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European Journal of Breast Health

Turkish Federation of Breast Diseases Societies

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

Société Internacionale 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.

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European Journal of Breast Health

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Review

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Value-Based Quality Care for Breast Cancer: More Than Guidelines

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ABSTRACT

Although guidelines recommend some of the most expensive diagnostic methods and therapies, some patients do have the opportunity to use them, but some others have overused or misused such methods. The cost of cancer care is increasing, but the satisfaction levels of patients and healthcare workers have not increased in line with this rise. Value-based care for cancer, especially breast cancer, should be implemented. For this reason, all unnecessary screening, tests, treatments, and follow-up parameters should be avoided.

Keywords: Cancer, breast, value, quality, cost

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Key Points

- The satisfaction of patients and doctors increases, the number of patients and disease severity decline.
- Better use of capacity, delivery of services in suitable conditions, balanced distribution of expenses, decreased cycle time and elimination of low-value or no-value care decrease cost.
- Value-based quality is assessed on three main primary parameters for value-based quality: clinical benefit, toxicity, and cost.
- VBQC in breast cancer may be related to the use of genomic testing, screening for early diagnosis, screening for systemic disease, targeted treatment and surveillance tools.

Introduction

Guidelines and pathways are the shared decision support tools that aid in better clinical decision making. Guidelines may not be appropriate at the bedside, because they incorporate all potential alternatives. In most situations, the aim of clinical pathways is to assist the practicing clinician in selecting the most effective method among the available choices for a particular patient (1). Thus, establishment of a disease-specific multidisciplinary breast cancer team is essential. The inability to form a multidisciplinary team could delay the start of treatment, resulting not only in loss of time but also economic losses, due to inclination toward unnecessary screening and treatments (2, 3). Most of the pathways involve some of the most expensive therapies, but the cost of treatment varies. Thus, we have to move toward practicing value-based care, which saves money and does not lead to a rapid increase in the cost of care while maintaining or improving quality standards.

The costs of delivering care are very high and rising at an unacceptable rate (4). Currently, United States health expenditures represent approximately 17% of its gross national product (GNP), with projections reaching over 20% of GNP in the not-so-distant future (5). However, all health services still face major problems, such as failure to prevent disease and disability (e.g., detection of breast cancer at stage III or IV), do not have the chance to perform sentinel lymph node biopsy and/or breast-conserving surgery, waste of resources through low-value activity, harm due to overuse even when quality is high, and inequity due to underuse by groups in high need. In addition, challenges are developing due to increasing expectations, increasing need, financial constraints, and climate change (6-9).

The Merriam-Webster Dictionary (2011) defines value as "a fair return or equivalent in goods, services, or money for something exchanged; the monetary worth of something; market price; or the relative worth, utility, or importance" (10). Variability in care delivery and payment systems is apparent at many levels. Even for those with access and ability to pay for care, unacceptable variability exists in the quality, safety,

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and effectiveness of care (11, 12). Warren Buffet once said, "Price is what you pay. Value is what you get." He means what you get is more important than what you pay (13), and this refers to improving value by reducing unnecessary costs (waste) and increasing efficiency while maintaining or improving healthcare quality. Value can be formulated as outcome achieved divided by the cost.

In healthcare, value is defined as "the health outcome per dollar of cost expended" (14). The cost of cancer care is rising by 15% each year. This increase has varied causes. One of them is delay in diagnosis and treatments. In our study that evaluated delay times in patients with breast cancer, as a part of a multinational survey, we reported that the mean total delay time was high (13.8 weeks) in Turkey. The system delay time was twice as long than the patient delay time, which called for implementation of nationwide, organized screening programs and comprehensive cancer centers by healthcare providers (15), because cancer care costs are rising faster than overall healthcare expenditure (16, 17). High prices of brand name drugs are creating a difficult situation for patients and oncologists, who are inadequately prepared for these challenges. The monthly and median costs of cancer drugs, once approved by the Federal Drug Agency, increased. In the United States, eight of the top ten most expensive drugs, covered by Medicare, are cancer drugs (18).

A value-based health system is needed to improve health insurance and deliver better health care so that patients receive better health care (19). Globally, the cost of cancer care is increasing, but the satisfaction levels of patients, in regard to unnecessary tests, unacceptable waiting time, ineffective treatment, and costs, and health care workers in regard to increased workload, malpractice, and low income, do not increase in a similar fashion (20). The aim of value-based cancer care (VBCC) is to provide consistent and sustainable health for patients, which can be delivered by a sustainable health system. VBCC can be achieved by increasing income through raising the price of per service, increasing the number of patients with expanding indications, and increasing the attractiveness of health delivery, and by decreasing healthcare costs through reducing the number of health care workers but creating better work distributions, work delegations, and decreasing unnecessary tests/treatments with less medical errors. While the satisfaction of patients and doctors increases, the number of patients and disease severity decline. With VBCC, balanced distribution of expenses, better use of capacity, decreased cycle time, delivery of services in suitable conditions, and elimination of low-value or no-value care decrease cost. The elimination of the latter, "Low (no)-value care", can be achieved by avoiding unnecessary tests, follow-up, screening, and treatment. Decreasing or stabilization of costs results in qualitatively increased or stabilized wellness. Better quality of services can be achieved and sustained by using guidelines and pathways. The American Society of Clinical Oncology (ASCO) value in Cancer Care Task Force was established in 2007, which defined the challenges related to the cost of cancer care and developed strategies to address these challenges. The goals of this task force were as follows: increase physicians' education and guidance about cost, increase patients' education and assistance regarding cost, promote high-value medical decision making, and assess the value of cancer care (21, 22). The "academy" concept in surgical education has had a considerable influence on good clinical practice for breast care in the last decade. Implementing "academy-based" training in all aspects of postgraduate medical education could improve the effectiveness of patient-centered service and outcome-based quality through efficient teaching methods (23). In the spring of 2013, the ASCO Board of Directors engaged in a strategic discussion on value around the following statement:

"Increasingly, the desired care for oncology patients will be assessed on the value of that care rather than the cost. ASCO defined value and suggested how value should be integrated into treatment decisions." Topics of VBCC can be outlined as follows:

1. Survival, quality of life, adverse events, tumor response, and time to progression.

2. Cost.

3. Aspects of care delivery, such as access, quality, communication, and social equity, and patient-centered attributes, such as compassion, respect, choice, hope, and opportunity for treatment benefit.

4. Opportunity for innovation and future discovery (24).

Value-based quality is assessed on three main primary parameters: (a) clinical benefit, (b) toxicity, and (c) cost. Clinical benefit and toxicity are equal to the "net health benefit score," and cost is integrated to derive an overall value assessment for an oncology regimen. With better conversations for informing patients about individual decisions, healthcare workers including breast surgeons, oncologists, radiologists, and nurses must support and consider individual patient circumstances; explain the best evidence available on a particular treatment's clinical effectiveness, toxicity, and cost; and compare a new treatment with an existing treatment or, if there is no effective therapy, with best supportive care. The aim of value-based quality care (VBQC) includes safety at hospital (patients who receive healthcare must be as safe as at home), effectiveness (avoiding unnecessary and insufficient use of health service), patient-centered service (considering patients' needs, preferences, and culture), timely service (decreasing waiting time for patients and health workers), productive care (decreasing the waste of manpower, equipment, etc.), and equity (decreasing differences owing to race, ethnicity, geographical, and socio-economic conditions). The need to ensure high-quality cancer care, in addition to rising costs with or without improving outcomes but with quality cancer care, varied depending on the countries, hospitals, and relation with the standards or ideal. Some patients cannot receive any beneficial treatment, or some patients have overused or misused unnecessary or harmful therapy. At this point, the "Guidelines or not Guidelines" is debatable. Quality concurs with evidence-based guidelines and measurement to quality. The measurement of diagnostic and therapeutic procedures, which details evidence-based quality indicators for breast cancer managements, is shown in Table 1 (25-27).

The outcomes of VBCC are survival, achieved health status, recovery level, time to recovery, rate of adverse effects, rate of secondary disorders due to treatments, continuity of recovery, and necessity for other procedures. VBQC is categorized into three levels. Level I includes health state and its degree, Level 2 includes duration of recovery and anxiety due to treatment, and Level 3 includes continuity of recovery and long-term effects of treatment (Table 2). Professional organizations have begun to establish guidelines for tests and procedures, the necessity of which should be questioned and discussed. Developing quality measures around these guidelines will be an significant next step (28).

Most importantly, efforts that identify the system, patient, and disease factors that have affected the relationship between quality, cost, and outcomes are critical for developing effective improvement strategies. The VBCC for each patient requires measurement of outcomes and costs. The satisfaction level of the patients and patients' family with

the use of care pathways, enhancement, and rehabilitation increases with the number of patients. At the same time, the satisfaction level of healthcare workers increases with motivation, and this satisfies the employee/enterprise/health authority (29).

VBQC in breast cancer, such as genomic testing, screening for early diagnosis, screening for systemic disease, targeted treatment, and surveillance tools, can be achieved by implementing the following suggestions:

• Is genomic tumor testing for breast cancer a standard today? Evidence must be followed. During practice, do we have to perform genomic testing? We have to prefer standards of evidence, rather than standards of practice. Unfortunately, there are many examples of standards of practice racing ahead of evidence and these may not add value to patient care and even cause serious harms (30).

• Assuming that individual testing for breast neoplasms is not yet universal, what are the key challenges for making this a standard practice? There is wide variation in the practice of medicine, which has not been explained. Such practices lead to patient harm and failure to realize the full potential of care innovations. Thus, use of these new technologies should be based on evidence (31).

• Breast screening rates have actually decreased among Caucasians in the last decade, remained stable among African Americans, and actually increased significantly among Asians (up to 66%). Is it realistic to expect attaining higher percentages? What type of focused interventions may help? Higher screening rates can be expected. However, conflicting recommendations put forth over the last several years have created confusion. This does not mean that recommendations should be frozen, but recommendations would gain much greater traction if they were consistent, based on a clear and consistent review of the evidence, and then implemented through reliable methods (32).

