological stage	Histological type	Tumor subtype	Ki-67 value (%)
1	IL:T1 N0 M0	IL:T1c N0 Mx	IDC	Luminal A	28.8
	CL:Tis N0 M0	CL:Tis N0 Mx	DCIS	ER/PR+	DCIS
2	T2 N0 M0	T3mf N0i+ Mx	IDC	Luminal A	14.2
3	T2 N0 M0	T2mf N1mi Mx	ILC	Luminal A	40
4	T2 N0 M0	T2 N1a Mx	IDC	Luminal A	20-25
5	T1 N0 M0	T2 N1a Mx	IDC	Luminal A	30–40
6	T1 N0 M0	T1a N0 Mx	ILC+ DCIS	Luminal A	<5
7	IL:T1 N0 M0	IL:T1b N0 Mx	ILC+ LCIS	Luminal A	2–3
	CL:Benign	CL:Benign	Benign	Benign	Benign
8	Tis N0 M0	Tis N0 Mx	DCIS	ER/PR+	DCIS
9	T2 N0 M0	T3 N2a Mx	Mixed	Luminal A	25–30
10	Tis N0 M0	Tis N0 Mx	DCIS	ER/PR+	DCIS
11	T1 N0 M0	T1c N0 Mx	IDC+DCIS	Luminal A	20–25
12	Tis N0 M0	Tis N0 Mx	DCIS	ER/PR-	DCIS
13	T1 N0 M0	T1c N1a Mx	IDC	Luminal A	10
14	T1 N0 M0	T1c N0 Mx	IDC	Luminal A	7–8
15	T2 N0 M0	T2mf N1mi Mx	IDC	Luminal A	30–40
16	T1 N0 M0	T2mf N1a Mx	IDC	Luminal A	10
17	T1 N0 M0	T1a N0 Mx	IDC+DCIS	Luminal A	Unknown
18	T2 N0 M0	T2 N0 Mx	IDC+DCIS	Luminal A	9.4
19	T1 N0 M0	T1c N0i+ Mx	ILC	Luminal A	10–15
20	T1 N0 M0	T1b N0 Mx	IDC	Luminal A	7–8
21	T1 N0 M0	T1b N0 Mx	IDC	Luminal A	10

IL: Ipsilateral breast, CL: Contralateral breast, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, Mixed: Mixed invasive ductal and invasive lobular carcinoma, DCIS: Ductal carcinoma *in situ*, LCIS: Lobular carcinima *in situ*, ER: Estrogen receptor, PR: Progesterone receptor

Table 3. Number of patients according to the preoperative clinical and postoperative pathological stages

Stages	Stage 0 (n)	Stage I (n)	Stage IIA (n)	Stage IIB (n)	Stage IIIA (n)
Clinical	3	12	6	-	-
Pathological	3	9	2	6	1

(3). In the current case series the NAC was removed, ischemic areas were excised early and autologous tissues were used instead of external materials for coverage of the prosthesis. Consequently, adjuvant therapies were started promptly, despite various complications, and no patient had local or systemic recurrence at a mean follow-up period of 43.38 months.

In early-stage invasive and *in situ* tumors, 65% of immediate reconstructions in mastectomies are IBRs (4). Two-stage reconstruction is preferred when postoperative radiotherapy is probable. One-stage reconstruction is performed in thin women with small-to-medium, nonptotic breasts when radiotherapy is not expected (5). We performed two-stage IBR in 18 patients who might upstage and one-stage procedure in three patients who were not expected to have radiotherapy. The mean size of the prosthesis in the two-stage procedure was larger.

In patients with lumpectomy who will receive whole breast irradiation, completion ALND is indicated only when three or more sentinel nodes are metastatic or when there are matted nodes intraoperatively (6). The ongoing SENOMAC trial has been randomizing mastectomy patients to either ALND or no ALND (7). The current approach in patients with mastectomy is completion ALND in the presence of any macrometastasis. Our five patients had completion ALND, and in three (60%), 1 or 2 metastatic nodes were found. If these patients had undergone BCS, they could have avoided ALND and, if tumor biology was favorable, also avoided axillary irradiation. Postponing the analysis of the sentinel nodes to the postoperative period and giving axillary irradiation instead of ALND is another option in patients with mastectomy.

Mastectomy protects the patient from receiving radiotherapy for a small mass with good prognostic features. Radiotherapy makes the resected breast smaller, darker and tough. Exposure of nearby organs can cause rare, aggressive tumors, such as angiosarcoma and myeloid neoplasms, pneumonitis and pulmonary fibrosis, cardiac failure, brachial plexopathy and lymphedema (8, 9). Normal tissues can be protected, to some extent, by intraoperative localization of the tumor bed, giving IMRT and using additional techniques during the procedure (10). In older patients, bypassing radiotherapy or giving partial-breast irradiation is controversial (11).

In the present series 13 (61.90%) patients avoided radiotherapy and its adverse effects by undergoing SSM. Eight (38.09%) patients upstaged and received radiotherapy. PMRT protects from recurrences but nearby organs are exposed to significant amount of radiation (12).

Table 4. Type of primary cancer surgery, prosthesis used, adjuvant therapies and follow-up period

Case number	Primary surgery	Adjuvant CT	Adjuvant RT	Adjuvant HT	Follow-up (month)
	SSM+ SLNB+TE				
1	SSM+ SLNB+TE	No	No	+	61
2	SSM+ SLNB+TE	ST	+	+	48
3	SSM+ SLNB+TE	ST	+	+	47
4	SSM+ ALND+TE	ST	+	+	46
5	SSM+ ALND+TE	ST	+	+	57
6	SSM+ SLNB+PI	No	No	+	33
	SSM+ SLNB+TE				
7	NSM+SLNB+TE	A	No	+	56
8	SSM+ SLNB+TE	No	No	No	57
9	SSM+ ALND+TE	ST	+	+	44
10	SSM+ SLNB+TE	No	No	+	43
11	SSM+ SLNB+TE	A	No	+	42
12	SSM+ SLNB+TE	No	No	No	42
13	SSM+ ALND+TE	ST	+	+	42
14	SSM+ SLNB+TE	No	No	+	42
15	SSM+ SLNB+TE	ST	+	+	42
16	SSM+ ALND+TE	ST	+	+	38
17	SSM+ SLNB+PI	No	No	+	36
18	SSM+ SLNB+TE	ST	No	+	34
19	SSM+ SLNB+TE	A	No	+	35
20	SSM+ SLNB+PI	No	No	+	34
21	SSM+ SLNB+TE	A	No	+	32

SSM: Skin sparing mastectomy, NSM: Nipple sparing mastectomy, SLNB: Sentinel lymph node biopsy, ALND: Axillary dissection, TE: Tissue expander, PI: Permanent breast implant, CT: Chemotherapy, RT: Radiation therapy, HT: Hormone therapy, ST: Sequential use of anthracycline and taxane containing regimens, A: Antracycline regimen

A carefully performed axillary ultrasound and a core biopsy giving detailed information of the tumor can prevent upstaging. Preoperative ultrasound and positron emission tomography were available in all patients in the present series. An additional ultrasound by the surgeon as an additional check may be safer. The author now confirms preoperative staging by performing an additional ultrasound herself.

In patients with reconstruction, complications and implant failure are detected more frequently when radiotherapy is necessary. The rate of implant failure is higher when TE placement occurs after radiotherapy (13). Giving radiotherapy over the submuscular TE and then replacing it with a PI, with or without latissimus dorsi flap, will be safe. PMRT was given to eight patients who had submuscular TE. Three (37.5%) had unwanted events requiring surgical correction. Four of the seven events were detected in one patient and resulted in implant failure. In this case the latissimus dorsi muscle was atrophic. In our patients with two-stage IBR, both the rate of complications requiring surgical corrections and the mean number of events recorded per patient were higher in the eight patients who had radiotherapy than in 10 patients without radiotherapy (37.5% vs. 27.7% and 2.3vs. 1.5, respectively).

Even if no radiotherapy was administered, SSM with submuscular IBR may result in unwanted events, such as hematoma, seroma, skin flap necrosis, infection ranging from cellulitis to sepsis, wound dehiscence and exposure. Explantation is reported to result from infection in 21% of cases (14). The long-term events may include rupture and deflation of the prosthesis, exposition with asymmetry, capsular contracture, impaired contour, chronic pain and discomfort (15). Besides radiotherapy, obesity, diabetes, smoking, and steroid administration increase complication risk (3). In patients not requiring radiotherapy, the risk for any complication is 52.4% in the first year and 76.4% within 8 years. The reoperation rate is reported to increase from 23.3% within the first year to 40.6% within 8 years. Skin-flap necrosis, reoperation and extrusion of the implant were more common after one-stage reconstruction (14, 16). In our cases who did not have radiotherapy, events requiring surgical corrections in five two-stage IBR patients were: skin flap ischemia; rupture of the TE; and capsular contracture. In two one-stage IBR patients these events included skin flap ischemia and wound dehiscence. In the present case series skin flap ischemia was more common in one-stage IBR (66.6% vs. 11.1%, respectively).

Table 5. Unwanted events after primary and secondary surgeries in patients with one-stage reconstruction and in those with two-stage reconstruction with and without radiotherapy, and completion of surgeries

Status		Case number	IL events after primary surgery	CL events after matching surgeries	Completion of the surgeries
no CT/RT	One-stage	6	Skin flap necrosis/ dehiscence	-	Discontinued
		17	-	Hematoma	Completed
		20	Skin flap necrosis	-	Discontinued
	Two-stage	1	Cellulitis/dermatitis	-	Completed
		8	Skin flap necrosis/TE rupture	-	Discontinued
		10	TE rupture/ TE removal	-	Discontinued
		12	-	Exposition of PI	Completed
		14	-	-	Discontinued
CT	Two-stage	7	Capsular contracture (BII/III)	-	Completed
		11	-	-	Completed
		18	-	-	Discontinued
		19	-	-	Completed
		21	-	-	Completed
CT + RT	Two-stage	2	TE exposition/capsular contracture (BII/III)	NAC ischemia, infection, Dehiscence	On going
		3	-	-	Discontinued
		4	PI exposure/infection/ dehiscence/PI removal	-	On going
		5	Dermatitis	-	Completed
		9	-	-	Completed
		13	Capsular contracture (BII/III)	-	Completed
		15	TE rupture/TE removal (before RT)	-	Discontinued
		16	Skin flap necrosis (before RT)	NAC ischemia/PI exposure, infection, PI removal	On going

CT: Chemotherapy, RT: Radiotherapy, TE: Tissue expander, PI: Permanent implant, IL: Ipsilateral breast, CL: Contralateral breast, NAC: Nipple-areolar complex, Capsular contracture (BII/III): Mild to moderate contracture (Baker classification, grade II-III)

Complications may occur when no breast tissue is left under the thin skin envelope, when the pectoral fascia is removed, or when using complete muscular coverage without an acellular matrix, in addition to other, patient-linked factors. The necessity of removing the pectoral fascia in tumors distant from the fascia is debatable. Case 1, who developed prolonged infection, had diabetes.

Secondary surgery is required following SSM and immediate submuscular IBR in order to achieve esthetically pleasing, soft and symmetrical breasts. These secondary surgeries might include autologous fat grafting, NAC reconstruction, and breast-matching surgery for ptotic, larger or smaller contralateral breasts (17). We performed ipsilateral fat grafting in 12 patients, NAC reconstruction in 10 and contralateral matching surgery in 11.

Secondary surgery may also result in unwanted events. Four patients (44%) had events after contralateral matching surgery, two after reduction and augmentation mammoplasties and two after NSM. Acellular matrix, derived from bovine pericardium, was used for coverage of the subcutaneous PI in those with NSM and both had NAC ischemia and infection, resulting in implant failure in one. Subcutaneous PI is usually covered with acellular dermal matrix (ADM) which relieves the pressure on the skin flaps and provides more natural pseudo-ptosis and inferior pole projection compared to a submuscular pocket (18). It decreases the rate of capsular contracture but causes increased seroma formation, implant failure, partial NAC necrosis and rippling (19).

Unwanted events increase both the number of surgeries requiring general anesthetic and the duration before a satisfying result is achieved for the patient. In patients who completed all surgery, the mean number of surgeries UGA was slightly lower in nine patients with two-stage reconstruction compared to one patient with a one-stage procedure (3.5 vs. 4.0, respectively). The mean duration for completion of all surgery was greater in two-stage patients who had chemo-radiotherapy compared to those who did not. In the three patients undergoing two-stage procedure but who have not yet completed because of complications, the mean number of surgeries was already 3.83 at a mean duration of 43.33 months post initial operation.

Submuscular two-stage reconstruction is safer in cancer patients, but it requires at least two operations with several outpatient visits for expander inflation. ADM-coverage of the lower pole provides more rapid filling, and prevents displacement. ADM use increases the mean intraoperative fill volume from 130.4 mL to 412.5 mL and decreases the number of fills needed from 4.3 to 1.7 (20). We did not use ADM on the diseased side and the mean intraoperative fill volume was 141.7 mL and the mean number of fills was high at 7.85. Rupture of the TE was observed in 16.6%.

SSM and immediate submuscular IBR negate the necessity of having radiotherapy for a small mass and relieve anxiety about recurrence. However, this technique may result in unnecessary ALND, PMRT because of upstaging, extra hospital visits, and extra surgeries UGA, both for complications and to achieve an acceptable appearance. Too many hospital visits, the discomfort from the implants, as well as the cost of secondary surgery and materials may result in exhaustion of the patient, which in turn can lead to discontinuation of secondary surgery or failure to attend follow-up for breast cancer, which is clearly undesirable. The discontinuation rate in our series was 33.3% in patients with two-stage procedures and 66.6% in patients with direct-to-implant IBR.

Although the number of patients in this series was low, it is evident that SSM and immediate submuscular IBR is not suitable in all patients with early-breast cancer. It is important to choose the right patient

Table 6. Performance of primary and secondary surgery

Type of surgery		Two-stage IBR without RT	Two-stage IBR with RT	One-stage IBR
Primary surgery	Number of patients	10	8	3
	Exchange of TE to PI	8	7	-
Secondary surgery performed	IL fat grafting	6	6	
	IL IMF	2		1
	IL NAC	6	3	1
	CL mastopexy	2	1	
	CL augmentation	1	2	
	CL reduction	2	2	1
	CL NSM with subcutaneous PI		2	
	CL IMF	2		
Other surgery	Rhinoplasty	1	1	
Surgery declined	Replacement of TE with PI	2	1	-
	NAC	1		
	NAC and CL corrective surgery	1		
	NAC, IL and CL corrective surgery			2

IBR: Implant-based reconstruction, RT: Radiotherapy, TE: Tissue expander, PI: Permanent implant, IL: Ipsilateral, CL: Contralateral, NAC: Nipple-areolar complex reconstruction, IMF: Inframammary fold repositioning, NSM: Nipple-sparing mastectomy, ADM: Acellular dermal matrix

for the procedure, not only with ultrasound and core biopsy, but also by evaluating the expectations and tolerability of the patient to the process. Cancer patients are very different from patients undergoing reconstructive surgery. It may be better to provide good appearance and an early return to normal life rather than trying to achieve a perfect reconstruction with multiple surgeries, except for those young and tolerant patients with high cosmetic expectations.

Ethics Committee Approval: This study was approved by the institutional Ethics Committee for Clinical Researches of University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK 2020/168).

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Original Article

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An Open-Label, Multinational, Multicenter, Phase IIIb Study with Subcutaneous Administration of Trastuzumab in Patients with HER2-Positive Early Breast Cancer to Evaluate Patient Satisfaction

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ABSTRACT

Objective: This study was designed to investigate treatment satisfaction in patients and Health Care Professionals (HCP) and to evaluate the safety and tolerability of subcutaneous (SC) trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (eBC).

Materials and Methods: Two-hundred and twenty-three patients with eBC were screened, of whom 173 patients met the eligibility criteria and received at least one dose of SC trastuzumab. The primary efficacy endpoint was to assess patient satisfaction via a questionnaire.

Results: The majority of patients (n = 166, 97.6%) reported satisfaction with the SC route. Patients and HCPs stated that SC trastuzumab was easy to use (93.5% and 62.5%, respectively) compared to the intravenous (IV) route and all HCPs (n = 16) expressed satisfaction with the SC route. Progression, disease recurrence or death was reported in 24 patients (13.8%) by two years of follow up. Four-year disease-free survival (DFS) and overall survival (OS) rates were 84.2% (±3.1) and 90.5% (±4.7), respectively. A total of 1299 adverse events (AEs) were recorded over 4-years follow-up, nearly 97% of which were judged non-serious. The most common AEs were arthralgia (n = 54, 4.2%), flu-like symptoms (n = 41, 3.2%) and nausea (n = 39, 3.0%). Fifty-four cardiac events, including left ventricular dysfunction, left ventricular failure and cardiotoxicity, were reported. Ejection fraction (EF) decrease [median decrease 3.5% (0.12–19.0)] was reported in 5.4% of cases. SC trastuzumab treatment was interrupted due to decreased EF in two cases.

Conclusion: SC trastuzumab was widely acceptable to both patients and HCPs. The safety and tolerability of SC trastuzumab was consistent with the known safety profile of SC and IV administration.

Keywords: subcutaneous, trastuzumab, breast cancer, HER2, patient satisfaction

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Key Points

- SC injection of trastuzumab was easy and satisfactory for both patients and healthcare professionals.
- A high percentage of patients receiving adjuvant therapy preferred subcutaneous trastuzumab over intravenous administration.
- The safety and tolerability of subcutaneous trastuzumab was consistent with the known safety profile for subcutaneous and intravenous administration.

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Introduction

Breast cancer (BC) is the most common cancer diagnosed among women and is the fifth leading cause of cancer deaths worldwide (1). Globally, there were 2.1 million new BC cases and 626,679 BC-related deaths reported in 2018, representing nearly 11.6% of all new cancer cases and 6.6% of cancer-related deaths.

Approximately 20% of BCs are characterized by amplification and/or overexpression of human epidermal growth factor receptor 2 (HER2, also called ErbB2), which is associated with poor prognosis and survival (2, 3). Trastuzumab, a humanized monoclonal antibody that targets and binds the HER2 protein, was approved by the US Food and Drug Administration (FDA) for therapeutic use in cases of metastatic BC in 1998 and HER2-positive eBC in 2006 (4, 5). Various randomized trials have shown that adjuvant trastuzumab for HER2-positive eBC improved disease-free survival (DFS) and overall survival (OS) (6, 7). Currently, adjuvant treatment with trastuzumab is a well-established treatment in HER2-positive eBC.

Trastuzumab was first licensed in clinical practice as an intravenous (IV) formulation, and in August 2013 subcutaneous (SC) trastuzumab (Herceptin® SC), which contains a fixed dose of 600 mg/5 mL and recombinant human hyaluronidase PH20, was authorized by the European Medicines Agency (EMA) (8), providing a shorter administration duration of 2 to 5 minutes, while the IV formulation is administered as a 90-minute infusion (9). Besides clinical benefits and a good tolerability profile, SC trastuzumab treatment may be associated with cardiac toxicities such as congestive heart failure (CHF), which may require close monitoring of left ventricular ejection fraction (LVEF) in all patients before and during treatment (10).

The Hannah study indicated that SC trastuzumab was non-inferior to IV formulation with a similar safety profile, and the PrefHer study showed that SC trastuzumab was the preferred treatment option among patients and health care professionals over IV administration (11, 12). Considering the two equally safe formulations of trastuzumab, patients' and health care professionals' (HCP) preference may be related to the improvement in quality of life, ease of administration and overall satisfaction with SC trastuzumab treatment.

This study was conducted as part of a global umbrella study "UmbHER1", which consists of a family of multiple studies with similar design, including MetaspHER (13), BELIS (14), Schearly (15) and SAPPHIRE (16), to assess the safety and tolerability of trastuzumab solution injected subcutaneously [vial or single-use injection device (SID)] in patients with HER2-positive BC. The preference of patients and HCPs was evaluated by implementing an in-house developed questionnaire for testing patient- and HCP-reported outcomes in terms of overall satisfaction and treatment experience with SC trastuzumab at hospitals in patients with HER2-positive eBC conducted as a daughter study of the umbrella program.