• Do you believe that human epidermal growth factor receptor 2 (HER2)-targeted agents can be used in combination in the future? A new development is not an innovation unless it can show its superiority to current treatments and can deliver higher performance and better outcomes at a better cost (33).

Table 1. Most important evidence-based quality indicators for breast cancer management dedicated by the European Society of Mastology

% of patients with breast cancer discussed in pretreatment by the multidisciplinary tumor board
% of patients discussed after first surgical treatment
% of patients who underwent surgery <4 weeks after definitive cancer diagnosis
% surgeons in the health care team who treat patients with breast cancers
% of patients who have been examined and received information from nurse specializing in breast cancer
% of patients with incomplete resection after the first breast-conserving surgery
5-year local recurrence rate after breast conservation therapy/mastectomy

Table 2. Value-based outcome metrics for breast cancer care (27)

Health state	Expectancy of life	**Mortality rate/survival**
	Health condition	Degree of pain
		Period without disease
		Performance quality upon return to work
Recovery	Time to recovery	**Start of treatment**
	Inconvenience and anxiety due to treatment	Hospitalization rate
		Delay and anxiety
		Pain during treatment
		Nosocomial ınfections
		Deep-vein thrombosis
		Time to physical activity and to work
		Redo surgery
		Lack of consciousness
		Medical errors
Continuity of health	Continuation of health	**Recurrence rate**
	Long-term effect of treatments	Degree of performance
		Necessity for revisions
		Insufficient rehabilitation
		Results of adverse effect
		Chronic pain

• Do you prefer to perform positron emission tomography, computed tomography, and bone scanning in patients with breast cancer at low risk for metastases? Careful history taking and physical examination can help detect symptoms that suggest metastases and signs of locally advanced breast cancer. Decision for imaging studies outside guidelines or clinical trial should be carefully reviewed with the patient and be based on symptoms and physical findings. Non-indicated scans can lead to unnecessary anxiety, testing, and morbidity. In the era of effective adjuvant therapy, micro-metastases are likely to be effectively treated. However, survival improvement in asymptomatic cases with newly identified ductal carcinoma *in situ* and clinical stage I or stage II breast cancer has not been confirmed by evidence. Thus, patient harm is inevitable (34).

• When is the right time to use surveillance testing, such as serum tumor markers and imaging after curative treatment for breast cancer? Randomized trials have not shown that tumor markers affect survival outcomes. The rate of false-negative or false-positive findings for these markers is still unknown. Thus, the use of these tests can result in false reissuance, increased anxiety, and unnecessary medical evaluation, and then increased cost (35, 36).

• At present, some patients have not received any beneficial treatments, but some have overused or misused unnecessary or harmful therapies. Therefore, there is a need to ensure delivery of high-quality cancer care, without increasing the cost of treatments. Measurement of outcomes and costs appears to be a major parameter for VBQC for cancer, including breast cancer. For a successful treatment, satisfaction levels of all including patients, healthcare workers, social insurance companies, and industry and health authority, must be increased.

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Systematic Review

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New Data on the Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma

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ABSTRACT

Objective: This study aimed to illustrate the epidemiological situation of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) by focusing on the changes published after 2019 and particularly the new approaches of cosmetic and reconstructive breast surgery.

Materials and Methods: Article search was performed from January 2019 to date using the PubMed database. Fourteen articles were included in the qualitative evaluation of international data. Moreover, the latest reports regarding the total number of BIA-ALCL cases and number of deaths were identified.

Results: Estimates of the risk and incidence have increased significantly recently, affecting 1 in every 2,969 women with breast implants and 1 in 355 patients with textured implants after breast reconstruction. The average exposure time to diagnosis was 8 (range: 0–34) years. Approximately 80% of BIA-ALCL cases were diagnosed at IA–IIA stages, for which the treatment was breast implant removal, full capsulectomy, and excision of all suspected lymph nodes. Globally, at least 949 cases were reported to date.

Conclusion: At present, BIA-ALCL is an emerging pathology of interest. Data collection initiated since 2016 through different case registration databases is essential to ensure surveillance and to continue to increase the number of studies on this recently discovered pathology.

Keywords: Breast cancer, breast cancer surgery, anaplastic large cell lymphoma

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Key Points

- At least 949 cases of BIA-ALCL worldwide were reported to date.
- The incidence of BIA-ALCL ranges from 1 in 2,969 women with breast implants to 1 in 355 women with textured implants after breast reconstruction.
- The absolute risk of developing BIA-ALCL in women with BRCA 1/2 mutation was 1/1,551 at age 75 years, compared with 1/7,507 in women from the general population.
- The most widespread and accepted hypothesis is that textured implants, with their greater surface areas and increased bacterial adhesion, lead to higher rates of biofilm formation and subsequent lymphocyte activation.
- As the incidence of BIA-ALCL increases, we can expect an increasing reluctance in using textured implants in breast reconstructions, in favor of round and smooth implants, at the expense of a less natural appearance of the reconstructed breast.
- Surgeons should fully inform their patients regarding the potential risks and advantages of each implant type and obtain their consent to receive the most appropriate alternative.

Introduction

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare form of non-Hodgkin's T-cell, CD30-positive, and anaplastic lymphoma kinase-negative lymphoma that develops around breast implants, especially those with a textured surface, used in both cosmetic surgery and reconstructive surgery (1, 2). The first case was reported in 1997 by Keech and Creech (3). In June 2011, the Food and Drug Administration (FDA) identified for the first time a possible association between breast implants and the development of large cell anaplastic lymphoma. In 2016, the World Health Organization admitted BIA-ALCL as a possible long-term complication of breast implants (4), and in 2017, this variant of T-cell lymphoma was included in the classification of lymphoid neoplasms (5).

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Generally, BIA-ALCL is diagnosed several years after implantation of the breast prosthesis. This is a rare but potentially serious condition, which can appear in two clinical forms: a localized form limited to the capsule [the most frequent and of good prognosis] or an infiltrating one (rarer and more serious). Only surveillance is required when the disease is localized, and explantation associated with total capsulectomy can be performed. When the disease is invasive, a systemic treatment (such as chemotherapy and radiotherapy) must be added to the surgery (6).

Breast implants are classified according to their surface: macrotextured, microtextured, nanotextured, smooth, and polyurethane surface implants. BIA-ALCL is associated with macrotextured breast implants, which led, in December 2018, to the decision of the French National Agency for the Safety of Medicines and Health Products to refuse renewal of the CE mark for Biocell and Microcell Implants (AllerganR, Dublin, Ireland). In April 2019, the French National Agency banned all macrotextured and polyurethane surface implants, a decision that affected several companies, including SebbinR (Groupe Sebbin SAS, Paris, France), PolytechR (Polytech Health & Aesthetics, Dieburg, Germany), NagorR (GC Aesthetics, Dublin, Ireland), EurosiliconeR (GC Aesthetics, Dublin, Ireland), and AllerganR (Dublin, Ireland). On July 24th, 2019, the FDA asked AllerganR to withdraw Biocell macrotextured implants from the market to limit the occurrence of new cases of BIA-ALCL, without recommending preventive explantation for women wearing such implants (7).

In the United States, approximately 450,000 breast implants are used annually and 5% of the female population is wearing breast implants, while over 35 million women are wearing implants worldwide (8, 9). In the United States, the priority choice is round-shaped, smooth breast implant, whereas in the United Kingdom, approximately 85% of implants used are textured and have an anatomical shape. European surgeons considered several cultural and medical factors for this preference. The breast has a more natural shape with anatomical implants; with round implants, more volume in the upper pole of the breast is obtained (6). Until now, determining the elements related to disease epidemiology (incidence, prevalence, risk, etc.) has been a difficult process because of factors related to the specificity of the disease (delay to onset, nonspecific symptoms), lack of awareness of the disease from both patients and surgeons, and difficult data collection (10).

Until July 2019, BIA-ALCL was the subject of numerous studies; it has since entered a plateau phase with few new data appearing in the literature. Thus, this study aimed to create a picture of the epidemiological situation of BIA-ALCL by reviewing scientific literature on the changes after 2019 in terms of how surgeons approached cosmetic and reconstructive breast surgery.

Materials and Methods

The PubMed database was searched for articles indexed from January 2019 to April 2021. The following search term strategy was used: breast AND (implant OR prostheses) AND anaplastic AND large AND cell AND lymphoma AND (epidemiology OR risk OR incidence OR prevalence). Only original research studies or literature reviews written in English were included. Articles that do not report epidemiological data regarding BIA-ALCL and single case report articles were excluded. Other publications were searched through FDA Reports.

Furthermore, using Google Chrome browser, we looked for each country's health regulator to identify the latest reports regarding the total number of BIA-ALCL cases and number of deaths.

Results

In total, 127 articles were identified, of which 56 were excluded. One article was added through FDA Reports. Of the remaining 72 articles, 19 were considered relevant, and their full texts analyzed. Finally, 14 articles were included in the qualitative evaluation of data (Figure 1).

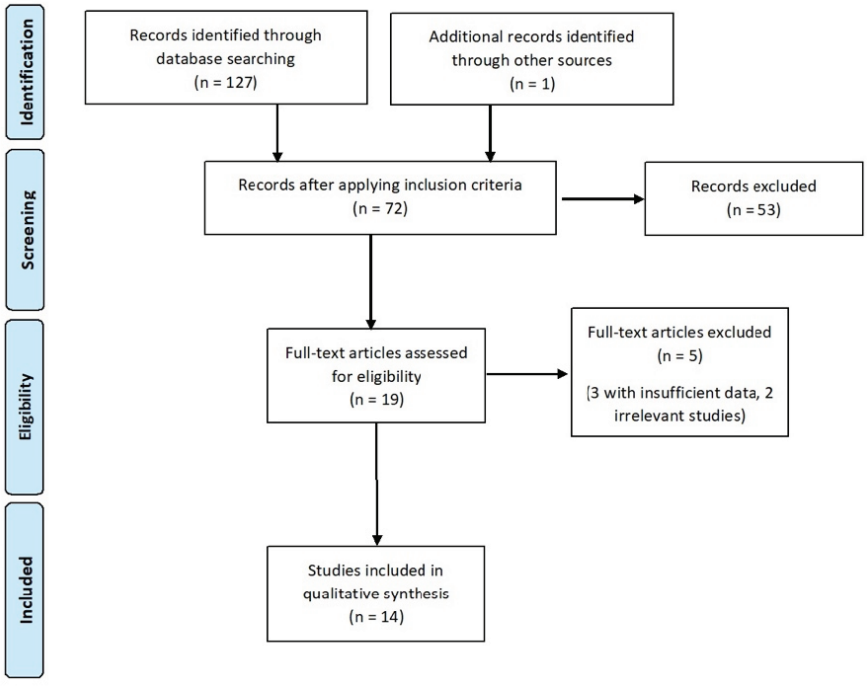

Figure 1. Flowchart

The latest report released by the FDA in August 2020 revealed a total of 733 BIA-ALCL cases worldwide, including 384 cases in the United States, 334 outside the United States, and 15 cases of unknown location. Of the 733 patients, 36 have died, and the average age at the time of diagnosis for deceased patients was 53 years (11).

Regarding the surface of involved implants, 496 were macrotextured and 28 smooth, while the surface type was not reported in 209 cases. Of the 28 BIA-ALCL cases associated with smooth prostheses, one case documented exposure to smooth prostheses only; in the remaining cases, patients had either a history of textured breast implant exposure or the history was unrecorded. To date, no cases associated with tissue expander devices have been reported (11).

The average exposure time to diagnosis was 8 (range: 0–34) years. In 50% of the cases, 26% clinically presented as a diffuse effusion around the implant, inflammation, or pain in the breast, 13% as capsular contracture, and 14% as peri-implant mass (11).

Estimates of risk and incidence have increased significantly recently, reaching 1 in 2,969 women with breast implants (12), and 1 in 355 patients with textured implants after breast reconstruction (13).

Approximately 80% of BIA-ALCL cases are diagnosed in IA–IIA stages according to the TNM classification, and these cases were treated with breast implant removal, full capsulectomy, and excision of all suspected lymph nodes. For the remaining 20%, which are represented by more advanced stages, the treatment was associated with systemic treatment and radiotherapy (9).

Using Google, 949 BIA-ALCL cases to date were identified from Health Regulators' reports from 19 countries. In these 19 countries, a total of 32 deaths were reported. In Germany, the number of deaths could not be identified (Table 1). Standardized diagnosis and management guidelines of BIA-ALCL have been established by the National Comprehensive Cancer Network, and many countries (Table 1) use these recommendations. However, some countries have particular policies. For example, in France, the diagnosis of BIA-ALCL made by a pathologist must be confirmed by the national "Lymphopath" network (14). Moreover, reporting of the occurrence of BIA-ALCL by French healthcare professionals to the *"Agence Nationale de Sécurité du Médicament et des Produits de Santé"* is mandatory, and therapeutic options should be discussed at a national multidisciplinary consultation meeting dedicated to this disease.

Discussion and Conclusion

Throughout history, the safety of breast implants has been continually questioned (15). Silicone breast implants were invented in 1962 by Thomas Cronin and Frank Gerow and were first banned by the FDA between 1992 and 2006, a measure that did not target saline implants. In 2010, France's health regulator decided to withdraw silicone implants produced by Poly Implant Prothese (La Seyne-sur-Mer, France) from the market after investigations showed that these implants contained a cheap, low-quality silicone, usually used in constructions. Women carrying these implants were recommended to explant, with costs borne by the Ministry of Health (6). The third crisis appears to be ongoing and to affect textured implants because of the increases incidence of BIA-ALCL (7).

Incidence of BIA-ALCL

To estimate the incidence and risk of BIA-ALCL, we should be aware of the prevalence of women with breast implants, which is difficult to quantify because of factors such as the lack of centralized databases and medical tourism (8, 9). The first study of an increased risk of developing BIA-ALCL (odds ratio; 18.2; 95% confidence interval; 2.1–156.8) was conducted by De Jong et al. in 2008 (16). Subsequently, they demonstrated a link between BIA-ALCL and macrotextured breast implants, indicating a cumulative risk of disease for women wearing breast implants of 29 per million at age 50 years, 82 per million at age 70 years, and 142 per million at age 75 years (17). In a literature review published in 2019, Collett et al. (8) noted that the latter study did not differentiate textured from smooth implants, which could have led to a significant underestimation of the actual incidence and risk. Nelson et al. (18) performed a cohort study of 9,373 patients who benefited from breast reconstruction between 1991 and 2017; of 16,065 silicone breast implants used, 9,589 were textured implants. Moreover, they identified 11 cases of BIA-ALCL all in patients who had received textured implants. The average exposure time was 10.26 (range: 6.4–15.5) years. The overall incidence of BIA-ALCL was 1.79 per 1000 patients with textured implants (1:559) and 1.15 per 1,000 textured implants (1: 871) – the difference is caused by the fact that several patients were exposed to more than one implant in their lifetime (18). After analyzing a cohort of 3,546 patients who also benefited from

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

breast reconstruction with textured implants, Cordeiro et al. (13) identified an overall risk of 1:355 patients after an average exposure time of 11.7 (range, 7.4–11.8) years. Moreover, 96.7% of the patients used Allergan Biocell implants (12). In France, Ruffenach et al. (19) recently reported 36 cases of BIA-ALCL, 70% of implants were made by Biocell, with an average exposure time to diagnosis of 11 years. In 2020, Santanelli di Pompeo et al. (12) collected data from European Association of Plastic Surgeons Research Council experts and found approximately 420 cases in the 28 EU member states compared with 5,772,913 women with breast implants, with a prevalence of 1:13,745. In the Netherlands, which has a national database for data on procedures involving breast implants, the prevalence was 1:2,969 women with breast implants (12).

Incidence of BIA-ALCL for BRCA 1 or 2 mutation carriers

In a 2020 study conducted in the Netherlands, de Boer et al. (20) identified 15 BIA-ALCL cases after breast reconstruction with silicone prostheses. Of these cases, 26.6% (4/15) were BRCA 1/2 mutation carriers. The absolute risk of women with BRCA 1/2 mutation to develop BIA-ALCL was 1:1551 at age 75 compared with 1:7507 in women from the general population (20).

Effect of implant surface on the incidence of BIA-ALCL

The type of implant surface appears to play an essential role in disease pathogenesis. Scientific evidence suggests a link between BIA-ALCL and implants with a textured surface rather than those with a smooth surface, and the risk appears to increase in implants with a more robust textured surface (15). Jones et al. (21) performed measurements of the area and roughness of the implant surface and proposed a new classification of breast implants in 4°. Their study showed a significant increase in bacterial growth over 24 hours on the surface of grade 4 implants and significantly slower bacterial growth in grade 1 implants (21). In 2019, Magnusson et al. (22) published an update on the epidemiological situation in Australia and New Zealand and reported that 78.9% of BIA-ALCL cases occurred in patients with grade 3 or 4 surface implants. All patients in whom the disease occurred following exposure to grade 1 surface implants had a history of exposure to high-grade surface implants (22). In another Australian study of 104 cases, Deva et al. (23) demonstrated a link between increased incidence of BIA-ALCL and use of rough surface implants ($p = 0.0001$) and those with a large surface area ($p = 0.0007$). In addition, the risk of developing BIA-ALCL varies between 1:1947 for Silimed Polyurethane implants (Mapamed-Silimed, Brasil, Brazil) and 1:36730 for Siltex-imprinted textured devices (Mentor, Santa Barbara, CA, USA) (24).

Different theories about the etiology of BIA-ALCL

Several theories have been proposed to explain the etiology of BIA-ALCL. Some authors believe that silicone degradation products would trigger an immune response via T helper cells (24). However, the most widespread and accepted hypothesis states that textured implants, with their greater surface areas and increased bacterial adhesion, lead to higher rates of biofilm formation and subsequent lymphocyte activation (23). Following the withdrawal from the market of Biocell macrotextured implants (Allergan), Danino et al. (25) identified 1,260 patients with this type of implant at the University of Montreal Hospital Center in Canada between 1960 and 2006. Of these patients, 92 opted for implant removal. No cases of BIA-ALCL have been identified, which, according to the author, raises the notion of clustering of cases that affect disease prevalence from a geographical perspective and supports the hypothesis of an infectious trigger (25). In 2017, Adams et al. (26) examined a cohort of 21,650 patients in whom 42,035 Biocell textured implants were used. After an average follow-up duration of 11.7 years, the 8 plastic surgeons who participated in the study and who complied with at least 13/14 points of the bacterial contamination avoidance plan proposed by Deva et al. (23) did not identify BIA-ALCL cases since 2013 (26). The theory that an infection triggers the disease would mean that the cause is related to the technique used by surgeons, a notion disagreed by several authors who believed that the discovery of a cluster of cases by certain surgeons does not indicate a lack of technical skills, but most likely an increased awareness for its diagnosis (12, 27).

New approaches of cosmetic and reconstructive breast surgery

Breast prosthesis manufacturers reported that 70%–80% of implants sold in the United Kingdom are textured, while 70%–80% of them sold in the United States are smooth (10). Regarding the surgeons' preferences for a certain type of surface of breast implants, Nelson et al. (18) noted that between 1991 and 2009, in the Memorial Sloan Kettering Cancer Center in the United States, textured implants by far exceeded smooth implants. Since 2009, a balance between the two types of implants was noticed, and after 2011, surgeons preferred smooth implants over textured implants (18). A multinational survey conducted in Europe and published in 2020 showed that most surgeons (70%) prefer textured implants and that only 29% of those who changed their preferences in terms of the implant surface and manufacturing company did so to prevent the occurrence of BIA-ALCL (28). A Portuguese study by Cunha et al. (10) showed that of 57 (27 state and 28 private) hospitals, one hospital mostly used breast implants with a smooth surface, whereas others preferred textured implants (10). This preference in Europe can be explained by the relatively low rates of capsular contracture and implant rotation associated with textured implants. Moreover, patients who require breast reconstruction look for a more natural shape of the breast, which is more likely to be obtained by using a shaped breast implant, which is always textured to allow better adhesion of the device to the surrounding tissues and thus prevent rotation (2).