Materials and Methods

Study design and patient population

The ML28851 study is a Phase IIIb, open-label, multinational, multi-center study to assess patient satisfaction with, HCP experience, and safety and tolerability of trastuzumab solution injected subcutaneously (SC; vial) in patients with HER2-positive eBC in a (neo)adjuvant setting.

Eligible patients were women and men aged 18 years or older with HER2-positive (immunohistochemistry 3+ or positive by *in situ* hybridization), histologically confirmed, non-metastatic primary invasive breast carcinoma with no evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy (neoadjuvant or adjuvant), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a baseline LVEF of 55% or more before the first dose of trastuzumab. HER2-positivity was assessed by local laboratories using a validated assay. Radiotherapy and/or hormone therapy were allowed. Patients could have been either trastuzumab-naïve or already received IV trastuzumab following neoadjuvant or adjuvant chemotherapy. All patients provided written informed consent. Approval for the protocol was obtained from the appropriate ethic s committees and regulatory authorities. This study was approved by the Ethics Committee of Hacettepe University, with the registration date: 03.10.2013/decision no: 2013/12-06 (KA-120089); (ClinicalTrials.gov Identifier: NCT01964391).

Procedures

SC trastuzumab was administered via a hand-held syringe over a period of 5 minutes with a fixed dose of 600 mg/5 mL (including 10,000 units rHuPH20; irrespective of body weight) throughout the study every 3 weeks (q3w) for up to 18 cycles. Dose reductions were not permitted. For non-naïve patients, the duration of SC trastuzumab treatment was expected to be shorter.

The primary objective of the study was the assessment of patient satisfaction by an internally developed Patient Satisfaction Questionnaire (PSQ) that consisted of 20 questions. The secondary objectives were the assessment of the safety and tolerability of SC trastuzumab treatment along with the overall satisfaction of HCPs via an HCP Experience Questionnaire comprising 14 questions. Both questionnaires were completed at the end of the treatment period, and the questionnaires themselves have been added to the manuscript as supplementary material. For the assessment of survival, a follow-up period of up to four years was defined for the evaluation of overall survival (OS) and disease-free survival (DFS).

Assessments

All enrolled patients who received at least one dose of the study medication (SC trastuzumab) were included in the safety population, and adverse events (AEs) and serious adverse events (SAEs) were monitored and documented at each tri-weekly treatment visit and during the safety follow-up visits. AEs and SAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.0; congestive heart failure (CHF) was classified using the New York Heart Association (NHYA) functional classification.

Cardiac function was monitored by measuring left ventricular ejection fraction (LVEF) using echocardiography or a multigated acquisition (MUGA) scan and electrocardiogram (ECG), and assessment of cardiac signs and symptoms. Cardiac safety assessments were performed at screening visits, approximately every three months during SC trastuzumab treatment, during the safety follow-up visits, and then at 6, 12 and 24 months after treatment cessation.

Statistical Analysis

The sample size calculation was based on the patient satisfaction rate defined for subcutaneous trastuzumab (75%), and to achieve adequate

power, a minimum 162 patients should be enrolled. Descriptive statistical methods were used to analyze and report the results of this single-arm study. Patient satisfaction was evaluated in the intention-to-treat (ITT) population who completed the PSQ (n = 171). HCP treatment satisfaction was evaluated among responding investigators (n = 16/30). Safety analyses were conducted in patients who received at least one dose of SC trastuzumab (n = 173), and AEs were graded per standard criteria. The Kaplan-Meier method was used to estimate the median DFS and OS. Hazard ratios (HRs) from timewise comparisons of results were estimated by Cox proportional hazards regression. Statistical analyses were performed with the Stata software (version 10.0).

Results

Study Population and Demographics

Between February 21, 2014, and November 12, 2018 (data cut-off date), a total of 174 patients (ITT population) were randomly assigned by 30 HCPs at 25 centers in Turkey, Algeria, Saudi Arabia, Morocco, and Tunisia. One patient was excluded due to violation of eligibility criteria after randomization. One hundred and seventy-three patients received at least one valid dose of SC trastuzumab and comprised the safety population. At the time of data cut-off, 148 patients (85.5%) had completed treatment as per protocol and were alive (Figure 1).

The median (range) age of patients was 49.5 (28–86) years. Left-breast cancer was more frequent (52.9%), and 13.2% had previously received radiotherapy before the initiation of trastuzumab treatment. The mean (± SD) primary tumor size was 35.3 (±29.1) mm (range: 2.1–250 mm) in terms of maximum diameter, and 162 (93.1%) patients were diagnosed with ductal carcinoma. Baseline demographics and tumor characteristics are shown in Table 1.

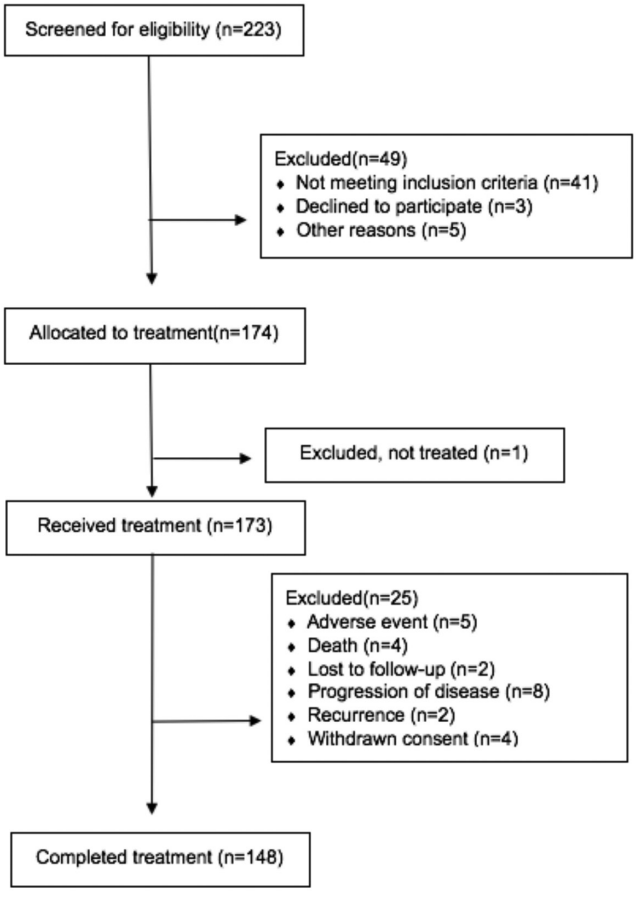


Figure 1. Trial profile

Table 1. Baseline demographics and tumor characteristics

Variable	(n=174)
Age (years)	
Mean (SD)	49.3 (9.9)
Median (min-max)	49.5 (28–86)
Sex, n (%)	
Female	173 (99.4)
Male	1 (0.6)
Race, n (%)	
Caucasian	172 (98.9)
Black	2 (1.1)
Time since initial diagnosis (months)	
Mean (SD)	7.1 (3.9)
Median (min-max)	6.9 (0.3–20.8)
Location of primary tumor, n (%)	
Left	92 (52.9)
Right	79 (45.4)
Bilateral	3 (1.7)
Distribution of primary tumor, n (%)	
Unifocal	133 (76.4)
Multifocal	35 (20.1)
Multicentric	6 (3.4)
Tumor size	
Primary tumor size (largest diameter, mm)	
Mean (SD)	35.3 (29.1)
Multiple foci (largest diameter, mm)[a]	
Mean (SD)	7.1 (7.4)
Breast Cancer Subtype, n (%)	
Ductal	162 (93.1)
Lobular	3 (1.7)
Other	7 (4.0)
Missing	2 (1.1)
Histological grade, n (%)	
Moderately differentiated	41 (23.6)
Poorly differentiated	34 (19.5)
Unknown	75 (43.1)
Well differentiated	24 (13.8)
Nuclear grade, n (%)	
Grade 1	4 (2.3)
Grade 2	75 (43.1)
Grade 3	63 (36.2)
Unknown	32 (18.4)

Table 1. Continued

Variable	(n=174)
HER2 status IHC, n (%)	
2 +	11 (6.3)
3 +	160 (92.0)
Missing	3 (1.7)
HER2 status FISH, n (%)	
Positive	91 (98.9)
Negative	1 (1.1)
ECOG performance status, n (%)	
0	148 (85.1)
1	26 (14.9)
Type of prior anti-cancer therapy, n (%)	
Chemotherapy	122 (70.1)
Hormonal therapy	40 (23.0)
Radiotherapy	46 (26.4)
Unknown	5 (2.9)
Current treatment status, n (%)	
eBC adjuvant	139 (79.9)
eBC neo-adjuvant	35 (20.1)

SD: Standard deviation, min: Minimum, max: Maximum, HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry, FISH: Fluorescence in situ hybridization, ECOG: Eastern Cooperative Oncology Group, eBC: Early breast cancer, n: Number

Patient Preference

A total of 170 patients completed the PSQ, and 97.6% (n = 166) reported satisfaction with administration via the SC route; only 2.4% reported dissatisfaction. The experience with SC trastuzumab was reported as "acceptable" by 95.6% of patients and "fairly unpleasant" by 4.1% of patients. The majority of patients (93.5%) revealed that the medical or nursing staff administering SC trastuzumab did not experience any difficulty during the infusion.

Patient satisfaction results showed that SC trastuzumab administered via handheld syringe caused no bruising, irritation, or infection around the injection site (67.6%, 75.9% and 91.8% of patients, respectively). Administration time was reported as less than 5 minutes by 76.5% of patients and 6–10 minutes by 22.9% of patients. Subcutaneous administration was described as painless by 66.5% of patients, painful by 30.6%, and very painful by 5.6% of patients. Three-quarters of patients (75.9%) did not experience any adverse reactions such as bruising or irritation during or after SC administration, and 75.6% of patients did not feel anxious during SC treatment. The questionnaire also tried to define the burden of attending a health care center for injections, with items on ease of travelling, time spent and costs. The results showed that attending the clinics required some effort on the part of at least 25% of patients, with a minimum public transportation time of over one hour (100%), and all patients had to be escorted by another person (58.5%). The questionnaire and outcomes of patient responses are presented in Appendix 1 - Patient Satisfaction Questionnaire.

HCP Preference

Approximately half of HCPs completed the treatment satisfaction questionnaire about their preferences (n = 16, 62.5% were principal investigators). All respondents were satisfied with SC trastuzumab. Responses demonstrated that 81.3% of HCPs would strongly recommend SC trastuzumab for their patients and 62.5% of HCPs reported SC administration was very easy, with the remainder reporting this administration route to be fairly easy.

The majority of HCPs found no bruising or infection caused by SC infusion around the injection site (81.3% and 93.8%, respectively) whereas 56.3% reported a few occurrences of irritation. The time spent on preparation and administration was reported as less than 5 minutes by 43.8% and 75% of HCPs, respectively, and patient chair time per cycle was found to be between 3 and 4 hours. The questionnaire and outcomes of HCPs are given in Appendix 2 - Healthcare Professional Experience Questionnaire.

Efficacy

Survival analyses were performed for DFS and OS in 173 patients. DFS events – progression, recurrence of disease or death – were observed in 24 patients. Nine patients (5.2%) died during a median follow-up time of 36.6 (±10.3) months [95% confidence interval (CI): 35.1–38.1]. One-hundred and forty-one patients were assessed for the survival analysis, while 23 patients were not subject to follow-up after withdrawing consent.

The median OS time was 54.1 months (95% CI: 52.5–55.6). The 1- and 4-year OS rates were 99.4% (±0.6) and 90.5% (±4.7), respectively. The median DFS was 50.9 months (95% CI: 48.8–53.0). The 1- and 4-year DFS rates were 97.1% (±1.3) and 84.2% (±3.1), respectively (Figure 2).

Safety and Tolerability

During the 4-year follow-up, 1,299 AEs were documented in 160 patients. There were 261 AEs defined as related to SC trastuzumab in 104 patients. There were 43 SAEs reported in 27 patients. Seven SAEs were evaluated as related to trastuzumab (Table 2). Ejection fraction decrease (5.4%), injection site erythema (5.0%), pain (5.0%) and rash (5.0%) were the most common treatment-related AEs.

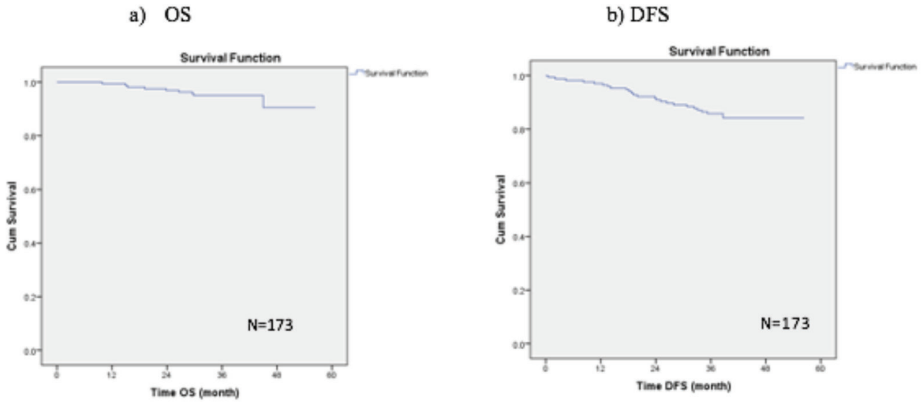
Five patients experienced AEs leading to permanent discontinuation of the study treatment. Two patients experienced grade 2 and grade 3 LVEF declines, and one patient experienced a SAE of grade 3 cardiotoxicity that led to discontinuation of the study treatment, whereas the remainder had grade 2 peripheral motor neuropathy and erythema. All events remained unresolved.

Twelve patients experienced 17 AEs that required a dose modification/temporary interruption of the study treatment, mostly due to ejection fraction decrease.

Cardiac Adverse Events

Forty-two patients (24.2%) experienced 76 cardiac-associated AEs of any grade, possibly related to treatment in 40 cases. Nineteen patients developed 21 (27.6%) events of trastuzumab-induced symptomatic left ventricular systolic dysfunction (LVSD), of which 15 events were recorded as AEs and six events as SAEs. Fifty-five events of asymptomatic LVSD were recorded in 32 patients, all of which were reported as AEs (Table 3).

Twenty-eight adverse events (24 considered as treatment-related) were recorded as decreased LVEF (including ejection fraction decrease, left



Total (n)	Number of events	Censored N	Censored %
173	9	164	94.8

Total (n)	Number of events	Censored N	Censored %
173	24	149	86.1

Kaplan-Meier – Cumulative Proportion Surviving at Cut-off

	Proportion	Std. Error
1. year	99.4%	0.6%
2. year	98.7%	0.9%
3. year	95.0%	1.7%
4. year	90.5%	4.7%

	Proportion	Std. Error
1. year	99.4%	0.6%
2. year	98.7%	0.9%
3. year	95.0%	1.7%
4. year	90.5%	4.7%

Figure 2. Overall survival (OS) and disease-free survival (DFS) curves

Table 2. Adverse events

Adverse event category	Incidence n (%)
Any AE, n (%)	**1299 (100)**
Non-serious AE, n (%)	**1256 (96.7)**
AEs related to study treatment	254 (19.6)
AEs leading to permanent discontinuation of study treatment	4 (0.3)
AEs leading to dose modification/interruption	12 (0.9)
AEs of suspected cardiac origin	70 (5.4)
SAE, n (%)	**43 (3.3)**
SAEs related to study treatment	7 (0.5)
Fatal SAEs	3 (0.2)
Fatal SAEs related to study treatment	0
SAEs leading to permanent discontinuation of study treatment	1 (0.1)
SAEs leading to dose modification/ interruption	5 (0.4)

AE: Adverse event, SAE: Serious adverse event, n: Number
Significant values are shown in bold.

ventricular dysfunction and failure, systolic and diastolic dysfunction, cardiotoxicity) in 23 patients (Table 4). The decline in median LVEF was found to be 3.5% (0.12–19.0). No fatal cardiac adverse events were reported.

Discussion

The ML28851 study is a prospective study to assess the impact of SC trastuzumab on the treatment experience and satisfaction of patients and HCPs, as well as the safety and tolerability of trastuzumab SC administered at healthcare centers. The study followed patients for a period of four years to define survival (OS and DFS) rates. Patients and HCPs voluntarily completed questionnaires developed by the investigators, and the majority of patients rated SC administration of trastuzumab as acceptable and satisfactory. Although only half of the HCPs completed the treatment satisfaction questionnaire, their responses indicated a strong rate of recommendation for SC trastuzumab for their patients.

Only a limited number of studies showing the preference of both patients and HCPs relating to long-term treatments, such as treatment of early breast cancer, have been published. The PrefHer study was the first clinical trial to assess patient preference for subcutaneous or intravenous administration of trastuzumab, as well as the satisfaction of healthcare professionals for the adjuvant treatment of HER2-positive early breast cancer (12). The MetaspHer study was conducted in a setting of metastatic disease and was designed to evaluate the preference of patients and HCPs between SC and IV administrations (13).

Our study results were consistent with those of these previous studies, wherein a high percentage of patients preferred SC trastuzumab over IV administration (12, 13). Despite the compatible results from these studies, the patient population enrolled in each study was different; the ML28851 study included patients with eBC in adjuvant and neoadjuvant settings. However, it should be noted that in the PrefHer study, SC trastuzumab was administered with a handheld syringe or SC injection device, whereas in our study the administration was performed with a syringe alone.

An important aspect of the study was the exploration of patient burden through an internally developed questionnaire for patients. The use of a SC injection of trastuzumab may provide the option of patient home care/treatment, as there is increasing demand among the patients for treatment in more comfortable treatment settings, or even at home. In a recent prospective study (BELIS) conducted in Belgium and Israel, the safety and patient experience of SC trastuzumab was

evaluated. The study results showed that the safety profile was similar to in-patient treatment, and patients almost always preferred home administration (14).

In a study conducted in Germany, 70%–90% of patients preferred SC administration of trastuzumab and stated that the main reason for SC preference was time saved during administration (17). Based on the results of our study, the administration time of SC trastuzumab was reported to be less than 5 minutes by 76.5% of patients and 6 to 10 minutes by 22.9% of patients. Patients receiving IV trastuzumab spent more time in the oncology unit than those receiving SC administration. A UK time and motion study showed that the time dedicated to preparation and administration of SC trastuzumab by any HCP was three times shorter than in the case of IV trastuzumab on average (30.0 vs. 94.5 minutes) (18). The time spent by HCPs on preparation and administration in our study was less than 5 minutes for SC infusion in 75% of all cases, thus presenting a unique advantage in terms of ease of use.

Another reason for the preference for SC trastuzumab administration was reduced pain and discomfort around the injection site, consistent with previous clinical trials (12, 19). However, in several clinical studies investigating SC trastuzumab, the most common AE related to SC administration was injection-site reactions (20, 21).

Previous studies showed that trastuzumab-induced cardiotoxicity is independent of dose and notably reversible following treatment discontinuation (21-23). Therefore, AEs of suspected cardiac origin were strictly monitored during the treatment period, and the cardiac safety profile of SC trastuzumab was observed in this current study. The number of patients that experienced cardiac-associated AEs of any grade was similar to those observed in the Zambetti et al's (15) Schearly study but higher than in the HannaH and the PrefHer studies (13, 18). However, only one severe left ventricular failure was reported during this study. LVEF decrease <55% was observed in 1.22% of the treatment population, and this decrease resolved completely during subsequent observation.

This study revealed that SC use of trastuzumab in eBC patients is a satisfactory treatment option, and indicated very high preference rates in patients and HCPs. These findings were also consistent with a recent prospective study showing that SC trastuzumab can be safely administered at home by an HCP, and patients clearly indicated such setting to be comfortable and overall beneficial.