Evaluation of data provided by the Dutch Breast Implant Registry showed that, before 2019, only 1% of implants used for breast reconstruction were smooth, while in subsequent years, the usage rate of smooth implants increased seven times. In cosmetic surgery, the usage rate of smooth implants increased from 7% to 11% after 2019, while textured implants were used in 88% of cases since 2019, compared with 91% before 2019 (29).

As the incidence of BIA-ALCL cases increased, we can expect an increasing reluctance to the use of textured implants in breast reconstructions, in favor of round, smooth implants, at the expense of a less natural appearance of the reconstructed breast. This could lead to a decrease in patient satisfaction and, in the long term, even to a decrease in the demand for breast reconstruction using prosthesis. Surgeons should fully inform their patients about the potential risks and advantages of each implant type when choosing alternatives more likely to be suitable for them.

In conclusion, BIA-ALCL is an emerging pathology of current interest. Although the symptoms, management, and follow-up have clearly been defined in most countries, its physiopathology remains unclear. As early as 2015, an inflammatory origin of BIA-ALCL was related to the implant surface. More recently, an infectious origin was evoked, in particular by the presence of a biofilm chronically activating lymphocytes. Data collection initiated since 2016 through different case registration databases is essential to ensure surveillance and continue research into this recently discovered pathology.

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Authorship Contributions

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

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Original Article

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Favorable Personality Traits in Women Who Have Undergone Cosmetic Breast Augmentation Surgery

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ABSTRACT

Objective: Breast augmentation surgery is one of the most common cosmetic procedures among women. In the present study, we compared personality traits, self-esteem, and body perception between women who had undergone breast augmentation surgery and a control group of women who had not. We hypothesized that the personality traits of women who had vs those who had not undergone breast augmentation surgery would differ.

Materials and Methods: According to the inclusion and exclusion criteria, patients who had undergone breast augmentation surgery and age- and education-matched, healthy women were included in the present study. The breast augmentation group and control group were compared in terms of personality traits under the Basic Personality Traits Inventory. Additionally, self-esteem, which was assessed with the Rosenberg Self-Esteem Scale, and body perception, which was evaluated using the Body Cathexis Scale, were measured and compared between the two groups.

Results: When the patients (n = 80) and the control group (n = 100) were compared, the Body Cathexis Scale, extroversion, and openness scores were statistically significant and were found to be higher in the breast augmentation group ($p<0.05$). In regression analysis, it was found that age, openness, and the Rosenberg Self-Esteem Scale score had statistically significant effects on extroversion.

Conclusion: We argue that there may be a presupposition, based on stigma, that women who undergo breast augmentation surgery are more neurotic than those who do not. Consequently, this may influence the outcomes of studies evaluating the personalities of these women. Our results indicate that women who had undergone breast augmentation had more positive personality traits than women in an un-operated control group.

Keywords: Breast, augmentation, personality, cosmetic

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Key Points

- Breast augmentation surgery is one of the most common cosmetic procedures among women.
- Data about personality traits in women who had undergone breast augmentation surgery are limited.
- The present study showed that the breast augmentation group had more positive personality traits than the control group.

Introduction

Breast augmentation surgery is one of the most common cosmetic procedures among women (1, 2). It is estimated that approximately 300,000 women undergo cosmetic breast augmentation annually in the United States alone (3). Several studies have found that breast augmentation has a positive impact on women in terms of improving self-esteem and depressive symptoms, getting having greater satisfaction with their breasts, enhancing body image, and increasing well-being (4-6). Despite the positive effects of breast augmentation on women's psychological state, surgeons must assess patients' motivations for surgery and determine their emotional status. Surgeons must determine that candidates do not have body dysmorphic disorder or unrealistic expectations before operating. Several studies have reported that women who undergo breast augmentation surgery are more likely to use tobacco and alcohol, as well as higher anxiety levels, and are more likely to have a neurotic personality (7, 8). It is vital that surgeons take these factors into consideration during preoperative patient assessment.

There has been much interest in the psychological status of women who undergo breast augmentation, but only a small number of studies have investigated personality traits among these patients. It has been well established that personality traits affect emotion, ideas, and behaviors (9). According to the Big Five Personality Traits, a high level of neuroticism is associated with higher levels of anxiety, as well as with affective

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disorders (10, 11). Extroversion is a characteristic of individuals with superior communication skills and a more positive outlook (12). People who have higher scores for "agreeableness" are considered to be tolerant, polite, and willing to share (12). People who have higher levels of conscientiousness are thought to be hardworking, tidy, and prudish. People with a high score for openness are described as productive, imaginative, and highbrow (13). Two studies have investigated changes in personality traits before and after breast augmentation surgery. In an earlier study, it was reported that women with breast augmentation surgery had a postoperative tendency to enter a neurotic state (14). However, in a more recent study, Zaborski et al. (2) demonstrated that breast augmentation surgery had no effect on levels of neuroticism.

In the present study, we compared personality traits, self-esteem, and body perception between women who underwent breast augmentation surgery and an unoperated control group. We hypothesized that personality traits would differ between women who underwent breast surgery operations and those who did not.

Materials and Methods

The study was performed in two centers. Patients were selected from the private clinic of one of the authors. To be included, patients were required to meet the following criteria: breast augmentation surgery for aesthetic purposes received at least one year earlier, education level sufficient to understand the assessment tools used in the study, and willingness to participate in the study. A senior psychiatrist (Y.A.) assessed the patients, either online or face-to-face, to determine the history or ongoing presence of psychiatric disorders. Patients who had been diagnosed with a psychiatric disorder, those who had a history of psychiatric disorders, and those who were not willing to participate in the study were excluded. Additionally, women who had chronic disease, those who had another cosmetic problem, and those whose Body Mass Index was greater than 25 or lower than 20 were also excluded from the study. Of 114 patients, 80 met the inclusion criteria. The control group was selected from among staff members of the university hospital. The staff members were consisted of medical doctors, nurses and medical school students. The exclusion criteria for the control group included having a psychiatric disorder or a history of psychiatric disorders, refusing inclusion in the study after receiving detailed information, having a chronic disease, having another cosmetic problem, and having a Body Mass Index greater than 25 or lower than 20. As in the patient group, senior psychiatrists assessed all candidates of the control group to determine a history or ongoing presence of psychiatric disorders. The control group consisted of 100 healthy subjects. The patient group and control group were matched in terms of age and education level. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Local Research Ethics Committee of the Non-Invasive Clinic Research. The study was approved by Tekirdağ Namık Kemal University Non-Invasive Clinical Research Ethics Committee (date: 30.05.2019/ approval no: 2019.101.06.22).

All participants gave written informed consent before participating in the study. Additional permissions were obtained from patients whose clinical images were used in the present study.

Tools

Basic Personality Traits Inventory

The Basic Personality Traits Inventory was created by Gençöz and Öncül (15) in 2012, based on the Big Five Personality theory and used to measure personality traits. This inventory includes 45 items with a five-point Likert-type scale and six personality traits (15).

Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale (RSES) was created by Rosenberg in 1965, and the validity and reliability of the scale was confirmed by Çuhadaroğlu (17) in 1986 (16, 17). The first 10 items of the scale are used for the evaluation of self-esteem. A total score of 0–1 on these items indicates high self-esteem, a total score of 2–4 indicates average self-esteem, and a total score of 5–6 indicates low self-esteem. Lower scores indicate higher levels of self-esteem (16).

Body Cathexis Scale

The Body Cathexis Scale (BCS) was created by Secord and Jourard (18) in 1953 and has 40 items. The items are ranked using a five-point Likert-type scale that ranges from 1, meaning I do not like at all, to 5, meaning I really like. One score is determined from the scale. The lowest possible score is 40, the highest is 200, and higher scores indicate more positive evaluations. The BCS vas validated into Turkish language by Hovardaoğlu (19).

Statistical analysis

Statistical analyses were performed using R version 3.5.3, SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA), and G*Power version 3.1.9.4. The normality assumption of parametric tests was tested with the Shapiro-Wilk test. When the assumption was satisfied, an independent-sample t-test was used to compare patients with the control group. The adequacy of the sample size was tested by a power analysis. Depending on the normality assumption for the correlation analysis, Pearson's coefficient of correlation was used. Step-wise multiple regression was applied to determine which potential dependent variables would affect the independent variables. This technique was also used to eliminate non-significant dependent variables. The following assumptions of the regression were checked: the relationship between the independent and dependent variables is linear, the mean of residuals is zero, the normality of residuals is accurate, there is no multicollinearity, there is no autocorrelation of residuals, and there are significant levels, at 0.05, of homoscedasticity of residuals or equal variance value.

Results

In the power analysis, two independent-sample t-tests were used. Figure 1 shows that the total sample size of 30 already achieved 65.1% power with a significance level of 0.05 to detect an effect size of 0.9060. In the study, a total sample size of 100 was determined, and the power was approximately 99%.

The descriptive data of the participants are shown in Table 1. When the patient and control groups were compared, the BCS, extroversion, and openness scores were statistically significant and were found to be higher in the breast augmentation group (Table 2).

Figure 2 shows the correlation between the body BCS, RSES, extraversion, agreeableness, conscientiousness, neuroticism, openness, and negative valance. Overall, no significant correlations ($p>0.05$) were found between the body image scale score and neuroticism, the

body image scale score and openness, extraversion and the BCS score, extraversion and conscientiousness, extraversion and negative valance, agreeableness and neuroticism, conscientiousness and openness, conscientiousness and neuroticism, openness and neuroticism, or openness and negative valance.