Moreover, with a similar safety profile to that of the IV form, and with comparable OS and DFS rates to previous studies for patients with HER2-positive eBC (11, 24) our study confirmed the efficacy of the SC administration route. The data obtained from this study demonstrate that SC trastuzumab is a valid and preferred option for improving patients' and HCPs' satisfaction in cases of HER2-positive eBC.

The limitation of our study was the use of two separate, non-validated, internally developed questionnaires. However, the aim and outcomes of these questionnaires showed that non-validated questionnaires may serve as a reliable source of information if they contain calculable, objective information such as time, conditions or outcome information.

Table 3. Cardiac adverse events

Adverse Event Category **Cardiac AEs**	**Incidence, n (%)**
Any cardiac AE, n (%)	**76 (100)**
Non-serious cardiac AE, n (%)	**70 (92.1)**
Symptomatic LVSD	**15 (19.7)**
Serious Cardiac AE, n (%)	**6 (7.9)**
Symptomatic LVSD	**6 (7.9)**
AEs associated with decreased LVEF	
Any cardiac AE, n (%)	**28 (100)**
Non-serious cardiac AE, n (%)	**25 (89.3)**
AEs related to study treatment	21 (75.0)
AEs leading to permanent discontinuation of study treatment	2 (7.1)
AEs leading to dose modification/ interruption	3 (10.7)
Serious Cardiac AE, n (%)	**3 (10.7)**
Serious AEs related to study treatment	3 (10.7)
SAEs leading to permanent discontinuation of study treatment	1 (3.6)
SAEs leading to dose modification/ interruption	1 (3.6)

AE: Adverse event; SAE: Serious adverse event; LVSD: Left ventricular systolic dysfunction; LVEF: Left ventricular ejection fraction
Significant values are shown in bold.

Table 4. Adverse Events Associated with Decreased LVEF

Adverse Event Category **AEs associated with decreased LVEF**	**Incidence, n (%)**
Investigations	**16 (57.1)**
Ejection fraction decreased	16 (57.1)
Cardiac disorders	**12 (42.9)**
Left ventricular dysfunction	8 (28.6)
Left ventricular failure	1 (3.6)
Cardiotoxicity	1 (3.6)
Systolic dysfunction	1 (3.6)
Diastolic dysfunction	1 (3.6)

AE: Adverse event; LVEF: Left ventricular ejection fraction, n: Number
Significant values are shown in bold.

Conclusion

These results have shown that both patients and HCPs favored SC trastuzumab for the treatment of HER2-positive eBC. The safety and tolerability of SC trastuzumab is consistent with the known safety profile of SC and IV administration.

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Appendix 1. Patient Satisfaction Questionnaire

PATIENT SATISFACTION QUESTIONNAIRE

Item	Category	Frequency n (%)
1. Where did you have your Herceptin study treatment?		
	Hospital chemotherapy department	169 (99.4)
	Other chemotherapy department	1 (0.6)
Total		170
2. Was this the same place as for your chemotherapy treatment?		
	Yes	157 (92.4)
	No	13 (7.6)
Total		170
3. How long did it take you to travel there?		
	<1 hour	60 (35.3%)
	>2 hours	47 (27.6%)
	1-2 hours	63 (37.1%)
Total		170
4. How easy was it for you to travel there?		
	Fairly	83 (48.8%)
	Not at all	46 (27.1%)
	Very	41 (24.1%)
Total		170
5. Did someone always have to take you there by car or public transport?		
	Always	102 (60.0%)
	Never	27 (15.9%)
	Sometimes	41 (24.1%)
Total		170
6. Was the cost of travelling there a problem for you?		
	Fairly	69 (40.6%)
	Not at all	82 (48.2%)
	Very	19 (11.2%)
Total		170
7. So, taking all these things above into consideration was travelling for Herceptin treatment overall a problem for you?		
	Yes	126 (74.1%)
	No	44 (25.9%)
Total		170
8. Did the medical or nursing staff ever have any difficulty giving the Herceptin injection subcutaneously?		
	Never	159 (93.5)
	Sometimes	9 (5.3)
	Very often	2 (1.2)
Total		170
9. How many minutes did it usually take?		
	<5 minutes	130 (76.5)
	6-10 minutes	39 (22.9)
	11-15 minutes	1 (0.6)
Total		170

PATIENT SATISFACTION QUESTIONNAIRE

Item	Category	Frequency n (%)
10. How painful was this usually?		
	Fairly	52 (30.6)
	Not at all	113 (66.5)
	Very	5 (2.9)
Total		170
11. How much were you bothered by any bruising around the SC site?		
	Never	115 (67.6)
	Somewhat	52 (30.6)
	Very much	3 (1.8)
Total		170
12. How much were you bothered by any irritation around the SC site?		
	Never	129 (75.9)
	Somewhat	39 (22.9)
	Very much	2 (1.2)
Total		170
13. How much were you bothered by any infection around the SC site?		
	Never	156 (91.8)
	Somewhat	14 (8.2)
Total		170
14. How much were you bothered by reactions to the SC infusion during or directly after it was given?		
	A little	38 (22.4)
	Never	129 (75.9)
	Very much	3 (1.8)
Total		170
15. How often were you bothered by these reactions?		
	Most infusions	10 (24.4)
	Only at 1st/ 2nd infusions	31 (75.6)
Total		41
16. How anxious did having the SC treatment make you feel?		
	Fairly	32 (18.8)
	Not at all	128 (75.3)
	Very	10 (5.9)
Total		170
17. In general, how would you describe these SC treatment sessions?		
	Acceptable	163 (95.9)
	Fairly unpleasant	7 (4.1)
Total		170
18. In general, how would you describe your experience regarding the Herceptin SC treatment?		
	Satisfactory	166 (97.6)
	Unsatisfactory	4 (2.4)
Total		170

Appendix 2. Healthcare Professional Satisfaction Questionnaire

HEALTHCARE PROFESSIONAL SATISFACTION QUESTIONNAIRE

Item	Category	Frequency n (%)
1. Did you personally administer the SC Herceptin in the study?		
	Always	2 (12.5%)
	Never	12 (75.0%)
	Sometimes	2 (12.5%)
Total		16
2. How many minutes preparation time was required after receiving the Herceptin vial from the pharmacy?		
	<5	7 (43.8%)
	6-10	6 (37.5%)
	16-20	1 (6.3%)
	>20	1 (6.3%)
	Not sure	1 (6.3%)
Total		16
3. How many minutes in total did it usually take to administer the Herceptin subcutaneously using the handheld syringe?		
	<5	12 (75.0%)
	6-15	4 (25.0%)
Total		16
4. How many patients do you think had irritation around the SC site?		
	A few	9 (56.3%)
	None	7 (43.8%)
Total		16
5. How many patients do you think had bruising around the SC site?		
	A few	3 (18.8%)
	None	13 (43.8%)
Total		16
6. How many patients do you think had infection around the SC site?		
	A few	1 (6.3%)
	None	15 (93.8%)
Total		16
7. Reactions related to the SC infusion - fever, chills, flu-like symptoms, rash, swelling of lips or face etc. - at time of administration or directly after?		
	A few	4 (25.0%)
	None	12 (75.0%)
Total		16
8. How long do you think the SC sessions usually lasted from patients' arrival until departure?		
	<2 hours	1 (6.3%)
	>2 but <3 hours	5 (31.3%)
	>3 but <4 hours	8 (50.0%)
	>4 hours	2 (12.5%)
Total		16
9. How anxious do you think the SC treatment made patients feel?		
	Not at all	16 (100.0%)
Total		16

HEALTHCARE PROFESSIONAL SATISFACTION QUESTIONNAIRE

Item	Category	Frequency n (%)
10. How reliable was using the handheld syringe to give Herceptin subcutaneously?		
	Very reliable	10 (62.5%)
	Fairly reliable	6 (37.5%)
Total		16
11. Overall, how easy did you/your staff find giving Herceptin subcutaneously using the handheld syringe?		
	Very easy	10 (62.5%)
	Fairly easy	6 (37.5%)
Total		16
12. How likely would you be to offer or recommend SC administration of Herceptin via a handheld syringe to your patients in the future?		
	Very likely	13 (81.3%)
	Fairly likely	3 (18.8%)
Total		16
13. In general, how would you describe your experience regarding the Herceptin SC treatment?		
	Satisfactory	16 (100.0%)
14. Do you have any other comments to make about the administration of Herceptin during the study?		
	I think that it is more effective than IV application for patients.	1 (50.0%)
	It is time saving for doctors, nurse and patients also it is comfortable for patients	1 (50.0%)
Total		16

Original Article

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What Has Changed During the COVID-19 Pandemic? - The Effect on an Academic Breast Department in Portugal

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ABSTRACT

Introduction: One year ago, Portugal entered its first lockdown because of the coronavirus disease-2019 (COVID-19) pandemic. The impact of this on delays in cancer diagnosis and treatment is a major concern, which may negatively affect the outcomes of these patients.

Materials and Methods: This retrospective, single-center analysis compared the clinical and pathological characteristics of breast cancer (BC) patients referred to a medical oncology first appointment between March 2020 and 2021, with the same period in the previous year.

Results: Strikingly, there was a 40% reduction in the number of BC patients during lockdown. However, there was a statistically significant increase in the proportion of metastatic BC patients admitted for the first time for systemic therapy (13.6% vs. 28.9%, p = 0.003). Additionally, a statistically significant increase in the number of patients with bilateral early BC at diagnosis after March 2020 was found (7.2% vs. 1.9%, p = 0.043).

Conclusion: These findings support international recommendations for an accelerated restoration of BC screening, to reduce incidence of advanced breast cancer at diagnosis and mitigate the expected impact of the COVID-19 pandemic on patients with cancer. Further work is needed to examine in detail the impact of measures to manage the COVID-19 pandemic on breast cancer outcomes.

Keywords: COVID-19, SARS-CoV-2, breast cancer, oncology department, tertiary hospital

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Key Points

- One year of COVID-19 pandemic: effects on a breast cancer oncology department.
- Increase of metastatic breast cancer patients admitted for systemic therapy.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated disease (COVID-19), first recognized in Wuhan, in December 2019, was declared by the World Health Organization (WHO) as a global pandemic on 11th March 2020 (1). On March 2nd, 2020, the first COVID-19 cases were confirmed in Portugal. Only sixteen days later, 642 cases and three deaths were reported. The Portuguese authorities took early action to control the COVID-19 outbreak, initiating lockdown measures and declaring a state of emergency on March 18th, 2020 (2). By the beginning of April 2020, over 1 million cases of confirmed infections and over 60 thousand deaths from COVID-19 were reported worldwide. Over the last year the COVID-19 pandemic has led to more than 100 million cases and 2.8 million deaths worldwide (3).

Older age and comorbid disease, such as cancer, have been identified as potential risk factors for poor prognosis in COVID-19, including the need for intensive care, invasive ventilation, and death (4). Despite data that suggest that COVID-19 is typically more severe and lethal among people with underlying medical conditions, including active cancer, such risk may be influenced by the type of cancer, treatment, time since treatment, patient age and comorbid medical conditions (5-7).

Moreover, the COVID-19 pandemic represents a global challenge, not only for reorganization of health care resources in order to minimize exposure risks, especially in oncology settings, but also in ensuring the continuity of care during cancer diagnosis and treatment (8).

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International guidelines have been published to guide patients and healthcare professionals for the prevention and management of COVID-19 in order to maximize the available resources. The European Society for Medical Oncology (ESMO) has established guidance for clinicians, defining levels of priorities regarding medical interventions, based on the ESMO Magnitude of Clinical Benefit Scale (MCBS), a public health tool intended to support the uptake of medical interventions in oncology (9). In parallel, local and national guidelines were published (10). The Portuguese Society of Oncology (SPO) published recommendations that were taken into account by the Portuguese health authorities to issue a standard of action in the provision of care to cancer patients, in April 2020 (11).

Despite cancer centers/departments continuing to function, the imposition of the national lockdown resulted in a reduction in the numbers of patients accessing healthcare. Delay in cancer diagnosis and treatment due to the COVID-19 pandemic is a major concern, but the true impact is not yet clearly established (12-14).

Although breast cancer (BC) is one of the most frequent cancers and represents the leading cause of oncological death among women worldwide, there has been an improvement in terms of prognosis over the last 20–30 years. The significant gains were largely attributable to early detection and systemic therapies. ESMO recommendations prioritized highest risk BC, in accordance with current clinical practice, to maintain improved survival (15).

The scale of the diagnostic and treatment delay attributed to the pandemic and whether it is equally distributed is currently unknown. Using data from a single center, our study aimed to evaluate the consequences of the pandemic on the referral of patients with BC to the medical oncology unit, compared with the previous year.

Materials and Methods

The purpose of this non-experimental, descriptive, retrospective, single-institution analysis was to evaluate the impact of the COVID-19 pandemic on the admission demographics and characteristics of BC patients between March 2020 and March 2021, compared to the same period one year previously. BC patients were evaluated who were referred to the medical oncology department after multidisciplinary board discussion, which had been taking place virtually since April 2020.

Clinical records were used for the data collection for each patient. Baseline demographic information included sex, age, Eastern Cooperative Oncology Group (ECOG) performance status and previous history of BC. Age at diagnosis was grouped into <40, 40-64 and ≥65 years. Tumor characteristics included histopathology, molecular subtypes based on hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status. HR and HER2 status were combined to form the variable “tumor subtype”, as follows: HR+/HER2+; HR+/HER2–; HR–/ HER2+; and HR–/HER2–. Clinical TNM stage was defined according to the eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual.

The research was conducted ethically according to the principles of the Declaration of Helsinki. The authors confirm that patient written informed consent was obtained. Data were extracted from clinical files and is completely anonymous with no personal information being collected. The paper is exempt from ethical committee approval due to its retrospective, non-interventional nature and non-identifiable data collected.

Statistical Analysis

Descriptive statistics were generated for all data collected. For categorical variables, frequency tables were created to evaluate distributions and analyzed using Fisher's exact test (two-sided). Two-tailed p values below 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software, version 23 (IBM Inc., Armonk, NY, USA).

Results

The demographic, clinical and pathological characteristics of the patients included in the analyses are listed in Table 1. Between March 2020 to March 2021, 97 individuals (94 women and 3 men) were referred to the medical oncology unit for suspected BC. From March 2019 to March 2020, 162 patients were referred (160 women and 2 men), a reduction in first appointment admission of 40.1%. No statistically significant difference in the distribution of ECOG performance status was observed between the two periods (p=0.366). Median age at diagnosis was 61 and 58 years, in 2020 and 2019 respectively, with a similar distribution of age groups <40, 40-64, ≥65 years in both periods (p=0.744).

At pathological examination in the lockdown period (2020-2021), most cases (n= 87, 89.6%) were reported as invasive ductal carcinoma, while five cases (5.2%) were lobular carcinoma and five cases (5.2%) were defined as "others". No statistically significant differences were found with this classification from the earlier pre-lockdown period. Regarding BC biological subtypes, after March 2020, 17 patients (17.5%) were HR+/HER2+, 56 (57.7%) were HR+/HER2–, 5 (5.2%) were HR–/HER2+, and 19 (19.6%) were HR–/HER2–. No statistically significant difference in the distribution of biological features was observed between the two periods (p=0.468). There was a statistically significant increase in the proportion of patients with bilateral BC at diagnosis after March 2020 (7.2% vs 1.9%, p=0.043).

Distribution by clinical prognostic TNM staging (8th edition AJCC) is shown in Table 2. There was a decrease in the number of stage I patients, from 30.9% in 2019 to 20.6% in 2020, however this was not significantly different (p=0.083). Overall, distribution of stages II-III BC did not significantly vary when compared between the two periods (stage IIA: p=0.761; stage IIB: p=0.702; stage III: p=1.000). By contrast, after initiation of lockdown measures in Portugal, a significant increase in the proportion of patients with metastatic BC at first admission for systemic therapy was found to have increased from 13.6% in 2019 to 28.9% in 2020 (p=0.003).

Discussion and Conclusion

As expected, we found that the COVID-19 pandemic had a negative effect on referral of BC patients, with a 40% reduction in first appointment admissions at the medical oncology department, compared with the previous year.

Understanding the implications of the delay in diagnosis and access to treatment for BC cannot be entirely captured unless contextualized to the biology of the cancer and patterns of clinical presentation, including stage and setting of care (16). Our single-institution analysis reported a significant increase in the proportion of metastatic BC patients admitted for the first time for systemic therapy after initiation

of lockdown measures in Portugal. There was no statistically significant difference in patients with early BC. As a limitation, these interesting data may not reflect the true disruption due to COVID-19, since there was no evidence of a stage migration, but only an increase in the proportion of ab initio metastatic BC. However, we also observed a significant increase in the number of patients with bilateral BC at diagnosis after March 2020.

This analysis only included data from a single center, located in Lisbon, which will impair the generalization of our results to other settings. However, we are currently working on increasing the patient sample with the inclusion of other centers in Portugal. This will allow a more detailed picture to emerge concerning differences in diagnosis rates or treatment strategies between regions.

The burden of COVID-19 on health systems worldwide has important implications for cancer care that we will need to address. From the onset of the lockdown, essential diagnostic services were suspended or operating at substantially reduced capacity. These suspensions were due to the risk of exposure to SARS-CoV-2 for patients and clinicians, and because of redeployment of staff towards critical care to manage patients with COVID-19. A national population-based modeling study, using English National Health Service (NHS) cancer registration estimated a 7.9–9.6% increase in the number of deaths due to breast cancer up to year 5 after diagnosis (12).

National screening services were widely suspended from the end of March 2020, and this will have contributed significantly to the decrease in the number of early breast cancers diagnosed and treated. There has been limited data about how the pandemic affected cancer care because of screening and treatment delays. Nyante et al. (17) reported maximum reductions in March 2020 for screening and diagnostic mammography and in May 2020 for biopsies. This deficit decreased gradually, with no significant difference between observed

Table 1. Baseline demographic and pathological characteristics of patients diagnosed with invasive breast cancer and admitted in Oncology department according to year

	2020–2021 97 patients		2019–2020 162 patients		p-value
	n	(%)	n	(%)	
Gender					
Female	94	96.9	160	98.8	0.366
Male	3	3.1	2	1.2	
ECOG performance status					
0–1	91	93.8	155	95.7	0.562
≥2	6	6.2	7	4.3	
Age at diagnosis (years)					
<40	10	10.3	21	13.0	
40–65	47	48.5	83	51.2	0.744
>65	40	41.2	58	35.8	
Histology					
Invasive ductal	87	89.6	144	88.9	
Invasive lobular	5	5.2	12	7.4	0.699
Other	5	5.2	6	3.7	
Subtype					
HR + / HER2 -	56	57.7	99	61.1	
HR + / HER2 +	17	17.5	32	19.8	0.468
HR - / HER2 +	5	5.2	3	1.9	
HR - / HER2 -	19	19.6	28	17.2	
Previous history of BC					
Yes	11	11.3	9	5.6	0.099
No	86	88.7	153	94.4	
Bilateral BC					
Yes	**7**	**7.2**	**3**	**1.9**	**0.043**
No	90	92.8	159	98.1	

Significant associations are bolded.
HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2 status, BC: Breast cancer, n: Number

Table 2. Clinical prognostic TNM stage of patients with invasive breast cancer according to year

	2020–2021 97 patients		2019–2020 162 patients		p-value
	n	(%)	n	(%)	
Clinical prognostic TNM stage					
I	20	20.6	50	30.9	0.083
IIA	21	21.6	39	24.1	0.761
IIB	11	11.3	22	13.6	0.702
III	17	17.6	29	17.8	1.000
IV	**28**	**28.9**	**22**	**13.6**	**0.003**

Significant associations are bolded.
TNM stage was defined according to the eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual.
TNM: tumor (T), nodes (N), and metastases, n: Number

and expected numbers by July and August 2020 compared with the pre pandemic population. A population-based analysis from the USA demonstrated that there was a substantial decrease in BC screening and diagnosis from March to July 2020 compared with March to July 2019 (18). For example, mammographic screening decreased by up to 85% and breast biopsies decreased by up to 71%.

Similar results are reported from Europe. In England, routinely collected NHS cancer waiting time data were analyzed to compare activity for BC in the first six months of 2020 compared to the same period in 2019. The number of referrals for suspected BC was 28% lower and the number of patients who received their first treatment for a BC diagnosis was 16% lower. These data suggest that, while there was undoubtedly a marked decrease in the number of referrals made that may have led to a decrease in the numbers of newly diagnosed BC, the magnitude of the decrease in the number of cancers was not as large as initially feared. The observed fall was proportionately much larger in patients referred non-urgently for assessment compared to those referred urgently (40% versus 23%) (19). A population-based study from the Netherlands showed that the incidence of BC started to decline after social lockdown and the temporary pause in screening. This decrease was seen in all age groups and all regions, compared with reference data from 2018/2019. However, the incidence of stage IV tumors did not decline. As the incidence reduction mainly occurred for the lowest stage disease, the authors suggested that the delay in diagnosis would not have had a large impact on long-term outcomes (20). A multicentric analysis from Italy, reporting the effects in the first three months after lockdown, showed a significant difference in waiting times, proportion of patients with lymph-node involvement, and cancer grading, compared with the similar period from the previous year. Nonetheless, after multivariate analysis, the significantly longer waiting time on list during the lockdown, was the only predictive factor for lymph node involvement progression (21). In a population- and registry-based study from Croatia, the average monthly percent change in referrals after the initial lockdown measures were introduced was –11.0%, resulting in a 24% reduction in newly diagnosed BC cases during April, May, and June compared with the same period of 2019 (22). Moreover, from the point of view of the patient, in a US national survey of BC survivors, nearly half of respondents reported delays in cancer care in the early weeks of the COVID-19 pandemic (23).

Recent multicenter analysis, including breast cancer patients, showed that chemotherapy was not associated with an increased risk of infection with SARS-CoV-2, suggesting that chemotherapy can be safely administered and should not be withheld, particularly when given for curative intent (24).

Despite available data, the real long-term impact of the pandemic on BC patients it is not yet known. In the near future, it will be crucial to make decisions at both institutional and national level in order to restart cancer screening and set new priorities for BC treatment.

In conclusion, one year after the first case, the COVID-19 pandemic still represents a substantial challenge in cancer care in Portugal. Our study showed a negative effect on the referral of BC patients to medical oncology, with a 40% reduction in first appointment admissions and a significant increase in these patients that did attend having metastatic BC. Further work is needed to assess the impact of measures to manage the COVID-19 pandemic on BC outcomes. On the other side, national authorities need to restore BC screening services are much as possible while taking into account the continuing pandemic to minimize cancer treatment delays.

Ethics Committee Approval: Data were extracted from clinical files and is completely anonymous with no personal information being collected. The paper is exempt from ethical committee approval due to its retrospective, non-interventional nature and non-identifiable data collected.

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Authorship Contributions

Conceptualization: D.S., Methodology: D.S.; Data Collection and/or Processing: M.S., Literature Search: M.S., Analysis and/or Interpretation: A.F.R.; Visualization: A.S.S.; Writing: S.O.; Review and Editing: S.O.; Supervision: R.L.

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Original Article

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The Value of Tyrer-Cuzick Versus Gail Risk Modeling in Predicting Benefit from Screening MRI in Breast Cancer

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ABSTRACT

Objective: Breast cancer is the most commonly diagnosed malignancy in US women. Risk assessment tools such as the Gail and Tyrer-Cuzick (TC) models calculate risk for breast cancer based on modifiable and non-modifiable factors in order to guide screening and prevention for high-risk patients. Screening with magnetic resonance imaging (MRI) in addition to mammography is recommended in high-risk patients (>20% lifetime risk on TC or other familial based models). Currently, no published data indicate these recommendations improve cancer detection.

Materials and Methods: With the aim to determine what percentage lifetime risk (LR%) is associated with a statistically significant increase in cancer detection, the Virginia Commonwealth University (VCU) breast imaging database was reviewed to identify patients who received screening MRI.

Results: The receiver operating characteristics (ROC) curves for the Gail and TC models and the rate of cancer detection correlated to 20% LR% were calculated. The Gail model was considered the control model as it is NOT considered a validated screening tool for MRI. TC is not more accurate than Gail when predicting benefit of breast MRI screening. (area under the curve (AUC): 0.6841, 0.6543 respectively, p = 0.828). Univariate analysis failed to demonstrate a statistically significant relationship between the Gail or TC LR % and diagnosis of breast cancer when using 20% as the cutoff for high-risk classification (p = 1.0, 0.369 respectively). Neither the TC nor the Gail risk calculators demonstrated a significant correlation between risk and the likelihood of diagnosis of breast cancer when screened with MRI.

Conclusion: Larger cohort studies are necessary to determine the risk percentage most predictive of a breast cancer diagnosis using MRI as screening.

Keywords: Breast cancer, breast cancer screening, MRI, risk factors

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Key Points

- Currently the Tyrer-Cuzick model is used for determination of MRI eligibility for high-risk patients whereas the Gail model guides eligibility for chemoprevention.
- Our study demonstrated that there might not be any additional predictive value using the Tyrer-Cuzick versus Gail model when determining screening MRI breast eligibility.
- The 20% lifetime risk, as calculated by Tyrer-Cuzick, did not appear to lead to a greater detection of breast cancers over our control, the Gail model. This calls into question the 20% cutoff but would require larger studies to determine a more appropriate cutoff value.

Introduction

Breast cancer is the most commonly diagnosed malignancy in women in the United States and the second most common cause of cancer death among women worldwide (1). On average, a woman's risk for developing invasive breast cancer in the United States (US) is approximately 1 in 8 or about 12.5%. This risk increases with age, with a woman aged 70 being almost 10 times more likely to develop breast cancer in the next five years as compared to a woman in her 30s (2). There are several other factors, both modifiable and non-modifiable, that can increase a woman's risk for developing breast cancer. Such modifiable factors include obesity, alcohol consumption, activity level, parity, breastfeeding, radiation therapy and use of hormone replacement therapy (HRT) (3). Non-modifiable factors include genetic mutations, family history of breast cancer, prior history of atypical lesions, as well as race and age (4, 5).

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Studies have demonstrated that early detection of breast cancer decreases the morbidity and mortality of the disease (6). Routine screening with mammography has decreased mortality, especially in women aged 50 to 69 years (7, 8). In fact, most women with clinically occult disease are diagnosed with breast cancer by mammographic screening alone. While breast cancer screening primarily relies on mammography, there are proven benefits in screening for breast cancer with contrast-enhanced breast magnetic resonance imaging (MRI). Contrast-enhanced breast MRI has superior sensitivity to mammography (9-11). Even when adding ultrasound to mammography, the two have relatively lower specificity and sensitivity to mammogram and MRI (12, 13). Some factors that have hindered the wider use of MRI for screening for breast cancer are its high cost, need for heavy metal (Gadolinium) contrast, the limited availability of MRI scanners and its low specificity for breast cancer detection. The specificity of MRI in multiple studies remains around 70%. Increased sensitivity and decreased specificity, as compared to mammography, results in MRI generating fewer false negative studies but a greater number of false positive studies, which can result in unnecessary biopsy (14, 15). Additionally, studies have shown that screening with MRI is not cost-effective in women with lower to average risk for breast cancer, which is reflected in its omission for these groups in the current American Cancer Society (ACS) recommendations (16, 17).

Women with genetic mutations associated with an increased risk for breast cancer, history of previous mantle radiation or those with an estimated lifetime risk greater than 20%, based on risk stratification tools, are classified as high risk for breast cancer (18). For these individuals, several organizations have recommended breast MRI for screening as an adjunct to mammography (19-22). The Claus model is the only validated model which predicts benefit from screening MRI, which mostly takes into account a woman's age and family history (23). Alternative models such as the Tyrer-Cuzick (TC), the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) and Gail attempt to be more comprehensive and include both family history, as well as non-familial risk factors (24, 25). Due to inherent differences in the data included in these models, there can be great variability in mathematical risk calculation, which can impact screening recommendations. In a previous study, 33 women were evaluated for MRI-based breast screening. Using 20%–25% lifetime risk as a minimum cutoff for MRI, the Claus model identified one eligible patient, while alternative models such as Gail model and the TC model identified nine and 12 eligible patients, respectively (26). The authors did not determine the benefit patients received from enhanced screening, such as an increase in cancer detection.

The Gail and TC models are readily available online risk calculators that account for family history, personal history and modifiable factors in some variation to determine risk. Currently the TC model is used to guide MRI screening eligibility for high-risk patients, whereas the Gail model has been designed to guide use of chemoprevention as determined by the NSABP STAR trial (27). In our study, we compared the TC and Gail Lifetime Risk (LR%) and their correlation with biopsy proven breast cancer diagnosis subsequent to MRI screening. We also aimed to determine if the largely accepted 20% lifetime risk is associated with a statistical increase in cancer detection in a cohort of eligible patients undergoing MRI breast cancer screening.

Materials and Methods

After receiving IRB approval, we performed a retrospective review of the Virginia Commonwealth University (VCU) Imaging Database from January 2005 to December 2015. We evaluated patients who received screening breast MRI as an adjunct to mammography, based on a variety of reasons including: presence of genetic mutations such as *BRCA1/BRCA2*; presence of atypia or other high-risk lesions on previous biopsy; LR% greater than 20% on TC or other risk models; presence of extensive breast or ovarian family history; or presence of extremely dense breasts on mammography.

The cohort included females, aged 18 to 75, who underwent screening breast MRI between January 2005 to December 2015 within a VCU Health affiliated hospital. In addition to screening MRI, patients received screening mammography, alternating mammogram and MRI every six months. Subjects who received a diagnostic breast MRI due to a diagnosis of breast cancer were excluded from the study. Additionally, subjects with a prior history of breast cancer, or those with breast cancer diagnosis with a screening method other than MRI, that is ultrasound, were also excluded.

We collected clinical and pathological data for all subjects. Variables associated with an increased risk of breast cancer including race, body mass index (BMI), parity, age at first birth, genetic testing, age of menarche, menopausal status, HRT and family history for breast cancer including first- and second-degree relatives were collected. Using those variables, we calculated the lifetime risk percentage for future development of breast cancer for every subject in our cohort using both the Gail and TC risk calculators. Of note, we did not calculate Gail risk on subjects aged less than 35 years at first presentation, as the model is not validated in women less than age 35. We chose not to include a Claus model risk score as it is no longer used in clinical practice. We recorded the results of the MRI report as well as patient age at the time of the first MRI used for screening and the age for patients diagnosed with biopsy proven breast cancer using MRI as a method for screening.

Ethics committee approval was obtained from Virginia Commonwealth University Institutional Review Board and the approval was given on May 31, 2018.

Statistical Analysis

We compared the accuracy of the Gail and TC models as lifetime risk calculators for breast cancer detection by calculating the receiver operating characteristic (ROC) curves for each test separately. The Gail model was considered our control model as it is a well validated standardized risk model used for other purposes but is not considered validated for determining utility of MRI. ROC curves are popular tools summarizing the trade-off between true positive and false positive rates for a predictive model (corresponding to the competing tests in this study) under various probability thresholds. Comparison of the ROC curves via the calculated area under the curve (AUC) corresponding to the Gail and TC models was performed using DeLong's test. Additionally, Fisher's Exact Test was utilized to determine the significance of cancer detection with screening MRI when the TC or Gail LR percentages are greater than 20%. A p-value of <0.05 was considered statistically significant for our analyses. All statistics were performed using SAS Software, version 9.4 (Cary, NC., USA).

Results

We identified 163 subjects in the VCU breast imaging database eligible for the study based on inclusion criteria. A total of five subjects were diagnosed with biopsy proven breast cancer after undergoing screening with MRI, representing 3.1% of our patient cohort. The mean age at first screening MRI was 48.2 years and the mean age at cancer diagnosis was 41.4 years (Table 1). The mean lifetime risk of developing breast cancer according to TC version 7 and Gail model was 25.5% and 16.9%, respectively. Furthermore, 20.2% of our cohort had undergone a prior breast biopsy with 24.2% having findings such as atypia, or lobular carcinoma in situ (LCIS). The majority (90.8%) of subjects had a first degree relative with known breast cancer and 71.8% were parous with a mean age of parity at 26.6 years. Lastly, 49 patients had undergone prior genetic testing with 19 testing positive for *BRCA1/BRCA2* or other hereditary unspecified genetic mutations (Table 1).

Logistic ROC analysis results showed that the AUC scores for TC and Gail were 0.6841 and 0.6543, respectively. There was no significant difference in predictive ability between the two calculators (p = 0.828) (Figure 1).

In order to determine whether utilizing a 20% lifetime breast cancer risk as an MRI screening cutoff clinically improves cancer detection, the relationship between biopsy proven breast cancer diagnosis with the Gail and TC calculators was explored when the cutoff value was set at 20%. Based on available information from electronic medical records, the Gail model was utilized in 134 of the subjects. (remaining subjects were age <35 years and did not qualify for Gail LR calculation). One hundred subjects were determined to have a LR ≤ 20%, with four subjects in this cohort later developing biopsy proven breast cancer (Table 2). Thirty-four subjects were determined to have LR% greater than 20%, with one subject later being diagnosed with breast cancer. There was no statistically significant difference in the diagnosis of breast cancer between the two Gail groups (p = 1.0) (Table 2). There were a total of 163 calculated TC lifetime risk percentages, with 78 corresponding subjects receiving ≤20% and 85 subjects receiving greater than 20% (Table 3). One subject with LR% less than or equal to 20% later developed biopsy proven breast cancer, while four subjects belonging in the high-risk group were diagnosed with malignancy during the study period. There was no statistically significant difference in the diagnosis of breast cancer between the two groups (p = 0.369) (Table 3).

Table 1. Population demographics

Number of subjects in the study	163
Mean age first screening MRI	48.2
Mean age of menarche	12.5
Mean BMI	28.9
Percentage of parity	71.8
Mean age of parity	26.6
Percentage with a breast biopsy	20.2
Percentage with atypia/LCIS in biopsy result	24.2
Percentage of first-degree relatives with breast cancer	90.8
Average Percentage of TC score	25.5
Average Percentage of Gail Score	16.9
Mean age of biopsy confirmed breast CA	41.4
Number of patients with genetic testing	49
Number of patients with genetic mutations known to predispose to breast cancer (eg. BRCA1, BRCA2)	19

MRI: Magnetic resonance imaging, BMI: Body mass index, LCIS: Lobular carcinoma in situ, TC: Tyrer-Cuzick, CA: Cancer

Discussion and Conclusion

Breast cancer risk calculators can provide valuable information that can be used to guide prevention, screening and chemoprophylaxis strategies in women. The Gail model, while not intended to determine MRI eligibility, has been utilized to guide chemoprophylaxis eligibility in women with a 5-year breast cancer risk of 1.67% or higher (28, 29). In contrast, the TC, in addition to the Claus and BOADICEA models, has been used to determine MRI eligibility for screening

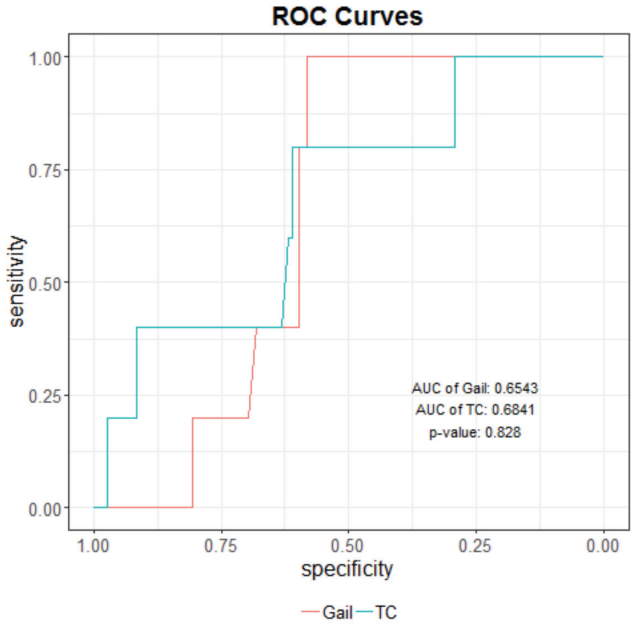

Figure 1. ROC curves of the Gail (red line) and TC (blue line) models when predicting MRI detection of breast cancer

ROC: Receiver operating characteristics curve, TC: Tyrer-Cuzick, MRI: Magnetic resonance imaging, AUC: Area under the curve

Table 2. Subject frequency and percentage of the diagnosis of breast cancer in Gail Risk Score Group [low risk (≤20%) vs. high risk (>20%)]

	Breast cancer diagnosis		
Gail group (%)	**No n (%)**	**Yes n (%)**	**Total n (%)**
≤20	96 (96.0)	4 (4.0)	100
>20	33 (97.1)	1 (2.9)	34
Total	129	5	134

The Fisher's exact test p-value 1.00 indicated that there was no statistically significant difference in diagnose breast cancer between the two Gail groups.

purposes (30). These risk assessment models, while commonly used in clinical practice, have been shown to have significant variability when identifying different populations of women eligible for screening MRI (31).

While all models have their strengths and weaknesses, the Gail and TC model are the only two that are readily available and free to all users. The Gail model contains fewer factors and can be easily run by patients themselves. However, it is not validated in women less than age 35 years, which limits its usefulness as a risk model for younger patients. TC is a more complex and robust risk model. However, it can be difficult to use and requires a provider to enter data, thus limiting its use outside of the clinic (24, 25). Conflicting data exist in the literature regarding the level of accuracy between these two models, with some studies indicating that the TC model is superior in terms of specificity, sensitivity, and positive and negative predictive value (32, 33), while others reporting greater AUC and specificity for the Gail model (34, 35). Guidelines warn against the use of the Gail model when assessing MRI eligibility for screening purposes due to accounting for limited family history (31). The TC model collects additional data, such as menopausal status, BMI, more extensive family history and the presence of LCIS, which theoretically can increase breast cancer risk prediction (Table 4). Additionally, variables such as mammographic density and genetic and non-genetic factors have been supported to aid in improved cancer risk prediction (36). When accounting for all the additional risk factors that the TC model takes into account, our data suggest that the TC lifetime risk percentage offers no additional accuracy in predicting breast cancer detection by MRI than the Gail model. These findings are supported by a recent study which found that the TC lifetime risk percentage failed to identify approximately 40% of women who were eligible for changes in their medical management, such as undergoing screening MRI (37) and another large cohort study that reported significant overestimation of breast cancer with the TC model when high risk lesions are found (38).

Breast MRI has been recommended as an adjunct to mammography in women classified as high-risk for development of breast cancer. The recommendations stem from a consensus panel which determined that a Claus LR% equal or greater than 20% is associated with increased cancer detection. The Claus model takes into account hereditary risk factors but fails to include non-hereditary risk factors that have been found to impact the lifetime risk of breast cancer in a woman. Since the TC and Gail models additionally account for non-hereditary risk factors and are widely available online, they are routinely used for risk stratification of MRI eligibility and chemoprophylaxis management, respectively. The 20% cutoff associated with increased cancer detection remains a criterion for classifying a woman as high-risk for breast cancer development, irrespective of the limitations of the Claus model. The TC and Gail models vary from the Claus model, as demonstrated in previous studies, with the TC and Gail models estimating a far higher lifetime risk than Claus (26). In fact, a more recent study found significant differences in the number of women that were eligible for MRI screening identified by the risk assessment models utilized in the study (TC, Claus, BRCAPRO) (31). In our study, we demonstrated no statistically significant correlation between the Gail or TC models when utilizing MRI as a screening modality with 20% lifetime risk cutoff to classify patients as high-risk. While the TC model is a rich source of information and risk stratification, this information calls into question the common practice of using 20% lifetime risk as cutoff for yearly MRI screening when the TC model is used to determine risk. Our data, along with others, suggest the 20% LR, as determined by testing the Claus model, may be too low when using a more sensitive model such as TC.