Significant correlations (p<0.05) were found in the control group (a) between RSES score and body image score, RSES score and neuroticism, RSES score and negative valance, BCS score and negative valance, extraversion and agreeableness, extraversion and openness, agreeableness and conscientiousness, openness and agreeableness, openness and conscientiousness and neuroticism and negative valance, and their correlations were positive (p = 0.292–0.685). In the patient group (b), significant correlations (p<0.05) were found between RSES score and conscientiousness, conscientiousness and openness, and neuroticism and negative valance, and their correlations were also positive (p = 0.332–0.451).

Multiple regressions were used to estimate extroversion and openness with two different models (Table 3) using the stepwise technique.

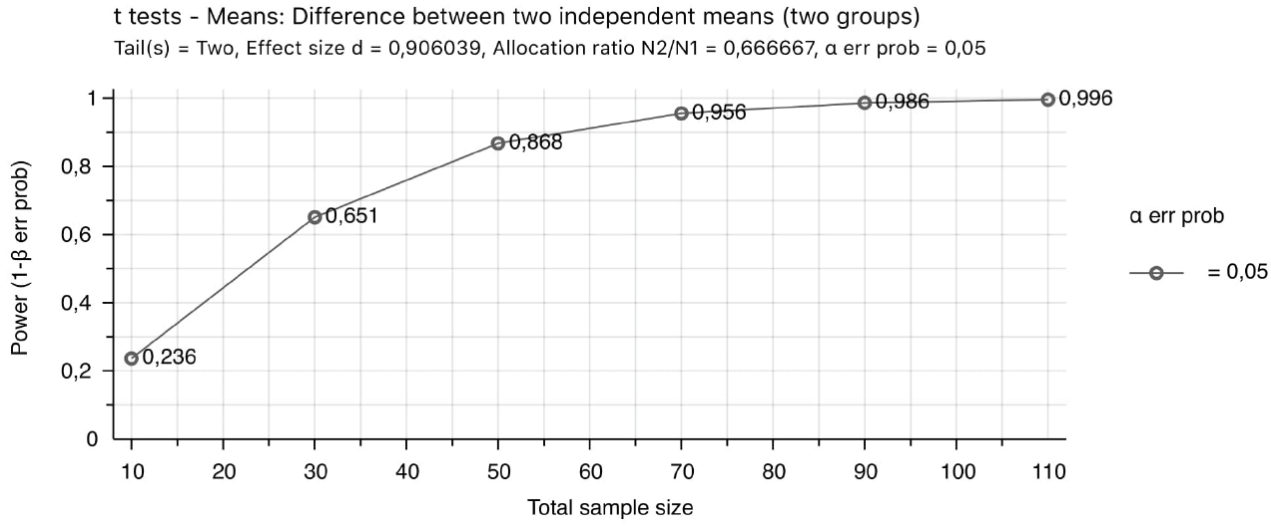

Figure 1. Power analysis

Table 1. Descriptive statistics

	Categories	n	%	$\bar{x}$	s	Median	IQR
Group	Control	120	60.0	-	-	1.00	1.00–2.00
	Patients	80	40.0	-	-	-	-
Age	-	-	-	29.320	6.014	28.00	25.00–32.00
Education (years)	-	-	-	15.380	2.627	16.00	13.00–18.00
Marital status	Married	68	34.0	-	-	2.00	1.00–2.00
	Single	132	66.0	-	-	-	-
Smoking	Presence	64	32.0	-	-	2.00	1.00–2.00
	Absent	136	68.0	-	-	-	-
Alcohol use	Presence	88	44.0	-	-	2.00	1.00–2.00
	Absent	112	56.0	-	-	-	-
Rosenberg's Self-Esteem Scale	-	200	-	0.928	0.588	0.75	0.50–1.25
Body Cathexis Scale	-	200	-	98.900	34.633	89.00	80.00–123.75
Extraversion	-	200	-	32.260	5.485	32.50	29.00–35.00
Agreeableness	-	200	-	29.360	6.741	28.50	25.00–34.00
Conscientiousness	-	200	-	31.500	7.189	34.00	28.00–37.00
Neuroticism	-	200	-	26.020	8.339	26.00	19.00–32.00
Openness	-	200	-	23.620	4.191	24.00	21.00–27.00
Negative valance	-	200	-	11.080	4.480	10.00	7.00–14.00

IQR: Interquartile range, n: Number

According to Table 3, model 1/step 3 accounts for approximately 35.1% of the change in extroversion. Model 1/step 3 is significant at the 5% significance level. Age, openness, and RSES scores have statistically significant effects on extroversion. Model 1/step 1 accounts for approximately 21.3% of the change in openness. Model 1/step 1 is significant at the 5% significance level. Only extroversion has a statistically significant effect on openness.

Figure 3 demonstrates pre-operative and one year post-operative images of a sample patient (Figures 3 a-f).

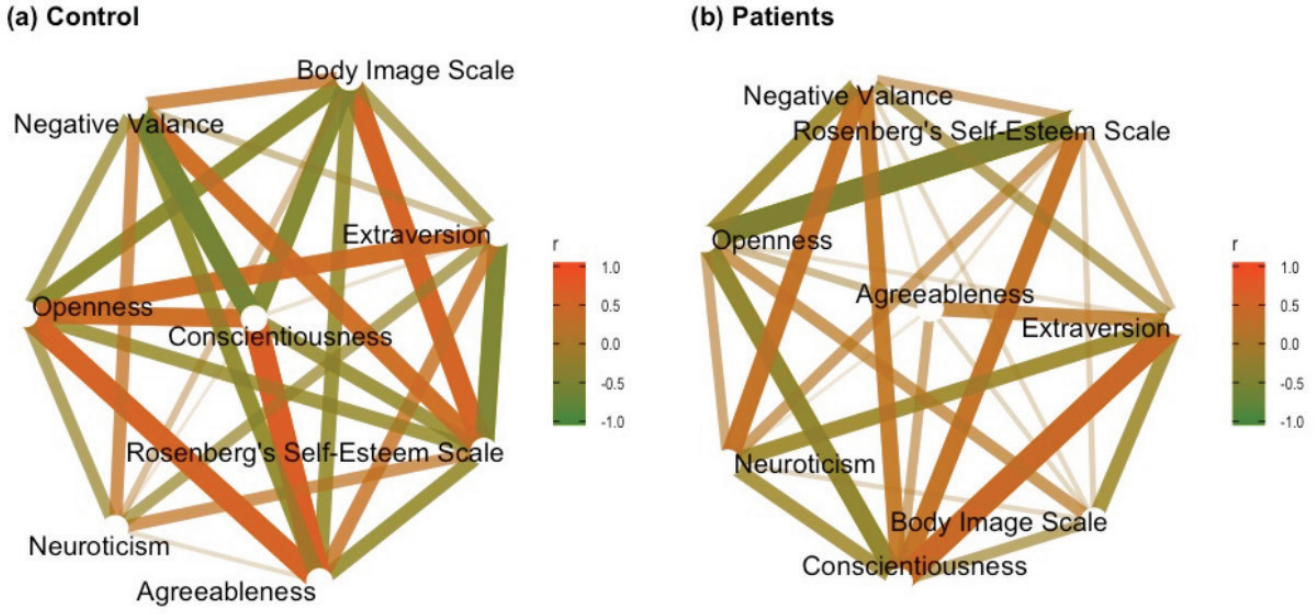

Figure 2. Pearson's correlation between scales according to **(a)** control and **(b)** patients

Table 2. Comparisons of study subjects (patients vs control) by using Independent-Samples t-test

	Group	n	$\bar{X}$	s	t	p-value
Age	Control	120	28.333	6.299	−2.041	0.051
	Patients	80	30.800	5.297		
Education (years)	Control	120	16.033	2.810	3.182	0.053
	Patients	80	15.400	1.984		
Rosenberg's Self-Esteem Scale	Control	120	0.947	0.724	0.390	0.697
	Patients	80	0.900	0.287		
Body Cathexis Scale	Control	120	92.866	36.005	−2.173	0.032
	Patients	80	107.950	30.717		
Extroversion	Control	120	30.933	6.232	−3.087	0.003
	Patients	80	34.250	3.295		
Agreeableness	Control	120	30.000	6.383	1.165	0.247
	Patients	80	28.400	7.221		
Conscientiousness	Control	120	32.466	7.731	1.661	0.100
	Patients	80	30.050	6.097		
Neuroticism	Control	120	25.666	8.193	−0.517	0.606
	Patients	80	26.550	8.631		
Openness	Control	120	22.266	4.333	−4.287	<0.001
	Patients	80	25.650	3.025		
Negative valance	Control	120	10.500	4.855	−1.598	0.113
	Patients	80	11.950	3.741		