The results of our study should be interpreted in the context of its limitations. A major limitation of our study was the limited number of subjects who underwent screening MRI at our center and the low number of patients that were diagnosed with biopsy proven breast cancer after undergoing screening with breast MRI. With only five subjects, or 3.1% of our high-risk patient population, diagnosed with

Table 3. Subject frequency and percentage of the diagnosis of breast cancer in TC risk score [low risk (≤20%) vs. high risk (>20%)]

	Breast cancer diagnosis		
TC group (%)	**No n (%)**	**Yes n (%)**	**Total n (%)**
≤20	77 (98.7)	1 (1.3)	78
>20	80 (95.2)	4 (4.8)	85
Total	158	5	163

The Fisher's exact test p-value 0.3689 indicated that there was no statistically significant difference in diagnose breast cancer between the two TC groups
TC: Tyrer-Cuzick

Table 4. Variable used in the Claus, Gail and Tyrer-Cuzick models

Variables	Gail	Claus	Tyrer-Cuzick
Personal information			
Age	Yes	Yes	Yes
Body mass index	No	No	Yes
Hormonal factors			
Menarche	Yes	No	Yes
First live birth	Yes	No	Yes
Menopause	No	No	Yes
Personal breast disease			
Breast biopsies	Yes	No	Yes
Atypical hyperplasia	Yes	No	Yes
LCIS	No	No	Yes
Family history			
First degree relatives	Yes	Yes	Yes
Second degree relatives	No	Yes	Yes
Age of onset of cancer	No	Yes	Yes
Bilateral breast cancer	No	No	Yes
Ovarian cancer	No	No	Yes
Male breast cancer	No	No	No

LCIS: Lobular carcinoma in situ, TC: Tyrer-Cuzick

breast cancer during the study period, it is possible that our lack of predictive value is due to a low event rate rather than lack of predictive value of either calculator. This study serves only as a pilot study to guide larger trials. A larger prospective clinical trial would be necessary to determine at what percentage lifetime risk we should recommend patients undergo MRI screening when using a more sensitive model such as TC.

In conclusion, the TC model is a risk stratification tool that is currently used to guide breast cancer screening recommendations, while the Gail model has mainly been utilized to guide chemoprophylaxis management in women with increased risk for development of breast cancer. Neither have been validated as a predictive model for utility of MRI screening in a large study. In our study, the TC model did not appear superior to the Gail model when predicting the benefit of breast MRI screening. Additionally, the current 20% cutoff that classifies a woman as high-risk for future development of breast cancer, which was originally determined based on calculations derived from the Claus model, was not found to be statistically significant between the Gail or TC LR calculators and a diagnosis of breast cancer. These findings suggest that we should use the 20% LR cutoff using the TC model with caution when making MRI recommendations. A larger, multicenter trial, with a higher event rate of cancer diagnoses would be necessary to determine a more appropriate cutoff value for initiating MRI screening using this widely available risk calculator.

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Original Article

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The Impact of the COVID-19 Pandemic on Breast Cancer Patients

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ABSTRACT

Objective: The coronavirus disease-2019 (COVID-19) pandemic causes delays in the diagnosis and treatment of cancer patients due to fear of contagion and lockdown. This study aims to investigate the effects of the COVID-19 pandemic on breast cancer patients treated in our breast center.

Materials and Methods: Patients who applied to our clinic with the diagnosis of invasive breast cancer in March 2020 and March 2021 (Study Group) when the COVID-19 pandemic was observed, and in March 2019 and March 2020 before the COVID-19 pandemic (Control Group) were compared in terms of demographic, clinical and pathological characteristics. Statistical analyses were performed using the SPSS software version 21.

Results: There were 176 (46%) patients in the study and 206 (54%) patients in the control group. Almost a 15% reduction was detected in patients admitted during the COVID-19 pandemic. The rate of pre-menopausal patients and patient-related delay time (PRDT) were significantly higher in SG (57.7% vs. %45, p=0.013, 2.58 vs. 1.82-month, p=0.001, respectively). There was a larger tumor size and more metastatic lymph nodes after NAC in the SG, but the differences were not significant. There was no difference regarding breast cancer stages and molecular subtypes between the two groups, but there was significantly more de novo stage IV breast cancer in the SG (p=0.009). The incidence of neo-adjuvant chemotherapy and type of surgical therapy was similar between the two groups.

Conclusion: COVID-19 pandemic caused a decrease in the number of patients who applied to our clinic and increased patient-related delay time due to fear of transmission and lockdown. The rate of de novo stage IV breast cancer was also significantly increased.

Keywords: Breast cancer, COVID-19, *de novo* breast cancer, metastatic cancer, pandemic, patient-related delay time

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Key Points

- Patient-related delay time increased during the COVID-19 pandemic.
- Frequency of de nevo metastatic breast cancer increased during the COVID-19 pandemic.
- Breast conservation rate did not change during the COVID-19 pandemic.

Introduction

Coronavirus disease-2019 (COVID-19) pandemic started as a cluster of cases with pneumonia reported by the Wuhan Municipal Health Commission on December 31, 2019. On March 11, 2020, WHO (World Health Organization) assessed that COVID-19 can be characterized as a pandemic (1). The first COVID -19 case in Turkey was reported on March 11, 2020 (2). With the increase in COVID-19 cases, elective and non-urgent surgical procedures, including cancer, have been delayed in hospitals all over Turkey as in the whole world (3, 4).

Along with the lockdowns, patients started to refrain from applying to hospitals. According to a report from Finland (5), the most common operation, laparoscopic appendicectomy, decreased by 32% three weeks before the lockdown in March 2020. According to the same report, hospital admissions decreased (5).

Care of breast cancer patients affected by COVID-19 pandemic. Breast surgery delayed for early breast cancer patients if they had hormone receptor-positive cancers. Those patients were managed by endocrine treatment until appropriate conditions were established. At the beginning of May 2020, lockdown and restrictions eased. Patients with breast lumps or biopsy-proven breast cancer started to come to hospitals, and breast surgery started with precautions.

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In a study from Turkey, the total delay time in breast cancer treatment was almost 14 weeks (6). Thus, nearly one-third of the whole delay time was patient-related delay time. In the COVID-19 pandemic, it can be estimated easily that the patient-related delay time (PRDT) would be longer.

The study aimed to compare characteristics of breast cancer patients treated in our breast center before and after the COVID-19 pandemic.

Materials and Methods

The data required for this study was obtained from the patient records in our archive. The study group (SG) consisted of patients with invasive breast cancer treated between March 2020 and March 2021. The control group (CG) was composed of patients treated in the pre-COVID-19 period (March 2019-March 2020). Demographic, clinical, pathological, and treatment characteristics of patients were recorded. PRDT (patient-related delay time) was defined as the time between the onset of first symptoms and the first medical visit (this analysis included only patients with self-detected cancers). System-related delay time (SRDT) was the time between the first medical visit and the start of therapy.

The breast cancer staging was done according to the AJCC 7th edition of the TNM cancer staging system. The Demiroğlu Science University Ethics Committee approved the study.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether or not they are normally disturbed. Mann-Whitney U test was used to evaluate parameters not normally disturbed, such as age and PRDT. The chi-square test was used to compare categorical parameters such as menopausal status, complaint, clinical-stage, pathologic stage, surgical treatment, molecular subtypes, and neoadjuvant treatment. A p-value of less than 0.05 was considered to show a statistically significant result.

Results

There were 176 (46%) patients in the SG and 206 (54%) patients in the CG (Table 1). Almost 15% reduction detected in patients admitted during the COVID-19 pandemic compared to last year. Median follow-up time was 6.4 (1–25) months for all patients. It was the median of 12.6 (1–25) months for the control group and the median of 2.5 (1-15) months for the study group (p<0.001) (Table 1). The median age was not different between the two groups [49 (27–88) vs. 47 (27–89), p = 0.09], while there were significantly more pre-menopausal patients in the SG (57.7% vs. 45%, p = 0.013, Figure 1). The most common symptom was a lump for both groups (Figure 2).

The patient-related delay time (PRDT) was substantially longer in the SG [(2.58±2.1) months vs. (1.82±1.4) months, p = 0.001]. On the other hand, system-related delay time (SDRT) was similar between the two groups (Table 1).

Table 1. Patients characteristics

Characteristics	Total	Control group	Study group	p-value
Number of patients	382	206 (54%)	176 (46%)	0.09#
Median age	48 (26–89)	49 (27–88)	47 (27–89)	
Menopausal status				
Pre-menopausal	193	92 (45%)	101 (57.7%)	**0.013***
Post-menopausal	187	113 (55%)	74 (42.3%)	
PRDT (months)	2.17±1.8	1.82±1.4	2.58±2.1	**0.001#**
SRDT (months)	0.39±0.9	0.4±1.06	0.37±0.7	**0.57#**
Follow-up time-months(median)	6.4 (1–25)	12.6 (1–25)	2.5 (1–15)	**<0.001#**
Staging method				
Patients with NAC				
Mammography	119	66 (100%)	53 (100%)	0.06*
Breast ultrasound	115	62 (94%)	53 (100%)	
Breast MRI	67	35 (53%)	32 (60.4%)	0.42*
PET CT	113	61 (93%)	52 (98 %)	0.15*
Other (PET MR, CT, Bone scintigraphy)	6	5 (7%)	1 (2%)	
Patients without NAC				
Mammography	263	140 (100%)	123 (100%)	
Breast ultrasound	252	135 (96.5%)	117 (95.1%)	0.59*
Breast MRI	127	68 (49%)	59 (48%)	0.92*
PET CT	91	42 (30%)	49 (39.8%)	0.09*
Other (PET MR, CT, Bone scintigraphy)	5	3 (2%)	2 (1.8%)	

Table 1. Continued

Characteristics	Total	Control group	Study group	p-value
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Other (PET MR, CT, Bone scintigraphy)	5	3 (2%)	2 (1.8%)	
Histologic grade				
Patients without NAC				
HG 1	22	13 (10%)	9 (8.3%)	
HG 2	107	57 (43.5%)	50 (46%)	0.44*
HG 3	109	61 (46%)	48 (44.4%)	
LVI				
No	167	87 (51%)	80 (61%)	0.07*
Yes	135	84 (49%)	51 (39%)	
Tumor size on USG (median)		19 (5–64)	21 (0–70)	0.1#
Metastatic lymph nodes (mean)		1.5±3.7	1.7±2.2	0.92#
Patients with NAC		1.9±3.4	2.2±3.3	0.63#
Patients without NAC		1.4±4	1.09±2.6	*0.33#*
Clinical stage				
Stage 1	134 (38%)	69 (35%)	63 (41%)	
Stage 2	201 (57%)	118 (60%)	83 (54%)	
Stage 3	17 (5%)	10 (5%)	7 (4.5%)	0.7*
Pathological stage				
Patients with NAC				
pCR	16	10 (18.2%)	6 (22%)	
Stage 1	19	15 (27.8%)	4 (15.4%)	
Stage 2	32	21 (38.9%)	11 (42.3%)	0.79*
Stage 3	11	7 (13%)	4 (15.4%)	

Table 1. Continued

Characteristics	Total	Control group	Study group	p-value
Patients without NAC				
Stage 1	109	58 (42.6%)	51 (46.4%)	0.32*
Stage 2	115	65 (47.8%)	50 (45.5%)	
Stage 3	20	13 (9.6%)	7 (6.4%)	
***De novo* Stage IV breast cancer**				
No	355 (93%)	198 (96.1%)	157 (89.2%)	**0.009***
Yes	27 (7%)	8 (4%)	19 (10.8%)	
NAC				
Yes	119 (31.2%)	66 (32%)	53 (30%)	0.68*
No	263 (68.8%)	140 (68%)	123 (70%)	
Surgical treatment				
Mastectomy	101 (29%)	56 (29%)	45 (29.4%)	0.88*
Breast-conserving surgery	247 (71%)	139 (71%)	108 (70.6%)	
Reconstruction with prosthesis				
No	49 (48.5%)	25 (44%)	24 (54.5%)	0.32*
Yes	51 (51%)	31 (55.4%)	20 (45.5%)	
Molecular subtype				
Lum A	125 (33%)	72 (35%)	53 (30.6%)	0.29*
Lum B	168 (44.4%)	91 (44.4%)	77 (44.5%)	
Her2 +	32 (8.5%)	19 (9.3%)	13 (7.5%)	
TNBC	53 (14%)	23 (11.2%)	30 (17.3%)	
Local recurrence				
Yes	15 (3.9%)	7 (3.4%)	8 (4.5%)	0.56*
No	367 (96.3%)	199 (96.6%)	168 (95.5%)	

#Mann-Whitney U test, *Chi-square test.
NAC: Neoadjuvant chemotherapy, PRDT: Patient-related delay time, SDRT: System-related delay time, LVI: Lymphovascular invasion, USG: Ultrasonography, pCR: Pathologic complete response, MRI: Magnetic resonance imaging, CT: Computed tomography, PET: Positron emission tomography, TNBC: Triple-negative breast cancer

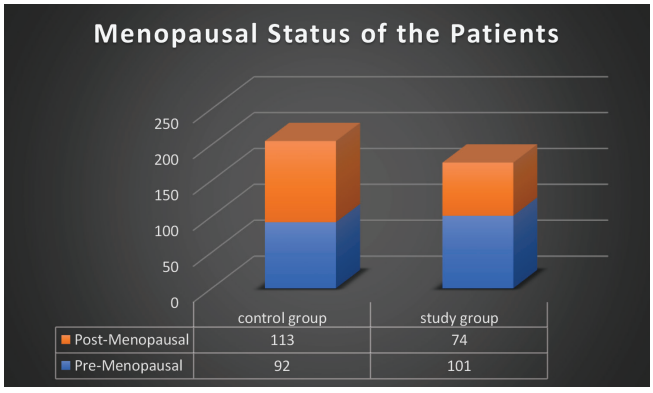


Figure 1. Menopausal status between the two groups

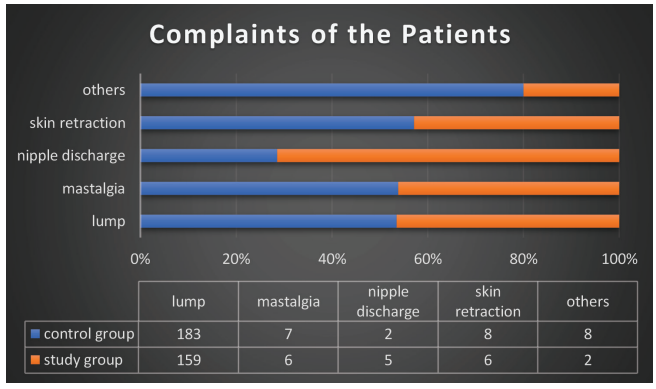


Figure 2. Complaints of patients during admission

There was no difference between early and locally advanced breast cancer between the two groups (Figures 3, 4a and 4b), but there was more de novo stage IV breast cancer in the SG (10.8% vs. 4%, p = 0.009) (Figure 5).

There was a larger tumor size and more metastatic lymph nodes after NAC in the SG, but the differences were not significant. Clinical and pathologic stages, LVI (lymphovascular invasion), histologic grade, molecular subtypes, neo-adjuvant chemotherapy, and type of surgical

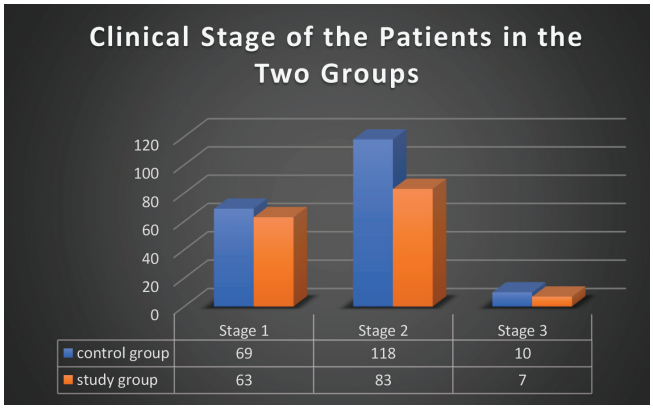
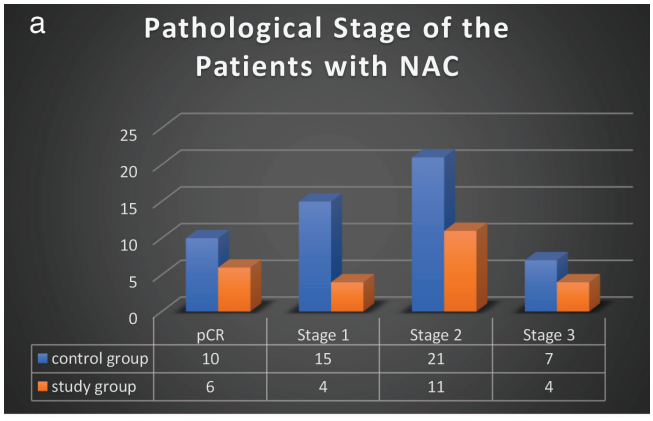


Figure 3. Clinical Stages of Patients



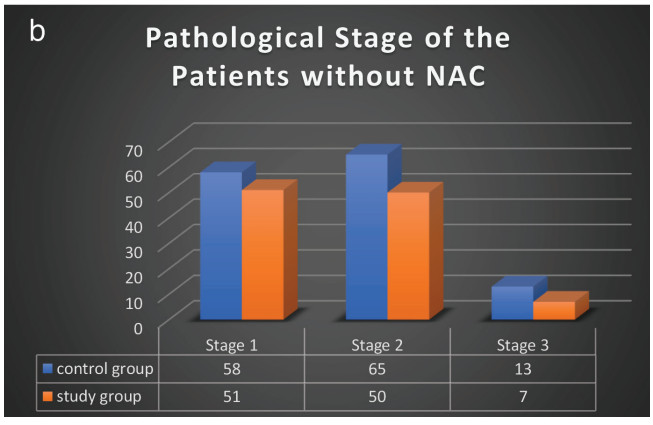


Figure 4. a) Pathologic Stages of Patients with NAC. **b)** Pathologic Stages of Patients without NAC

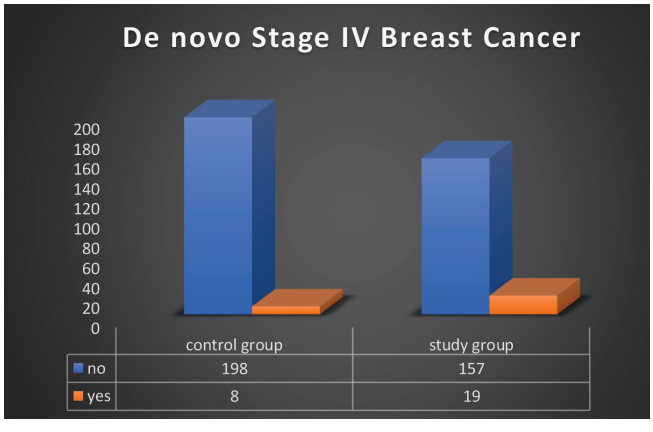


Figure 5. *De novo* Stage IV breast cancer

therapy were similar between the two groups (Table 1). The staging was made mostly mammography and breast ultrasound. Almost half of the patients underwent breast magnetic resonance imaging (MRI) (Table 1).

Discussion and Conclusion

The number of urgent and elective surgical procedures and patient admissions to hospitals during the COVID-19 outbreak has decreased significantly compared with the pre-COVID-19 period. For example, Filipe et al. (7) found an overall decrease in the number of breast cancer patients undergoing surgery. Also, Dauti Işıklar et al. (8) detected a decline in the number of patients who consulted at their oncology clinic. Similarly, compared to last year, we observed an almost 15% reduction in the number of patients admitted to our center during the COVID-19 pandemic.