n: Number

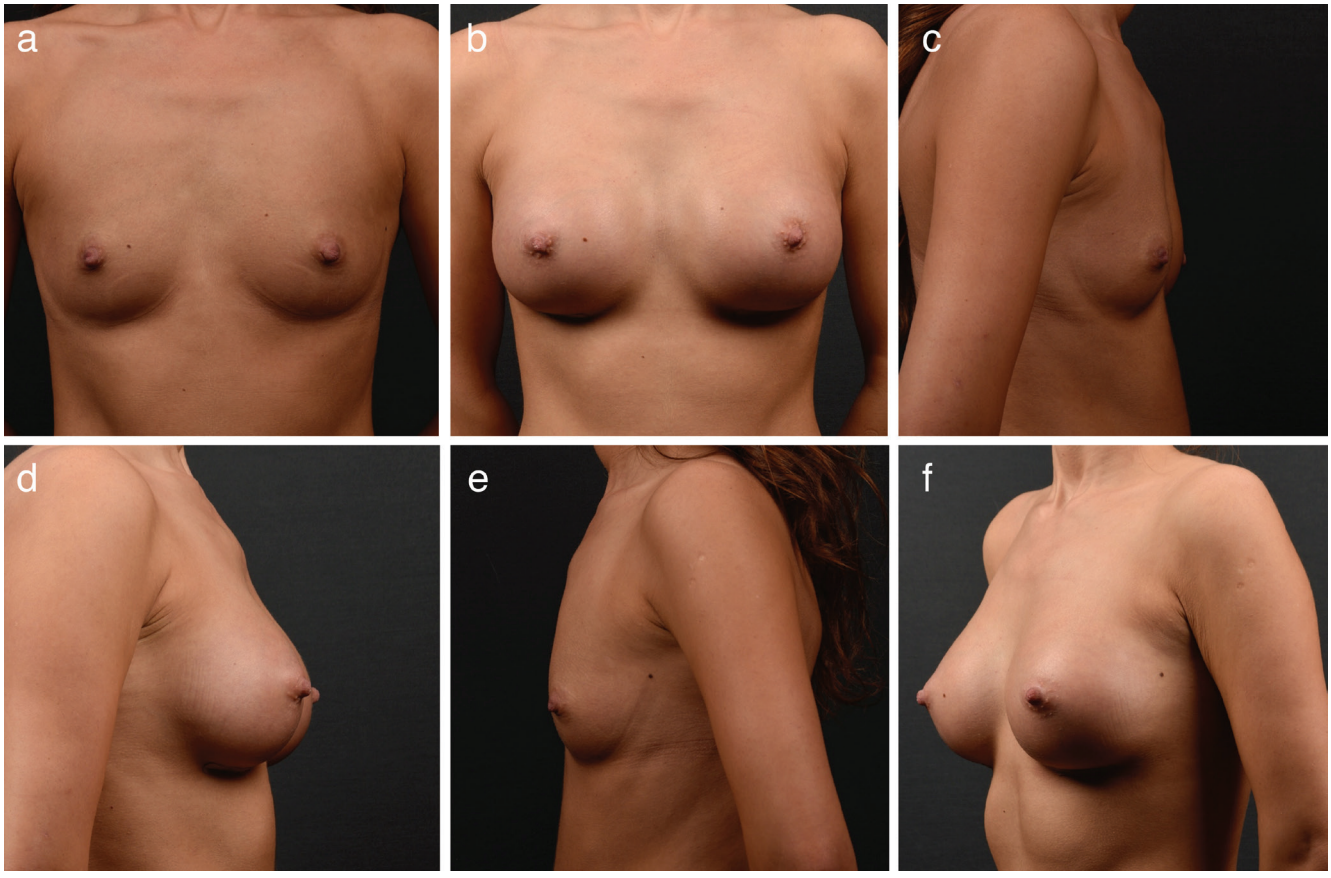

Figure 3. a. Preoperative frontal image of a sample patient. **b.** Postoperative frontal image of a sample patient. **c.** Preoperative lateral image of a sample patient (right side). **d.** Postoperative lateral image of a sample patient (right side). **e.** Preoperative lateral image of a sample patient (left side) **f.** Postoperative lateral image of a sample patient (left side) (33-year-old female patient; photo was taken 12 months after operation)

Table 3. Results of Step-Wise regression analysis

		Model 1 (Extraversion)				Model 2 (Openness)				
		B	s.e.	t	p-value		B	s.e.	t	p-value
Step 1	Constant	17.977	2.812	6.393	<0.001	(Constant)	12.230	2.240	5.460	0.000
	Openness	0.605	0.117	5.158	<0.001	Extraversion	0.353	0.068	5.158	0.000
Step 2	Constant	24.088	3.173	7.591	<0.001	-	-	-	-	-
	Openness	0.463	0.118	3.922	<0.001	-	-	-	-	-
	Rosenberg's Self-Esteem Scale	−2.971	0.841	−3.533	<0.001	-	-	-	-	-
Step 3	Constant	17.976	3.844	4.676	<0.001	-	-	-	-	-
	Openness	0.464	0.114	4.055	<0.001	-	-	-	-	-
	Rosenberg's Self-Esteem Scale	−2.748	0.820	−3.350	0.001	-	-	-	-	-
	Age	0.200	0.075	2.655	0.009	-	-	-	-	-
n		100					100			
df		(3.96)					(1.98)			
F statistic		17.294					26.602			
p-value		<0.001					<0.001			
R^2		0.351					0.213			

Discussion and Conclusion

Cosmetic surgery is considered to improve the quality of life of women who undergo breast surgery for various reasons. Longitudinal studies that investigated the effects of breast augmentation on the psychological status of women have also found that the surgery improved their psychosocial and sexual well-being, increased their satisfaction level with their breasts, and enhanced their body image, which consequently boosted their self-esteem, decreased depressive symptomatology, and alleviated their eating disorders (4-6). However, few studies have focused on the personality traits of women who undergo breast augmentation surgery solely for cosmetic reasons. Furthermore, there were no previous studies comparing personality traits between women who underwent breast augmentation surgery and a control group.

The concept of personality shifts from similarities to differences between individuals over time (14). The five-factor model of personality was developed to define variations between individuals to discover consistent cognitive, emotional, and behavioral patterns, otherwise known as traits (17). The taxonomic model has five orthogonal factors in English, in both self- and peer-rated measures, that can be applied regardless of the factor analytic method (19). These factors are surgency (extroversion), agreeableness, conscientiousness, emotional instability (neuroticism), and intellect (culture/openness). These five factors have been reported to be consistent with almost all personality theories. These five factors are extroversion, agreeableness, conscientiousness, neuroticism, and openness, respectively (20).

As previously mentioned, studies that focus on the personality of women who undergo breast augmentation surgery are quite limited. Previous studies reported that women who underwent breast augmentation were more likely to suffer from depression and anxiety and have a neurotic personality (21-24). Neuroticism is one of the main temperament types and is characterized by a tendency to react in an inappropriate and often excessive manner in stressful situations (13, 25). Thus, individuals with higher levels of neuroticism are reported to have behavioral disengagement and feelings of helplessness (25). Davis et al. (26) reported an association between neuroticism and undergoing aesthetic surgery, including breast augmentation. Groenman (27) assessed women who received breast augmentation and reported that neurotic behavior decreased after surgery. A relatively recent study assessed levels of neuroticism and life satisfaction before and after breast augmentation surgery. In this study, Zaborski et al. (2) found that there was no significant change in neuroticism levels before and after surgery, based on the Big Five model.

Considering the inconsistency in the results of previous studies, we wondered whether there could be a pre-acceptance of neuroticism for women who undergo breast augmentation surgery. While previous studies have focused on determining the level of neuroticism before and after breast augmentation surgery, our study focused on a comparison between women who undergo the surgery and women who do not. We hypothesized that the claim that women who undergo breast augmentation have higher levels of neuroticism may be the result of stigmatization. To test this hypothesis, we compared the personality traits of women who underwent breast augmentation surgery with those of age- and education-level-matched women who did not have the surgery. We found that the extroversion score was higher in the breast augmentation group, as compared with the control group. Unlike neuroticism, extroversion is associated with positive affectivity (11, 13, 28), and extroverted people are considered to be agreeable in social interactions (29). Moreover, low extraoversion and high neuroticism levels are reported to be associated with a tendency to experience depression and anxiety disorders (30). The other personality dimension that differed in the present study was openness. The mean openness score was also found to be higher in the breast augmentation group. Openness is considered to be part of the personality pertaining to flexibility (13, 31). Higher scores on this measure were found to be positively associated with higher self-esteem and positive affect. Openness to experiences is also associated with psychological well-being and better coping strategies (32). The other dimensions of personality were found to be similar between groups.

These results reveal that women who underwent breast augmentation surgery have higher levels of advantageous personality traits in terms of psychological well-being, social interactions, and coping strategies. Based on this, we suggest that beliefs regarding the personality traits of women who undergo breast augmentation surgery may be influenced by myth and stigmatization. Moreover, the breast augmentation group scored higher on the BCS compared with the control group. No significant correlation was found between the personality traits of extroversion and openness to experience and the BCS score in the breast augmentation group. Moreover, the regression analysis showed no significant associations between extroversion and openness and BCS score. An explanation for these results might be that these positive personality traits are independent of body satisfaction.

Although we attempted to determine the associations between personality dimensions and other variants, such as the BCS, the higher extroversion and openness to experience scores may be dependent on surgical success. Thus, the cross-sectional design of the present study can be considered a limitation.

In conclusion, we argue that there may be a presupposition, based on stigma, that women who undergo breast augmentation surgery are more neurotic than those who do not. Consequently, this may influence the outcomes of studies testing the personalities of these women. Our results indicate that the breast augmentation group after having undergone surgery had more positive personality traits than the control group. Further studies are needed to confirm these results.

Ethics Committee Approval: The study was approved by the Tekirdağ Namık Kemal University Non-Invasive Clinical Researches Ethics Committee (date: 30.05.2019/approval no: 2019.101.06.22).

Informed Consent: All participants gave written informed consent before participating in the study. Additional permissions were obtained from patients whose images were used in the present study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: G.Ö.; Design: G.Ö., E.B., M.B.; Supervision: E.B., Y.A., M.B.; Data Collection and/or Processing: Analysis and/or Interpretation: G.Ö., E.B.; Literature Review: G.Ö., Y.A., M.B.; Writing: E.B., Y.A., M.B.; Critical Review: E.B., Y.A., M.B.

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Original Article

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The Effect of Breast Size and Density in Turkish Women on Radiation Dose in Full-Field Digital Mammography

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ABSTRACT

Objective: The purpose of this study was to look into the relationship between breast size and mammographic breast density in women and breast radiation dose on full-field digital mammography (FFDM), as well as the factors that influence radiation dose.

Materials and Methods: The study included a total of 2,060 FFDM images from 515 consecutive participants. The participants were divided into two groups: those exposed to high doses (>3 mGy) and those exposed to low doses (<3 mGy). Moreover, the researchers analyzed the relationship between mean glandular dose (MGD) of the breast and patient age, compressed breast thickness, compression force, mammographic breast composition, and mammographic breast size.

Results: The mean mammographic breast volume was 936.2 ± 425.2 (114.5–3,018) mL, and the mean compressed breast tissue thickness was 56.75 ± 10.44 mm. Moreover, the mean MGD in the high-dose group was 3.51 ± 0.48 mGy and 1.92 ± 0.56 mGy in the low-dose group. The high-dose group had greater breast thickness, diameters, volume, compression pressure, and surgical rate. However, the high-dose group was younger and had less dense breasts. In multivariate logistic regression analysis, the most important predictors of dose determination were breast thickness [odds ratio (OR): 1.178, 95% confidence interval (CI): 1.156–1.200, p<0.001], history of previous surgery (OR: 2.210, 95% CI: 1.417–3.447, p<0.001), compression force (OR: 1.008, 95% CI: 1.004–1.013, p<0.001), and breast density (OR: 1.873, 95% CI: 1.359–2.580, p<0.001).

Conclusion: Women with larger breast volumes are subjected to higher doses of radiation. Therefore, breast-screening programs can be individualized to young women with larger breast volumes and women who have had breast-conserving surgery.

Keywords: Breast volume, mammography, radiation dose

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Key Points

- Breast cancer is the most common type of cancer in women worldwide.
- Breast tissue of women over the age of 40 is repeatedly exposed to ionizing radiation due to periodic screening programs.
- It is essential to know the factors affecting the amount of radiation dose to which breast tissue is exposed during routine screening programs and to use individualized screening programs in women to reduce radiation exposure.

Introduction

The link between radiation and cancer was discovered primarily through the victims of the Hiroshima and Nagasaki atomic bombings (1, 2). In order to reduce the risk of cancer caused by radiation, the frequency and dose of radiation exposure are kept as low as possible. The widespread use of radiation-based imaging modalities raises concerns about the risk of radiation-induced cancer.

Breast cancer is the most common type of cancer among women in Turkey, as it is in the rest of the world (24.8%) (3, 4). As a result, early detection of breast cancer is critical. Breast cancer screening programs aim to detect the disease at an early stage, before clinical symptoms appear. Mammography is the most commonly used imaging modality for breast cancer screening because of its high sensitivity and low cost (5-6). Moreover, breast cancer screening programs can reduce mortality by up to 30% (7). However, the breast tissue of women over the age of 40 is repeatedly exposed to ionizing radiation as part of a periodic screening program (8). Although it varies depending on the radiosensitivity of the tissue, it is known that the frequency of many cancers increases after radiation exposure (9).

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The purpose of this study was to look into the relationship between breast size and mammographic breast density in women and breast radiation dose on full-field digital mammography (FFDM), as well as the factors that influence radiation dose.

Materials and Methods

This retrospective study was approved by our institutional ethics committee for clinical trials. For a period of three months, consecutive mammographic images obtained in the mammography unit (Selenia, Hologic; Bedford, MA, USA) of our hospital were collected. Patients with unilateral mastectomy, mammography images with spot compression and magnification, mammograms taken during interventional procedures, patients with previously known large benign or malignant lesions, and male patient mammograms were excluded from the study. The study included all bilateral craniocaudal (CC) and mediolateral oblique (MLO) projection mammography images from eligible participants during the study period.

Breast composition was determined by two radiologists in consensus, using the Breast Imaging Reporting and Data System (BI-RADS) (10). Breasts in BI-RADS categories "a" and "b" were referred to as "nondense," while breasts in BI-RADS categories "c" and "d" were referred to as "dense." The mammographic size of the breast was determined using CC graphs and the measurement formula described by Kalbhen et al. (11) BV = 1/4π x Hcc x Wcc x Ccc (12). In this formula, the diameter of the breast parallel to the chest wall, the distance from the nipple to the chest wall, and the compressed breast thickness were all used (Figure 1). Patients who had previously undergone breast-conserving surgery were identified.

Data on the mean glandular dose (MGD) value, compressed breast thickness, and breast compression force were extracted from the Digital Imaging and Communications in Medicine (DICOM) labels of each image sent to our Picture Archiving and Communication System (PACS).

According to the Food and Drug Administration and the International Commission on Radiological Protection (ICRP), the safe limit for a single projection mammogram is 3 mGy MGD. This dose value was accepted as a cutoff, and the participants were divided into two groups: those who received a high dose and those who received a low dose. Furthermore, the relationship between MGD and the age of the participants during mammography, breast diameters, compressed breast thickness, breast compression force, mammographic breast composition, and the mammographic breast volume were investigated using univariate and multivariate linear regression analyses.

Definitions

Total glandular dose: the total dose to which a breast is exposed during MLO and CC projection

MGD: the average dose of a breast exposed in MLO and CC projections.

Statistical analysis

SPSS 15.0 for Windows (IBM Inc., Armonk, NY, USA) was used to analyze all of the data. The Kolmogorov-Smirnov test was used to determine whether the data distribution was normal. The student's t-test was used to compare data with a normal distribution. Linear regression analysis was also used to test the data's predictive effect on MGD. Furthermore, the forward elimination model was preferred for variable elimination. Continuous data were expressed as mean ± standard deviation, and categorical data as percentages. Statistical significance was indicated by $p<0.05$.

Results

A total of 2,060 images from 515 consecutive patients who had routine CC and MLO investigations were included in the study. The mean age of the patients was 55.9 ± 8.8 years. The mean mammographic volume of the breast per person was 936.2 ± 425.2 (114.5–3,018) mL. In addition, the mean compressed breast tissue thickness was 56.75 ± 10.44 mm, and the mean compression force was 127.13 ± 30.89 N. When the patients were classified based on mammographic breast composition, 657 breasts (63.8%) were classified as "nondense," while 373 breasts (36.2%) were classified as "dense" (Figure 2). A total of 78 breasts (7.6%) had a history of breast-conserving surgery. The mean MGD per image for CC images was 1.75 ± 0.64 mGy and 2.61 ± 0.71 mGy for MLO images. For a single image, the mean MGD was 2.18 ± 0.80 mGy. For a single breast, the total dose from two-projection mammograms was 4.36 ± 1.2 mGy. The mean MGD in the "nondense" and "dense" groups, 2.22 ± 0.82 and 2.10 ± 0.76 mGy

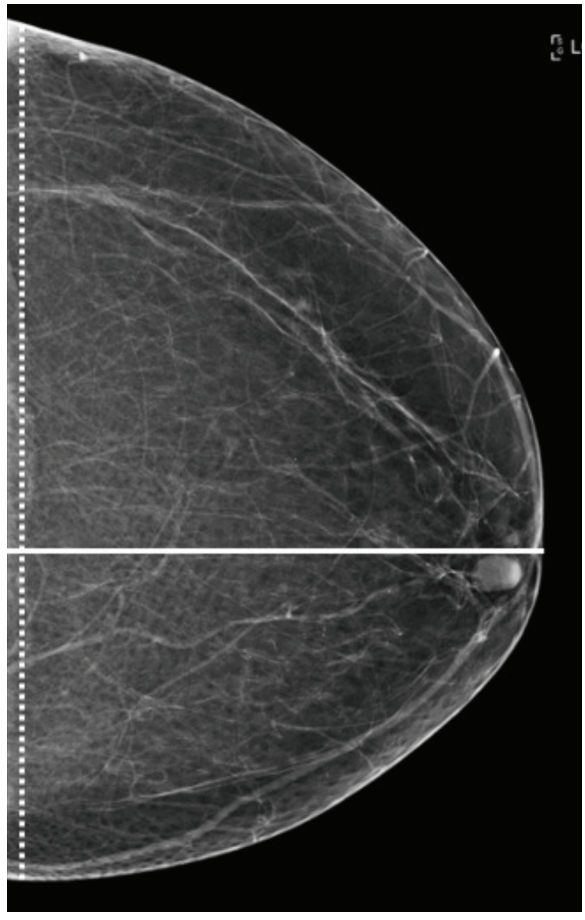


Figure 1. In craniocaudal projection, the following measurements were used to calculate breast volume: posterior-anterior height (dashed line), lateral-medial width (straight line), and breast thickness

respectively, was significantly different (p = 0.006), respectively. The volume of the breasts in the "dense" group was significantly lower than the volume of the breasts in the "nondense" group (689.5 ± 322.7 vs 1,076.3 ± 412.5, p<0.001). In patients who had previously undergone breast surgery, the surgical side had higher MGD values (2.63 ± 0.99 vs 2.15 ± 0.77, p<0.001) (Table 1).

In 16.3% of the images, the radiation dose to which the breast tissue was exposed was greater than 3 mGy. The mean MGD in the high-dose group was 3.51 ± 0.48 and 1.92 ± 0.56 in the low-dose group (p<0.001). The high-dose group had greater breast thickness, diameters, and volume, compression pressure, and surgical rate. However, patients in the high-dose group were younger and had lower breast density (Table 1).

In univariate logistic regression analysis, age and breast density were found to be negatively correlated with high MGD, whereas breast thickness, breast compression force, and surgical history were found to be positively correlated. On the other hand, in multivariate logistic regression analysis, the best model for predicting high MGD included breast thickness [odds ratio: (OR): 1.178, 95% confidence interval (CI): 1.156–1.200, p<0.001], previous surgery history (OR: 2.210, 95% CI: 1.417–3.447, p<0.001), compression force (OR: 1.008, 95% CI: 1.004–1.013, p<0.001), and breast density (OR: 1.873,