Immediate implant-based breast reconstruction is the treatment of choice after mastectomy. However, due to using the healthcare system more efficiently during the COVID-19 pandemic, many authors suggested keeping breast cancer surgical treatment simple and deferring reconstructive procedures (9). We observed a non-significant reduction in reconstructive surgical procedures in the COVID-19 period in our center. Mastectomy rates remained similar with the pre-COVID-19 period. The molecular subtypes and the number of patients with early or locally advanced disease were not significantly different between the two groups in our study. This may explain the lack of difference between patients who underwent neoadjuvant chemotherapy in both groups and the similarity of mastectomy rates.

Although patient age was not different between the two groups, the number of pre-menopausal women was significantly increased in the study group. This could result from the easing of lockdown only for women under 65 years in Turkey. A higher number of pre-menopausal women in SG may be a reason for more de novo metastases.

Several studies reported increased morbidity and mortality related to breast cancer diagnosis and treatment delays. These delays are related to patients and the healthcare system (10-12). In their study, Vanni et al. (13) concluded that the surgical refusal rate increased during the pandemic. COVID-19 related anxiety and fear of infection can be reasonable reasons that prevent patients from being admitted to the hospital. Accordingly, we found that the PRDT was significantly longer in the SG.

Delays in breast cancer diagnosis during the COVID-19 may affect oncological outcomes. Maringe et al. (14) calculated an estimated 8%–10% increase in deaths due to breast cancer after diagnosis. Vanni et al. (15) compared breast cancer patients operated on in COVID-19 period and before. Their study showed significantly more lymph node metastasis and advanced histological grade in patients operated in the COVID-19 period. However, there was no difference in tumor size and molecular subtypes. The proportion of metastatic disease was similar. Eijkelboom et al. (16) detected an increase in metastatic disease in April 2020 compared to the same period of the previous year. In our study, there was no significant difference between the two groups regarding tumor size, metastatic lymph nodes, histologic grade, LVI, clinical and pathologic stage. However, there was a significant increase in de novo metastatic disease in the study group. Shen et al. (17), found that ER, PR, and Her-2 status, high tumor grade, and race were significantly associated with an increased risk of *de novo* metastasis. More *de novo* metastatic disease might be explained by longer PRDT,

more TNBC, and slightly higher-grade patients in SG, although non-significant. Also, there may be other factors rather than PRDT to explain the higher incidence of de novo stage IV breast cancer in SG. In 2012, a study from the United States found that median delay time was almost four weeks (29 days) in 72,586 women diagnosed with invasive breast cancers who had not received neoadjuvant treatment (18). In a multinational study, delay time was 11.5 weeks in Poland, 15.8 weeks in Bulgaria, and 25.5 weeks in Romania (12). Ozmen et al. (6) found that total, patient, and system-related delay times were 13.8, 4.8, and 10.5 weeks in breast cancer patients in Turkey. In the current study, PRDT during the COVID-19 pandemic was ten weeks (mean 2.55±2.1 months), and it was two times longer than PRDT in our previous study.

In conclusion, The COVID-19 pandemic has reduced patients' admission to our clinic, significantly increased patient-related treatment delay, and PRDT may cause the high frequency of de novo stage IV breast cancer in the COVID-19 pandemic.

Ethics Committee Approval: This study was approved by Demiroğlu Science University Clinical Researches Ethics Committee (date and decision no: 16.11.2021/2021-23-01).

Informed Consent: It was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and/or Medical Practices: S.İ., V.Ö.; Concept: S.İ., V.Ö.; Design: S.İ., V.Ö.; Data Collection and/or Processing: S.İ., V.Ö.; Analysis and/or Interpretation: S.İ., V.Ö.; Literature Search: S.İ., V.Ö.; Writing: S.İ., V.Ö.

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

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

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Case Report

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A New Modality for Breast Cancer Diagnosis During the COVID-19 Pandemic: A Case Report

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ABSTRACT

Organized screening for breast cancer (BC) was suspended in most countries of the world during the coronavirus disease-2019 (COVID-19) pandemic. Computed tomography (CT) scans of the chest, frequently performed in patients with severe forms of COVID-19, may detect asymptomatic breast abnormalities. A 72-year-old patient, with a severe form of COVID-19 underwent a diagnostic CT scan. This led to the unexpected discovery, at an early stage, of a 12 mm, high grade, Human epidermal growth factor receptor 2 positive BC, with a high proliferation index. After responding to chemotherapy, she was managed with conservative breast surgery with sentinel lymph node biopsy. Delayed management of BC can be responsible for poor outcomes. Patients with severe forms of COVID-19 are also at risk for developing BC due to common risk factors. Thirty percent of incidental breast lesions discovered on CT scans are undiagnosed BC. Careful study of the mammary glands on CT scan of patients with COVID-19 may allow early diagnosis of a malignant tumor in a high-risk population for BC and deprived of routine screening mammography.

Keywords: Breast cancer, COVID-19, SARS-CoV-2, screening, chest scan

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Key Points

- Breast cancer screening was suspended in many countries around the world during the COVID-19 pandemic.
- Computed tomography scans of the chest are often performed on the patients with severe COVID-19.
- 30% of breast lesions incidentally discovered on chest scans are due to cancer.
- Careful study of mammary glands on chest scans in patients infected with SARS-CoV-2 may allow early diagnosis of a malignant tumor in a high-risk population for breast cancer in the absence of routine screening mammography.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for a pandemic of the condition coronavirus disease-2019 (COVID-19) that has disrupted global health care systems since 2020. Initial publications suggested an increase in the frequency of severe forms of COVID-19 in the elderly or those with significant comorbidities (1). Recommendations were modified for the management of patients with breast cancer (BC). The objective was twofold, not to result in a loss of chance from an oncological perspective, while protecting from a possible COVID-19 infection. The suspension of screening was one of these measures (2, 3). Computed tomography (CT) scans, frequently performed in patients infected with SARS-CoV-2, have thus become one of the ways of detecting asymptomatic breast abnormalities.

We report here the case of a patient with high-grade BC diagnosed at an early stage by a CT scan carried out in the context of a SARS-CoV-2 infection, to emphasize the crucial role of chest CT scans.

Case Presentation

A 72-year-old female patient presented in July 2020 with worsening dyspnea, anosmia and agueusia, after a positive PCR test for SARS-CoV-2. The injected chest CT scan findings with multiple bilateral frosted glass ranges with fibrosis were consistent with a SARS-CoV-2 infection (Figure 1). An incidental 12 mm breast mass, located in the right breast, was highlighted (Figure 2). Clinical examination of the breast did not

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reveal a mass and there was no suspicious axillary lymph node (LN). The patient was discharged from the infectious disease department after a 10-day hospitalization.

The mammogram carried out a month later revealed a spiculated mass measuring 12 mm, containing microcalcifications that had been absent one year earlier (Figures 3a and b). Breast ultrasound found a hypoechogenic mass, with irregular contours (Figure 4). No suspicious LNs were visualized. A needle core biopsy confirmed a Grade III, infiltrating, ductal carcinoma with highly positive estrogen and progesterone receptors, overexpression of Human epidermal growth factor receptor 2 (HER2), and high proliferation index. Magnetic resonance imagining (MRI) of the breast confirmed these data. Brain and thoracic-abdominal-pelvic CT scans, combined with a bone scan, did not reveal any metastases. The multidisciplinary meeting opted for neoadjuvant chemotherapy and trastuzumab, followed by breast conservation surgery with sentinel LN biopsy, radiotherapy and aromatase inhibitors. The pathological examination of the surgical specimen revealed a complete response.

Discussion and Conclusion

We report the incidental finding of an early-stage BC during chest imaging carried out as part of the assessment of a SARS-CoV-2 infection in a patient with a normal mammogram one year earlier.

Interruption of BC screening during the pandemic had been recommended by many international (3) scientific societies. The rationale for this measure was the potential high risk of SARS-CoV-2 contamination associated with visiting health care centers. Thus, in the absence of a clinical mass, patients did not have access to screening mammograms.

Breast scans present several advantages for diagnosing BC, even in cases of high breast density, without painful manipulation and compression. The diagnostic performance of breast scans is improved by contrast product injection with a reported sensitivity of 90% [95% confidence interval (CI): 0.785–0.956] and a specificity of 79% (95% CI: 0.709–0.85) (4). In addition, it is more accessible than MRI. In contrast to breast scans, chest CT scans are not dedicated to studying the mammary gland. However, organs present in chest CT scan sectional images, such as the two breasts, can be studied systematically and carefully.

Late diagnosis of BC and therefore delayed surgery and treatment may be responsible for worsening tumor stages at diagnosis and decreased survival. Bleicher et al. (5) in 2016 and Mateo et al. (6) in 2019 studied 115,790 and 351,087 patients respectively with invasive, non-inflammatory and non-metastatic cancers. They showed a 10% overall survival decrease per additional month between diagnosis and surgical management (95% CI: 1.07–1.13; p<0.001; and 95% CI: 1.08–1.13; p<0.001, respectively). A large study with more than

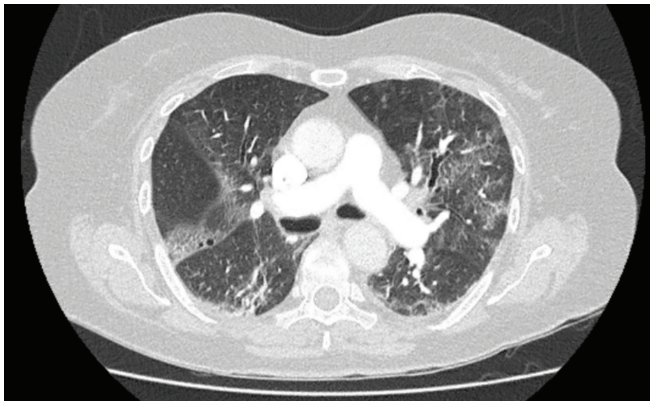

Figure 1. Chest CT scan with multiple, bilateral, frosted glass ranges with fibrosis

CT: Computed tomography

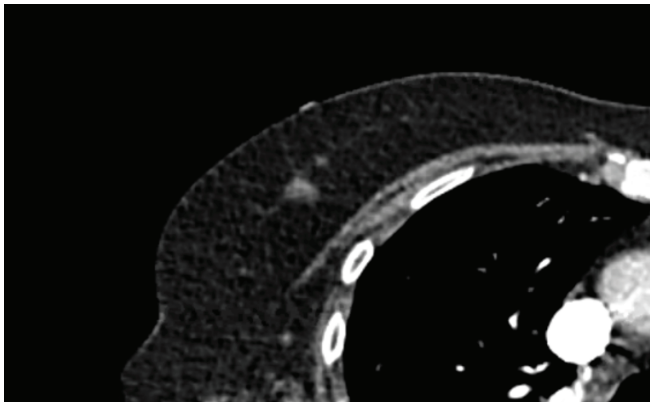

Figure 2. An incidental right breast mass of 12 mm on chest CT scan

CT: Computed tomography

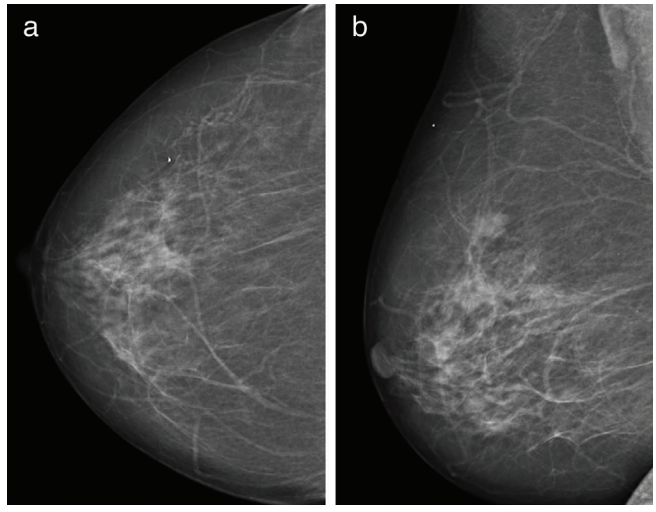

Figure 3. a) The mass was seen on the mammogram (frontal) as a dense, poorly limited, spiculated mass, containing microcalcifications. **b)** The mass was seen on the mammogram (lateral) as a dense, poorly limited, spiculated mass, containing microcalcifications

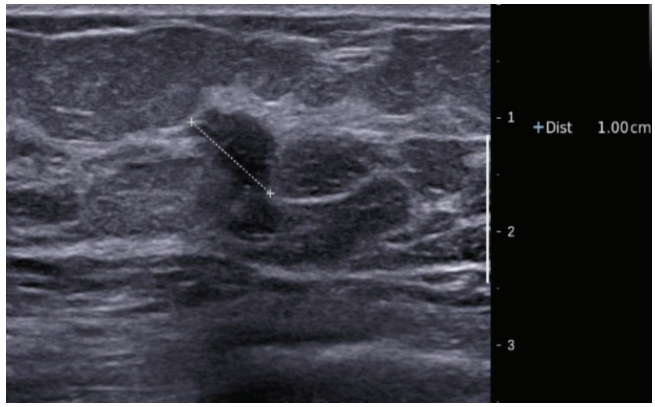

Figure 4. The breast ultrasound found a hypoechogenic mass, with irregular contours and a large vertical axis

420,000 cases confirmed an excess of mortality [hazard ratio (HR): 1.14, 95% CI: 1.09–1.20] in cases of surgery performed more than 12 weeks after the initial diagnosis, for stage I (HR: 1.19, 95% CI: 1.11–1.28) and stage II (HR: 1.16, 95% CI: 1.08–1.25) disease (7). The impact on survival may be related to significant tumor growth, particularly for "aggressive" tumors such as triple negative phenotypes or those overexpressing HER2. A meta-analysis of 2,533,355 patients (8) showed that delayed surgical management of three months resulted in a survival decrease, notably for stage I (HR: 1.27, 95% CI: 1.16–1.40) and II cancers (HR: 1.13, 95% CI: 1.02–1.24).

A few months after the onset of the COVID-19 pandemic, the impact of screening cessation on tumor characteristics and survival was studied. Vanni et al. (9) found a statistically different LN invasion rate when comparing 220 patients treated during the pandemic and a similar group of patients treated a year earlier. N2 stages were more frequent (8% vs. 2%, p<0.05). This locoregional invasion was statistically associated with an extended delay before surgical management [odds ratio (OR): 1.07, 95% CI: 1.01–1.13, p=0.017]. Thus, according to the predictions of an English group (10), BC mortality could increase from 7.9 to 9.6% at 5 years due to a delay in diagnosis.

Given screening interruption, the study of the mammary glands on chest CT scans, very often carried out in patients suspected of having COVID-19, appears to be essential. People at risk of serious SARS-CoV-2 infections who require further examination or even hospitalization also present an increased risk for BC. Both diseases have common risk factors, such as advanced age, obesity, and type 2 diabetes (3, 11, 12). Chest scans performed as part of the diagnosis of COVID-19 infection are generally not accompanied by administration of iodized contrast, except when a pulmonary embolism is suspected, particularly in severe forms (13). However, the injected CT scan is better for exploring the mammary gland. In fact, out of a series of 2,945 patients of all ages who received a chest CT scan, 32 breast lesions were incidentally detected (1.1%) and 29 of these were identified in injected scans. After further examination, 31% of the identified lesions were malignant (14). Moyle et al. (15) studied 105,372 scans performed in the general population over a 14-year period. Of the low number of lesions identified (<1%), mostly on injected scans (66/78; 84.6%), 28% were cancerous. The most common cancers identified were invasive carcinomas (14). The lower rate of *in situ* carcinomas may be explained by the inability to visualize microcalcifications on chest CT scans (15).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and/or Medical Practices: V.F., Ca.M., R.A.I., S.A., C.M.; Concept: V.F., Ca.M., R.A.I., S.A., C.M.; Design: V.F., Ca.M., R.A.I., S.A, C.M.; Data Collection and/or Processing: V.F., Ca.M., R.A.I., C.M.; Analysis and/or Interpretation: V.F., Ca.M., R.A.I., C.M.; Literature Search: V.F., Ca.M., C.M.; Writing: V.F., Ca.M., S.A., C.M.

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

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Case Report

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Cystic Neutrophilic Granulomatous Mastitis Regression with the Tumor Necrosis Factor-α Inhibitor, Adalimumab

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ABSTRACT

Idiopathic granulomatous mastitis (IGM) is a rare, benign, inflammatory breast disease that primarily affects parous women within a period of five years post-partum. Cystic neutrophilic granulomatous mastitis (CNGM) is clinically identical to IGM, but histopathology demonstrates distinct central lipid vacuoles rimmed by neutrophils with an outer cuff of epithelioid histiocytes/granulomas, with inconsistent presence of Coryneform bacteria within the vacuoles. There is no consensus on the treatment for either IGM or CNGM, which may be managed surgically with wide local excision or mastectomy or medically with antibiotics, steroids, and steroid-sparing immunosuppressive agents. We present a 30-year-old woman with plaque psoriasis and CNGM whose breast symptoms resolved after treatment with the tumor necrosis factor alpha (TNF-α) inhibitor adalimumab, which has not previously been described as a treatment option for CNGM.

Keywords: Cystic neutrophilic granulomatous mastitis, idiopathic granulomatous mastitis, adalimumab, tumor necrosis factor alpha inhibitor, case report

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Key Points

- Cystic neutrophilic granulomatous mastitis (CNGM) has an identical clinical presentation to idiopathic granulomatous mastitis (IGM)
- IGM and CNGM are managed surgically and/or with antibiotics, steroids, and steroid-sparing immunosuppressives
- Tumor necrosis factor alpha (TNF-α) inhibitors are considered safe and effective as long-term treatment for chronic autoimmune granulomatous diseases, such as inflammatory bowel disease and sarcoidosis
- TNF-α inhibitors may be a potential non-steroidal, non-anti-microbial and non-surgical treatment alternative for refractory IGM and CNGM

Introduction

Idiopathic granulomatous mastitis (IGM) is a rare, benign, inflammatory breast disease, the etiology and management of which are poorly defined in the literature. Patients classically present with a painful, unilateral inflammatory breast mass. Cystic neutrophilic granulomatous mastitis (CNGM) presents identically to IGM. Although no treatment consensus exists, IGM and CNGM may be managed surgically with wide local excision or mastectomy or medically with antibiotics, intralesional or systemic steroids, or other immunosuppressive therapies, such as methotrexate (1-4). Adalimumab is a humanized monoclonal antibody to tumor necrosis factor alpha (TNF-α) that is used to treat a variety of autoimmune conditions, including plaque psoriasis. We describe a case of CNGM that responded to adalimumab prescribed for the patient's comorbid plaque psoriasis. Adalimumab has not previously been reported as a treatment option for CNGM.

Case Presentation

A 30-year-old Hispanic woman presented with a one-week history of a firm, tender mass under the left nipple. She was a gravida 1 para 1, who delivered at age 25 and did not breastfeed. Her medical history was significant for poorly controlled psoriasis, treated latent tuberculosis infection, and a prolactinoma.

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Physical examination of the left breast revealed a firm, subcutaneous mass measuring 2.5 centimeters at the 9 o'clock position under and medial to the nipple, centered at 1 cm from the nipple. There were no overlying skin changes, although there were psoriatic plaques affecting the skin on both breasts and over 10% of her body surface area. No other masses or nipple discharge were observed.

Ultrasound revealed a heterogeneous, hypoechoic, irregular mass with extension to the skin/nipple (Figure 1a).

A round, isoechoic and hypervascular lesion, less than 1 cm in diameter, was also found within the mass, correlating with the physical exam finding. Given the appearance of an abscess, the patient was started on a course of trimethoprim/sulfamethoxazole.

Aspirate fluid from the mass was sent for culture and revealed moderate *Corynebacterium tuberculostearicum*. However, as the patient felt well after her antibiotic course, she opted for observation only.

About one month later, her symptoms persisted, and the mass had slightly enlarged. Ultrasound-guided vacuum-assisted core needle biopsy revealed sheets of histiocytes and mixed acute and chronic inflammation with granulation tissue formation in a background of a few benign breast lobules. Interspersed granulomas with central neutrophilic abscess formation or large "punched out" spaces were present. The gram stain highlighted gram-positive bacilli within the cystic spaces. In the absence of features suggestive of a more specific etiology, these findings were most consistent with IGM. Specifically, the neutrophilic micro-abscesses within granulomas, in association with punched-out spaces and gram-positive bacilli, were morphologically consistent with CNGM (Figure 2a-d).

The patient elected to try co-managing her psoriasis and CNGM with adalimumab. She injected herself with 40 mg/0.8 mL of adalimumab subcutaneously every 14 days. After one month of treatment, the patient reported her breast pain had resolved, and repeat ultrasound revealed decreased size of the mass (Figure 1b). Her skin significantly improved after treatment with adalimumab, with her psoriasis affecting only about 1% of her body surface area.

During a temporary discontinuation of adalimumab two months later, her breast symptoms recurred. One week after resuming treatment, the breast mass again decreased in size and induration, and her pain and swelling again resolved.

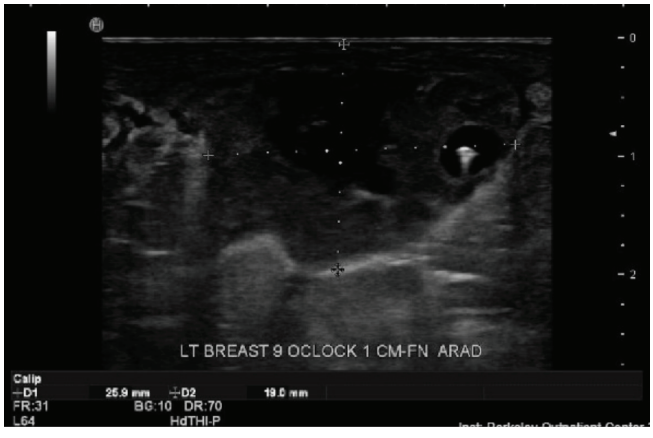

Figure 1a. Ultrasound image of left breast mass after core biopsy, prior to start of treatment (hypoechoic mass measures 26 x 19 x 21 mm)

Discussion and Conclusion

Adalimumab and other TNF-α inhibitors are considered safe and effective as long-term treatment for other chronic autoimmune granulomatous diseases, such as inflammatory bowel disease and sarcoidosis (5). Only one previously published case described successful treatment of IGM with a TNF-α inhibitor (etanercept), in combination with methotrexate (6). The immunological etiopathogenesis of IGM is poorly understood. Investigations are limited to a single study,

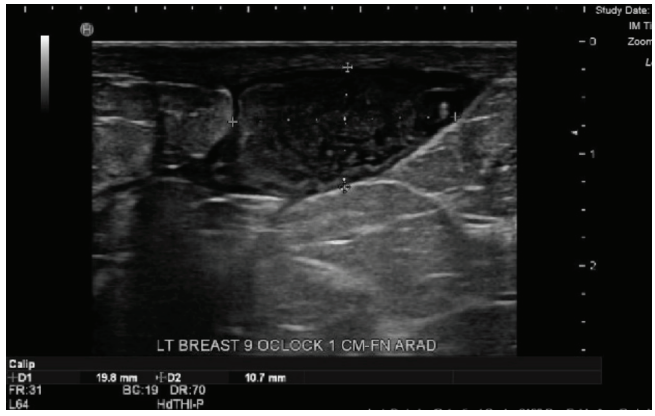

Figure 1b. Follow-up ultrasound image of left breast mass 1 month into treatment (hypoechoic mass measures 20 x 11 x 19 mm)

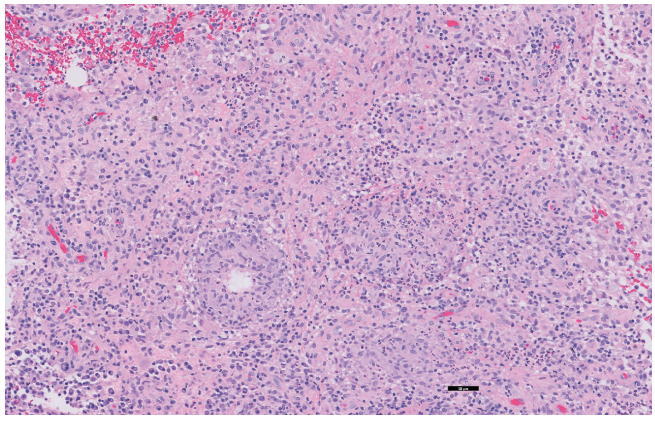

Figure 2a. Non-necrotizing granulomatous inflammation with a mixed inflammatory infiltrate and destruction of lobules (H&E, 200x)

H&E: Hematoxylin and eosin

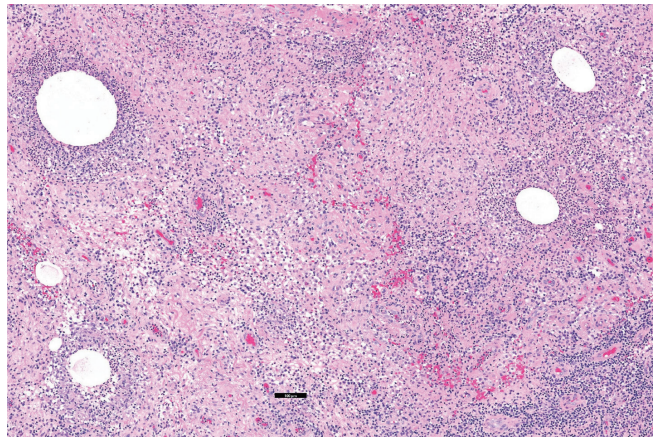

Figure 2b. Granulomatous inflammation with cystic spaces (H&E, 200x)

H&E: Hematoxylin and eosin

which found serum levels of proinflammatory cytokines, such as interleukin-8 (IL-8) and interleukin-17 (IL-17), were elevated in cases of IGM compared with controls (7). While TNF-α levels have not been reported to be significantly higher in patients with IGM or CNGM, other T helper 17/IL-17- driven diseases, such as psoriasis, and diseases exhibiting elevated IL-8 levels, such as rheumatoid arthritis, respond to TNF-α blockade (8). Notably, treatment with adalimumab resolved the CNGM symptoms in our patient without requiring prolonged antibiotic therapy or surgical management, which is associated with high morbidity and recurrence rates (9, 10). TNF-α inhibitors are widely viewed as having a more favorable safety profile than systemic steroids, which are associated with potentially serious sequelae, including weight gain, osteoporosis, hypertension, glucose intolerance, and risk for opportunistic infection. Though further study is needed to determine the efficacy of TNF-α inhibitors in CNGM, their therapeutic potential for this challenging condition is evident.

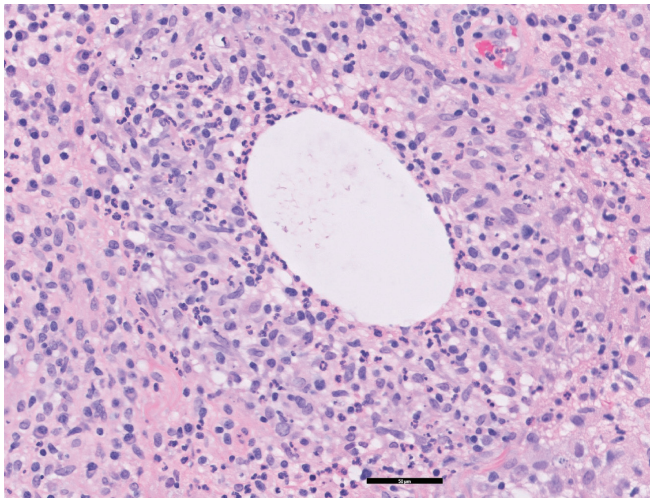

Figure 2c. Cystic vacuoles lined by neutrophils with surrounding histiocytes and lymphocytes (H&E, 400x)

H&E: Hematoxylin and eosin

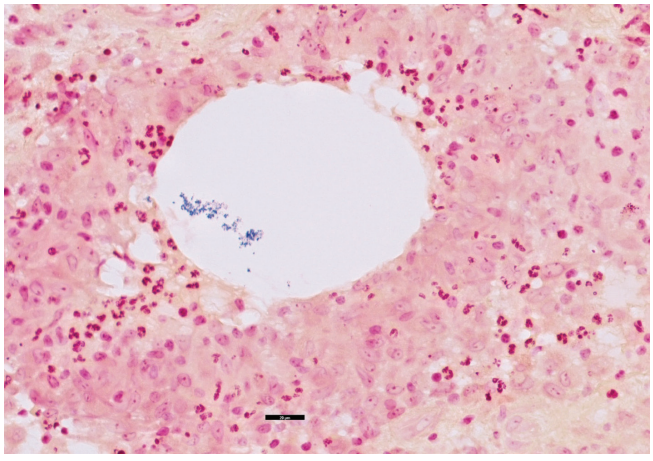

Figure 2d. Gram-positive bacilli with palisaded arrangement typical for *Corynebacterium* species are identified within cystic spaces (Gram stain, 400x)

H&E: Hematoxylin and eosin

While the clinical presentations of IGM and CNGM are indistinguishable, CNGM has been described as a histologically distinct entity characterized by clear spaces/vacuoles rimmed by neutrophils and cuffs of epithelioid histiocytes/granulomas in the background of a mixed inflammatory infiltrate comprised of lymphocytes, giant cells and neutrophils (11). Distinguishing features of CNGM and IGM are summarized in Table 1. CNGM has been reported to be often, but inconsistently, associated with various *Corynebacterium* species (3, 6, 12) with gram-positive rods localized in the clear cystic spaces, which are absent in the non-cystic neutrophilic presentation of IGM (13). Non-diphtheriae *Corynebacterium* species have not been reported to cause adverse systemic sequelae in the setting of TNF blockade.

A summary of published cases describing CNGM is presented in Table 2. Many cases of both IGM and CNGM are treated with variable, serial combinations of surgery, antibiotics, and/or immunosuppression, such as intralesional or systemic steroids or methotrexate (1-4) with one study reporting the protracted clinical course of both to range from 6 to 50 months (3). Some authors have suggested CNGM should be treated with long-term lipophilic antibiotics targeted at *Corynebacterium* spp. (6, 12, 14). However, of 328 cases previously described in the literature, only one report of three patients (12) clearly describes improvement after four weeks or less of tetracycline antibiotics as monotherapy. A recently published report describes 18 patients who improved after an average of seven months on antibiotic monotherapy, the majority of whom received a course of clarithromycin (5). The remaining cases report varying clinical outcomes, from recurrence of mastitis in the contralateral breast (14), to persistent symptoms after antibiotic and surgical management (2, 3, 15), to eventual resolution after combination therapy with empirical antibiotics, immunosuppression, and/or multiple procedures including incision and drainage, lumpectomy, and/or mastectomy (2-4). Many cases of IGM spontaneously resolve without intervention (15). We believe that there are insufficient data to clearly conclude that antibiotics lead to improved outcomes for CNGM compared with other forms of IGM.

Our patient's swift response to adalimumab provides supporting evidence that patients with CNGM may respond to immunosuppression alone, and the distinction between IGM and CNGM may be histopathologic rather than clinical. Our case illustrates the near-immediate improvement of symptoms, compared with an average of 6–8 months reported for improvement of CNGM with antibiotic

Table 1. Features of cystic neutrophilic granulomatous mastitis and idiopathic granulomatous mastitis

Diagnosis	Cystic neutrophilic granulomatous mastitis	Idiopathic granulomatous mastitis
Pathologic findings	Suppurative lipogranulomas comprised of central lipid vacuoles rimmed by neutrophils and an outer cuff of epithelioid histiocytes Some lipid vacuoles may contain Gram-positive bacilli	Noncaseating granulomatous inflammation, with epithelioid histiocytes, centered on breast lobules, with or without microabscesses No lipid vacuoles No Gram-positive bacilli
Treatment options	Antibiotic therapy, immunosuppression, surgery	Antibiotic therapy, immunosuppression, surgery

Table 2. Summary of case reports describing CNGM

Diagnosis	Authors, year	Number of cases	Clinical features	Histopathologic features	Treatment	Time from treatment to resolution
Granulomatous lobar mastitis	Paviour et al, 2002	24	Breast abscess, mastitis	- Lobule-centered inflammation - Granulomas with an outer cuff of epithelioid histiocytes and giant cells around a central collection of polymorphonuclear leukocytes (PMNs) surrounding an empty space - Coryneform Gram-positive bacilli within the empty spaces surrounded by PMNs	- Surgery (incision and drainage, biopsy, excision, aspiration) - Antibiotics (penicillin, doxycycline, unspecified)	Unknown
Granulomatous mastitis (GM)	Taylor et al, 2003	34	Fever, neutrophilia, unilateral and bilateral nipple inversion, nipple discharge, sinus formation	- Suppurative lipogranulomas with microabscesses outside of the granulomas - Coryneform bacteria confined to empty spaces, which were surrounded by numerous neutrophils	- Surgery (excisional, drainage procedure) - Antibiotics (unspecified) - Immunosuppression (steroids)	Unknown
Cystic neutrophilic granulomatous mastitis (CNGM)	Renshaw et al, 2011	3	Breast mass, erythematous and indurated mass, breast abscess	- Neutrophilic inflammation with cystic spaces and granulation tissue - Gram-positive bacilli in a single cystic space	- Surgery (debridement, biopsy) - Antibiotics (tetracycline, doxycycline)	2 to 4 weeks
CNGM	D'Alfonso et al, 2015	12	Palpable, tender breast mass with skin erythema, persistent abscess, nipple inversion, breast firmness, swelling, draining sinus	- Lobulocentric granulomas with epithelioid histiocytes, Langhans giant cells, lymphocytes, plasma cells, and neutrophils - Clear vacuoles in the center of granulomas, surrounded by neutrophils	- Surgery (incision and drainage, excision, biopsy) - Antibiotics (cephalexin, ciprofloxacin, doxycycline, vancomycin, trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, tetracycline) - Immunosuppression (prednisone)	2 weeks to 6 months
CNGM	Troxell et al, 2016	19	Unknown	- Clear space, surrounded by a rim of neutrophils, surrounded by granulomatous inflammation - Lobular and periductal involvement	- Surgery (aspiration, excision, incision and drainage, biopsy, mastectomy) - Antibiotics (daptomycin, vancomycin, ceftriaxone, cephalexin, dicloxacillin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, metronidazole, moxifloxacin, ciprofloxacin, clindamycin, tetracycline, doxycycline) - Immunosuppression (steroids)	6 to 50 months
CNGM	Helal et al, 2016	35	Breast mass with or without skin ulceration, inflammation, or sinus formation	- Noncaseating granulomas on lobules - Cystic vacuoles in the center of the granuloma rimmed by neutrophils	- Unknown	Unknown

Table 2. Continued

Diagnosis	Authors, year	Number of cases	Clinical features	Histopathologic features	Treatment	Time from treatment to resolution
CNGM	Johnstone et al, 2017	15	Unilateral and bilateral breast mass	- Granulomatous inflammation centered on vacuolated spaces surrounded by neutrophils in a background of neutrophils, plasma cells, lymphocytes, and eosinophils - Gram-positive organisms within vacuolated spaces	- Surgery (lumpectomy, biopsy) - Antibiotics (β-lactams, flucloxacillin, doxycycline, clindamycin, rifampicin, clarithromycin, trimethoprim-sulfamethoxazole, isoniazid)	Unknown
CNGM	Shoyele et al, 2018	7	Tender breast mass, nipple discharge, ipsilateral axillary lymphadenopathy	- Non-necrotizing granulomatous inflammation with neutrophilic microabscesses surrounding clear cystic/vacuolated spaces, admixed with plasma cells, eosinophils, and lymphocytes - Gram-positive bacilli within clear cystic spaces surrounded by neutrophilic microabscesses, surrounded by epithelioid granulomas	- Surgery (incision and drainage, biopsy, excision) - Antibiotics (minocycline, cefuroxime, dalbavancin, daptomycin) - Immunosuppression (steroids, hydroxychloroquine, methotrexate) - Topical anti-inflammatory agent	6 to 11 months
CNGM	Wang et al, 2018	1	Tender breast mass	- Neutrophilic inflammatory infiltrate with lipogranulomas in a lobulocentric distribution - Cystic spaces lined by a cuff of neutrophils - Gram-positive cocci within and at the edge of cystic spaces	- Unknown	Unknown
CNGM	Patel et al, 2018	7	Palpable, painful mass, draining sinus	- Epithelioid histiocytes, multinucleated giant cells, and granulomas with cystic spaces	- Surgery (biopsy) - Antibiotics (unspecified)	Unknown
CNGM	Gautham et al, 2019	6	Painful palpable mass, cutaneous erythema, nipple discharge, abscess	- Large expanses of mononuclear inflammatory cells with histiocytes and focal well-formed granulomata - Neutrophil invested microcysts, with and without Gram-positive bacilli within	- Antibiotics (cephalexin, trimethoprim/sulfamethoxazole, doxycycline, daptomycin, dicloxacillin, vancomycin, piperacillin, tazobactam, ciprofloxacin, clindamycin) - Corticosteroids (high dose parenteral steroids and low-dose oral therapy)	2 to 13 months
CNGM	Maung et al, 2020	12	Painful breast mass, isolated breast pain, palpable breast mass	- Neutrophilic and granulomatous inflammation surrounding clear cystic spaces	- Surgery (biopsy, excision, lumpectomy, incision and drainage, mastectomy) - Antibiotics (doxycycline, vancomycin, penicillin V, cephalexin, clindamycin, cefazolin, amoxicillin/clavulanic acid)	Unknown

Table 2. Continued

Diagnosis	Authors, year	Number of cases	Clinical features	Histopathologic features	Treatment	Time from treatment to resolution
CNGM	Naik et al, 2020	24	Painful breast mass, retracted nipples, nipple discharge, multiple sinuses	- Lobular inflammation in solid lesions, with clear spaces rimmed by neutrophils surrounded by epithelioid cells, lymphocytes, plasma cells, histiocytes, and giant cells - Abscess cavities filled with sheets of neutrophils rimmed by granulomatous inflammation with cystic spaces	- Surgery (lumpectomy, bilateral mastectomy) - Antibiotics (amoxicillin/clavulanic acid, doxycycline, cefotaxime, amikacin)	1 to 6 months
CNGM	Sangoi, 2020	19	Mass, abscess	- Organizing epithelioid histiocytes with intimately admixed neutrophils rimming discrete cystic spaces - Gram-positive bacilli restricted to the cystic spaces	- Surgery (biopsy, excision) - Other treatments unknown	Unknown
CNGM	Patel and Hoda, 2020	1	Unilateral breast pain and central breast swelling	- Multiple suppurative lipogranulomata with round cysts lined by neutrophils with a cuff of epithelioid histiocytes admixed with lymphocytes, plasma cells, and multinucleated giant cells - Some vacuoles with rare Gram-positive bacilli	- Surgery (excision) - Antibiotics (tetracycline)	Unknown
CNGM	Chalmers et al, 2020	1	Unilateral breast pain, swelling, chills, night sweats, skin changes, mass	- Granulomatous inflammation of the lobules with well-formed granulomas and multinucleated giant cells - No bacterial organisms on Gram or Acid-Fast Bacilli stains	- Surgery (incision and drainage, biopsy - Antibiotics (trimethoprim-sulfamethoxazole, moxifloxacin) - Immunosuppression (methylprednisolone, prednisone)	Improved at 6 months but not resolved
CNGM	Tan et al, 2021	1	Unilateral, tender breast mass with edema	- Extensive mixed chronic inflammation centered around lobules - Neutrophils arranged around microcystic lipid spaces, some of which contained Gram-positive bacterial organisms	- Surgery (biopsy, aspiration) - Antibiotics (cephalexin)	Improved after 2 weeks but recurred
CNGM	Patel et al, 2021	1	Unilateral breast swelling, pain, fever, generalized malaise, decreased appetite	- Periductal and perilobular inflammation consisting of lymphocytes, plasma cells, polymorphs, foamy macrophages, histiocytes, Langhans' type of giant cells with acid-fast bacilli - Cystic spaces surrounded by neutrophilic aggregates	- Surgery (incision and drainage) - Antibiotics (anti-tubercular therapy, clarithromycin, amikacin)	6 months

Table 2. Continued

Diagnosis	Authors, year	Number of cases	Clinical features	Histopathologic features	Treatment	Time from treatment to resolution
CNGM	Li et al, 2021	31	Breast mass, pain, abscess, fistula, erythema, nipple retraction, swelling	- Cystic vacuoles encircled by varying numbers of neutrophils in the setting of granuloma and inflammation - Gram-positive bacilli within vacuoles	- Surgery (incision and drainage) - Antibiotics (targeting Corynebacterium kroppenstedtii) - Immunosuppression (corticosteroid)	Unknown
GM	Williams et al, 2021	36	Breast mass or lump, pain or tenderness, erythema	- Lobulocentric active granulomatous inflammation with or without chronic inflammation and no evidence of malignancy - Associated abscess, fat necrosis, stromal fibrosis - Diphtheroids (presumptive Corynebacterium species) commonly identified	- Surgery (incision and drainage, aspiration, excision) - Antibiotics (clarithromycin, macrolides) - Immunosuppression (prednisone)	8 months
CNGM	Tariq et al, 2021	38	Palpable painful breast mass, erythema of the skin overlying, nipple inversion and discharge	- Clear spaces surrounded by a rim of neutrophils, further surrounded by histiocyte-rich granulomatous inflammation - Rare Gram-positive bacteria exclusively inside cystic spaces	- Unknown	2 weeks to 1 year
CNGM	Wang et al, 2021	1	Painful palpable breast mass and worsening open lesions	- Lobulocentric granulomas with mixed inflammation and central cystic spaces lined by neutrophils containing Corynebacterium species	- Surgery (biopsy) - Antibiotics (β-lactams)	Unknown

CNGM: Cystic neutrophilic granulomatous mastitis

therapy in some reports (2, 13). The patient's symptoms recurred after a brief interruption of her adalimumab, then rapidly (one week) improved again with reintroduction of the drug, indicating that the adalimumab was controlling her symptoms, rather than representing a case of spontaneous resolution that happened to coincide with introduction of therapy. This robust response to adalimumab suggests that TNF-α inhibitors should be further explored as a potential non-steroidal, non-antimicrobial and non-surgical, well-tolerated treatment alternative for IGM and CNGM to alleviate symptoms until spontaneous resolution occurs.

The treatment of CNGM remains therapeutically challenging, given the absence of consistent response to surgical or medical treatment. Adalimumab or other TNF-α inhibitors may provide a novel therapeutic approach for refractory IGM or CNGM.

Informed Consent: It was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Case Report

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Nipple Eczema Causing Galactorrhea by Reactive Hyperprolactinemia, Complicated by a Galactocele

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ABSTRACT

We present a case of atopic nipple eczema leading to reactive hyperprolactinemia, by mechanical nipple stimulation. This reactive hyperprolactinemia caused an aggravation of the eczema because of the resulting galactorrhea, by local irritation and inflammation, and was complicated by a galactocele. This benign tumour was a source of concern for the patient and required several diagnostic radiographic examinations.

Keywords: Nipple eczema, hyperprolactinemia, galactocele

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Key Points

- Nipple eczema is a manifestation of atopic dermatitis and constitutes a known topography.
- Mechanical nipple stimulation causes reactive hyperprolactinemia.
- The occurrence of galactorrhea, hyperprolactinemia, or galactocele in a patient who is not breastfeeding should lead to clinical inspection of the skin to search for mechanical factors responsible for mechanical stimulation of the nipple area.

Introduction

Nipple eczema may be a manifestation of atopic dermatitis and constitutes a known topography (1). Bilateral presentation is the most common, with a chronic course involving successive periods of remission and aggravation, particularly in cases of additional contact eczema or during breastfeeding (2, 3).

Hyperprolactinemia is defined as an increase in plasma prolactin concentration to levels beyond the upper limit of the normal range, which is mostly between 15 and 25 ng/mL (corresponding to about 500 IU/mL), according to the method used (4). The typical etiologies of hyperprolactinemia are pituitary diseases (hypophysitis, macroadenoma), hypothalamic diseases (sarcoidosis, meningioma), drug treatments (neuroleptics), and endocrinological conditions (hypothyroidism, polycystic ovary syndrome, pregnancy and breastfeeding). Clinical manifestations are dominated by amenorrhea and galactorrhea.

Reactive hyperprolactinemia in response to external stimulation of the nipple is a known phenomenon that contributes to milk secretion during breastfeeding. The stimulus provided by breastfeeding leads to the secretion of prolactin through activation of the vagal nerve. Repeated stimulation of the nipple in non-lactating women can also activate similar mechanisms, triggering reactive hyperprolactinemia (5-7).

To the best of our knowledge, eczema due to contact of the nipples with maternal breast milk has never previously been reported.

We describe the case of a 48-year-old woman presenting with bilateral atopic eczema of the nipples causing galactorrhea through reactive hyperprolactinemia, resulting in clinical aggravation through secondary local irritation and inflammation, and galactocele. The patient gave her written and informed consent for this publication.

This study was presented as a poster in Journée dermatologiques de Paris in 2019.

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Case Presentation

A 48-year-old, postmenopausal woman had a history of atopic dermatitis diagnosed in childhood, with no other relevant medical history, and without current medical treatment. She had presented with regular flare-ups of generalized eczema, treated with class II topical steroids, but often insufficiently due to a strong fear of steroids. No systemic treatment was attempted, at the request of the patient who did not want to have oral treatment.

An allergology evaluation performed between 1995 and 2019 identified multiple sensitizations. The elimination of these allergens improved the patient's eczema everywhere, with the exception of the nipples, where the lesions persisted. The patient attended because of extremely debilitating, bilateral severe eczema of the nipples, of about twelve months duration. The manifestations were yellow crusty lesions of the nipples, discharging large amounts of a thick milky liquid, emanating from the pores of the lactiferous ducts (Figures 1, 2 and 3). The areolae were thickened and inflamed, and several eczema-like lesions were observed on the patient's back and arms. One nodular lesion of the right breast, a centimeter or so across, was detected on palpation. The rest of the clinical examination was normal.

Pathological examination of a skin biopsy specimen taken from the internal right periareolar region revealed a histological appearance consistent with chronic eczema, with no signs of bacterial or fungal infection.

Bilateral mammography and breast ultrasound examination revealed the presence of a micronodule of pseudocyst-like appearance, consistent with a galactocele of about a centimeter across, under the right areola.

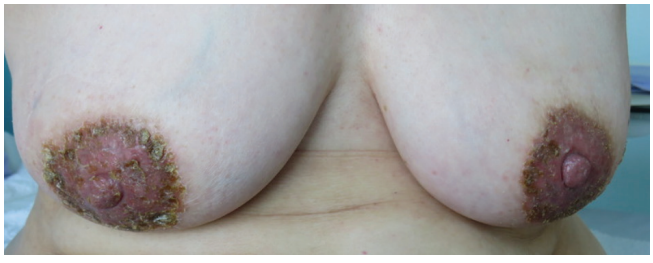

Figure 1. Severe eczema of both nipples. The clinical manifestations were as: crusty yellowing lesions of the nipples, with the discharge of large amounts of a thick milky liquid from fissures and the pores of the lactiferous ducts

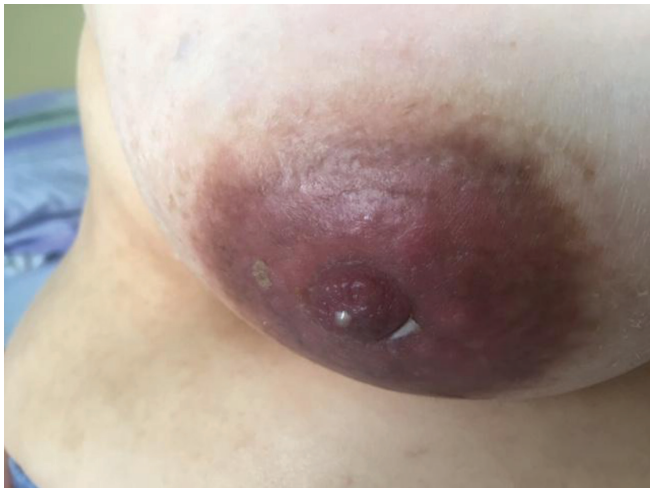

Figure 2. Galactorrhea of the right breast, after initial local care

The examination was classified as bilateral ACR 2 (American College of Radiologists).

Blood tests revealed hypereosinophilia (up to 1798 cells/mm3), and hyperprolactinemia (93.10 ng/mL). Determinations of the plasma concentrations of other hypothalamus-pituitary gland axis hormones (thyroid stimulating hormone, estradiol, follicle stimulating hormone, luteinizing hormone, cortisol and adrenocorticotropic hormone) were normal.

Brain magnetic resonance imaging (MRI) centered on the pituitary gland was performed to rule out pituitary macroadenoma. The results were entirely normal.

Galactocele induced by galactorrhea, secondary to hyperprolactinemia due to mechanical stimulation of the nipples in a context of bilateral atopic nipple eczema, was diagnosed (Figure 4).

Treatment with class I topical steroids, the application of which was checked during hospitalization, replaced by topical tacrolimus, resulted in the complete remission of the nipple eczema and the total cessation of galactorrhea. Tests on biological samples demonstrated a decrease in the prolactin blood level to 37.6 µg/L after 72 hours from the start of treatment, and to 22.9 µg/L (normal) after one month (Figure 5). Six months later she is still in complete remission without any recurrences after only 20 g of topical tacrolimus per month.

Discussion and Conclusion

Galactocele is a complication well known to gynecologists. It occurs postpartum, during breastfeeding, and is not a cause of clinical concern in these contexts. Nipple eczema is a problem well known to patients with atopy; it can greatly affect the quality of life and may be difficult to treat.

Outside the context of breastfeeding, several cases of galactocele in association with galactorrhea and hyperprolactinemia, secondary to prolactinoma have been described (8, 9). The present case is novel due to

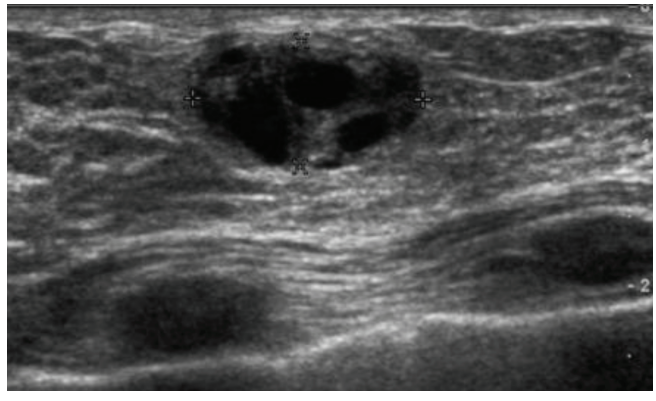

Figure 3. Ultrasound examination of a galactocele

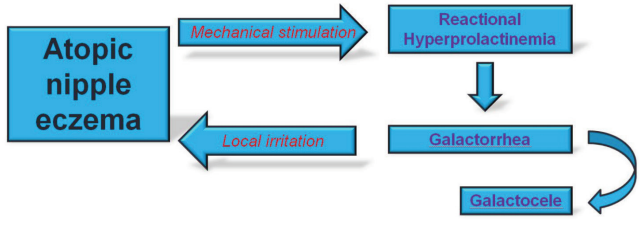

Figure 4. Graphical abstract

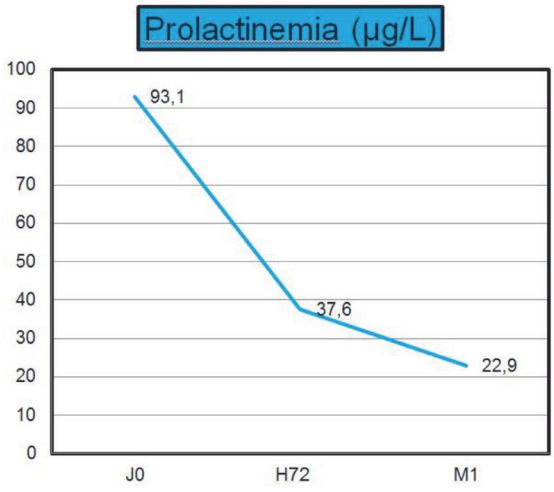

Figure 5. Decrease in prolactin levels

the absence of pituitary macroadenoma. Some cases have been reported after breast enlargement surgery (10-13), or following vacuum-assisted core biopsy of the breast (14) but the etiology in these cases remains unclear, but probably occurs by post-surgical obstruction of the milk ducts. Pediatric cases are also described, especially in male infants, which could represent a developmental anomaly, possibly promoted by an obstructive phenomenon involving a defect of hollowing of some primary epidermal buds (15, 16). However, galactocele has never been described as occurring secondary to a dermatological condition affecting the nipples. The common features of all these etiologies are probably the association of hyperprolactinemia and galactorrhea with a certain degree of obstruction of the milk ducts.

In conclusion, we describe the first case of nipple eczema, probably leading to the appearance of a galactocele through galactorrhea, secondary to reactive hyperprolactinemia.

Nipple eczema led to excessive mechanical stimulation of the nipples and the areolae, due to discharge from the lesion, itching and local care (including non-adhesive dressings in particular). This mechanical effect increased the pituitary secretion of prolactin through a hormonal response to local stimuli, thereby triggering the onset of galactorrhea outside the normal lactation period.

The occurrence of galactorrhea and/or hyperprolactinemia in a patient who is not breastfeeding should lead to clinical inspection of the skin to search for mechanical or traumatic factors responsible for mechanical stimulation of the nipple area. An increase in serum prolactin concentration is classically observed in cases of chronic nipple stimulation and MRI examinations of the pituitary gland are not necessarily required in this context. It is crucial to explain the importance of treatment to avoid such significant consequences.

Informed Consent: Written and informed consent of patient was obtained for publication.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: K.C.; Design: K.C., C.B.P.; Supervision: C.B.P., H.M.; Materials: A.V., E.C.; Data Collection and/or Processing: A.V., E.C., C.B.P.; Analysis and/or Interpretation: H.M.; Literature Review: K.C.; Writing: K.C.

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

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Letter to the Editor

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Undefined Oncological Risk of Fat Grafting Procedures in the Breast

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Dear Editor,

Over time, radiation-induced changes in the skin and soft tissues result in deformities such as induration, decreased elasticity and mobility, atrophy, xerosis, pigmentation, and local tissue changes (1). Chronic radiation-induced injury leads to both cosmetic and functional impairment (1). Management is aimed at reversing these changes by use of radioprotective agents, tissue debridement, skin grafting, local and free vascularized flaps, and more recently, adipose tissue grafting (2). The concept of fat grafting was first introduced in 1893 by German plastic surgeon Gustav Neuber. Based on current evidence, Kenny et al. (1) described its benefits in the breast, extremities, orbit, head and neck.

An important question raised by them was the undefined risk of oncological recurrence resulting from fat grafting into the irradiated breast tissue (1). The relationship between fat grafts and breast cancer cells has been explored in the past. One of the most extensive patient series was published by Petit et al. (3) in 2011, consisting of a multicenter analysis of 513 patients undergoing fat grafting after breast cancer. With an average follow-up time of 19.2 months, the study revealed a local recurrence rate of 2.4% (1.5%/year) and an overall recurrence of 5.6% (3.6%/year). A higher locoregional recurrence rate was observed in carcinoma in situ patients compared to those with invasive cancer.

A retrospective study by Rigotti et al. (4), published data including 137 mastectomy patients (105 with infiltrating breast cancer and 31 with cancer in situ) between 1988 - 2009, with a three-year minimum follow-up period. Five patients (3.6% of the overall population) were diagnosed with local recurrence post fat grafting compared to four patients (2.9% of the overall population) between surgery and the first fat grafting procedure. It was concluded that fat grafting after mastectomy did not increase local oncological recurrence.

Basic science and clinical studies have provided contradictory data on these procedures' safety profiles, making it difficult to make a definitive claim about their oncologic safety. The primary concerns are the lack of an ideal control group for comparison, retrospective analysis by most publications, and inadequate follow-up. The lack of standardization of fat harvesting, processing, and technique further adds to the challenge. As proposed by Kenny et al (1), better animal models and a larger working group with a longer follow-up period can provide these answers. Additionally, we strongly feel that high-quality research focusing on irradiated tissue's oncological potential following fat grafting can provide a better clinical correlation.

We propose that basic science models be based on samples from the same patient as opposed to laboratory-stored cell lines. This can be done for individual case reports for better homology. Guidelines with a longer definite follow-up period and a strong control group must be accomplished. A definite wait time from previous procedures (if any), based on individual risk factors, must be implemented for any clinical trial in the field. The need for prospectively controlled long-term clinical trials must be encouraged. These measures will help answer these questions sooner and enable healthcare providers to safely use the fat grafting technique.

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In the article by Ionescu et al., entitled **"New Data on the Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma"** (Eur J Breast Health 2021; 17: 302-307. DOI: 10.4274/ejbh.galenos.2021.2021-5-6) that was published in the 2021/4 (October) issue of European Journal of Breast Health, the authors made the below-mentioned mistakes inadvertently, and corrected them in this erratum.

Ionescu P, Vibert F, Amé S, Mathelin C. New Data on the Epidemiology of Breast Implant Associated Anaplastic Large Cell Lymphoma. Eur J Breast Health 2021; 17(4): 302-307.

The aforementioned manuscript can be accessed through the following link:

https://doi.org/10.4274/ejbh.galenos.2021.2021-5-6

The error and the correction in the article have been demonstrated in the following list:

Error

Table 1. Global number of BIA-ALCL cases and related deaths

Country	Year of report	Cases	Deaths
Argentina (30)	2020	13	0
Australia (23)	2019	104	4
Brazil(30)	2020	28	1
Canada (31)	2019	31	1
Chile (30)	2020	5	0
Colombia (30)	2020	18	1
France (32)	2021	78	3
Germany (33)	2021	35	NA
Italy (34)	2021	72	2
Mexico (30)	2020	13	0
Netherlands (20)	2019	49	1
New Zeeland (22)	2019	6	1
Portugal (30)	2020	1	0
PANAMA (30)	2020	1	0
Spain (30)	2020	26	0
Sweden (35)	2018	6	2
Venezuela (30)	2020	1	0
United Kingdom (36)	2020	78	3
United States (11)	2020	384	13
Total		949	32

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma, NA: Not available

Correction

Table 1. Global number of BIA-ALCL cases and related deaths

Country	Year of report	Cases	Deaths
Argentina (30)	2020	13	0
Australia (23)	2019	104	4
Brazil(30)	2020	28	1
Canada (31)	2019	31	1
Chile (30)	2020	5	0
Colombia (30)	2020	18	1
France (32)	2021	78	3
Germany (33)	2021	35	NA
Italy (34)	2021	72	2
Mexico (30)	2020	13	0
Netherlands (20)	2019	49	1
New Zeeland (22)	2019	6	1
Portugal (30)	2020	1	0
PANAMA (30)	2020	1	0
Spain (30)	2020	26	0
Sweden (35)	2018	6	2
Venezuela (30)	2020	1	0
United Kingdom (36)	2020	83	1
United States (11)	2020	384	13
Total		949	32

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma, NA: Not available

We apologize for any confusion this error may have caused.