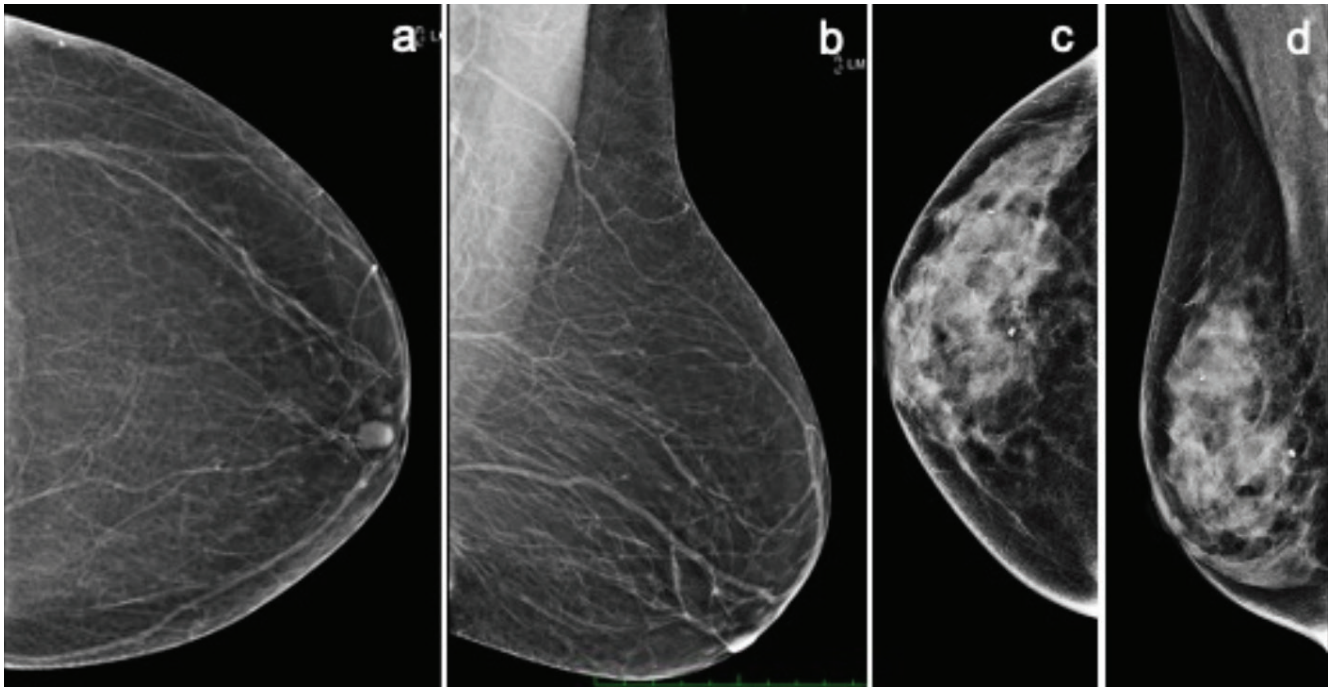


Figure 2. A 68-year-old woman with large breasts and a "nondense" breast composition. The average MGD per view was 1.19 mGy **(a, b)** a 46-year-woman with "dense" breast composition and small breasts. The average MGD per view was 2.87 mGy **(c, d)**

MGD: Mean glandular dose

Table 1. Baseline characteristics

	All images (n = 2060)	Low dose (n = 1725)	High dose (n = 335)	p-value
Age, years (n = 515)	55.92 ± 8.78	56.21 ± 8.7	54.45 ± 8.6	0.001
Breast thickness (mm) (n = 1030)	56.7 ± 10.44	54.7 ± 9.7	67.1 ± 7.2	<0.001
Breast diameter 1 (mm) (n = 1030)	198.10 ± 24.65	195.4 ± 24.3	212.1 ± 21.5	<0.001
Breast diameter 2 (mm) (n = 1030)	100.63 ± 25.32	98.5 ± 25.1	111.9 ± 23.6	<0.001
Volume (mL) (n = 1030)	936.23 ± 425.24	869.6 ± 392.8	1279.2 ± 420.4	<0.001
Compression (N) (n = 2060)	127.13 ± 30.89	126.3 ± 30.1	131.3 ± 34.6	0.015
Radiation dose, mGy (n = 2060)	2.18 ± 0.80	1.92 ± 0.56	3.51 ± 0.48	<0.001
Surgical history, n (%) (n = 2060)	156 (7.6)	103 (6)	53 (15.8)	<0.001
Dense breast, n (%) (n = 2060)	746 (36.2)	654 (37.9)	92 (27.5)	<0.001

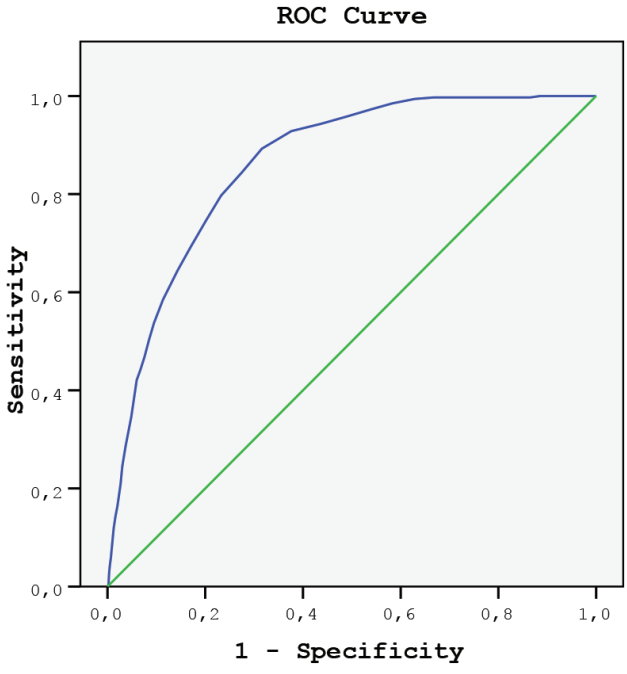
Breast diameter 1: the diameter of the breast parallel to the chest wall on CC projection; Breast diameter 2: the distance from the nipple to the chest wall on CC projection. N - Newton
n: Number

95% CI: 1.359–2.580, p<0.001). The high-dose determination power of this model was 86%. Interestingly, the power of breast thickness alone to detect high MGD was 85% (OR: 1.168, 95% CI: 1.148–1.189, p<0.001). In the receiver operating characteristic analysis, the sensitivity of the 60-mm thickness to determine high dose was 79.7%, while the specificity was 76.8% [area under the curve (AUC) = 0.862 p<0.001] (Graph 1).

In univariate regression analysis, breast density was negatively correlated with MGD but positively correlated with MGD in multivariate regression analysis (p<0.001) (Table 2).

Discussion and Conclusion

Mammography is the mostly widely used imaging modality used for breast cancer screening, but the most significant disadvantage of the examination is radiation exposure. The mean dose absorbed by all fibroglandular tissue in the breast is referred to as MGD. MGD is linked to an increased risk of radiation-induced breast cancer.



Graph 1. In the ROC analysis, the sensitivity of the 60-mm thickness to determine high dose was 79.7%, while the specificity was 76.8% (AUC = 0.862, p<0.001)

ROC: Receiver operating characteristic, AUC: Area under the curve

Therefore, radiation doses should be kept as low as possible in all imaging techniques using X-ray.

Hauge et al. (13) conducted a risk prediction study on 100,000 Norwegian women aged 50–69 years who were screened with mammography at 2-year intervals and calculated the risk of radiation-induced breast cancer as 10/100,000 for a dose of 2.5 mGy. Using the same parameters, the number of radiation-induced breast cancer deaths was calculated as 1/100,000 (6). According to Warren et al. (14), the number of deaths caused by radiation-induced breast cancers was 150 times lower than the number of lives saved by screening. Although the risk of radiation-induced-cancer from mammography is extremely low, repeated radiation exposure has been linked to an increased risk of breast cancer (15).

Radiation dose is proportional to the size and density of the breast. In general, obese women with large, dense breasts and thick compressed breast tissue are exposed to higher radiation doses.

In our study, 25% of the participants were between the ages of 25 and 49, and a significant relationship was discovered between young age and high MGD. This could be explained by the dense breast pattern often found in younger women, which necessitates higher doses. On the other hand, since the radiosensitivity of breast tissue is negatively correlated with age, being young is associated with an increased risk of radiation-related cancer and death. As a result, careful radiation dose regulation is critical in young women undergoing mammography.

Breast screening programs employ standard CC and MLO projections for each breast. In our study, MGD per projection was 1.75 ± 0.64 mGy for CC images and 2.61 ± 0.71 mGy for MLO images, with a total MGD of 4.36 ± 1.2 mGy for a single breast. In a similar study on Saudi women, the MGD for single breasts was 1.02 ± 0.2 mGy (0.4–1.8) for CC projections and 1.1 ± 0.3 mGy (0.5–1.8) for MLO projections, for a total of 2.12 mGy per breast (16). In a similar study on Korean women, Baek et al. (17) reported a total MGD for a single breast at two-projection mammograms of 3.62 mGy and an average effective dose of 0.43 mSv. Considering the tissue weighting factor (0.12 for breast tissue) of the ICRP, the mean effective dose for a single breast in our study was calculated to be 0.52 mSv (18). In the ACRIN-Digital Mammographic Imaging Screening Trial by Hendrick et al. (19), MGD was reported as 3.7 mGy on two-projection digital mammography. The MGD determined by Food and Drug Administration for a single projection in digital mammography

Table 2. Univariate and multivariate logistic regression analysis to determine high dose (>3 mGy)

Predictor	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age, (years)	0.977	0.963–0.990	<0.001	-	-	-
Compression, (N)	1.005	1.001–1009	<0.007	1.008	1.004–1.013	<0.001
Surgery, (Y/N)	2.960	2.076–4.219	<0.001	2.210	1.417–3.447	<0.001
Breast thickness, (mm)	1.168	1.148–1.189	<0.001	1.178	1.156–1.200	<0.001
Dense breast, (Y/N)	0.620	0.479–0.803	<0.001	1.873	1.359–2.580	<0.001

Y/N: Yes or No; N: Newton; CI: Confidence interval

(standard breast thickness: 42 mm, 50% fibroglandular tissue, 50% adipose tissue) should not exceed 3 mGy (20). The ICRP recommends a dose limit of 3 mGy for each projection (18). In the European protocol, a reference dose limit of 2.5 mGy per image is recommended for a standard breast of 53-mm thickness (21). In our study, the MGD of women was higher than the doses reported in other studies, but it was still within the allowed dose limits.

While the mean breast tissue volume in Western women is 551.95–774 mL, Baek et al. (17) found that breast volume in Korean women ranged from 380.9 to 466.4 mL. In our study, the mean breast tissue volume was calculated to be 936.2 ± 425.2 (114.5–3018) mL. Moreover, women in our study had larger breast volumes than both Asian and Western women. In terms of breast density, 36.9%–51% of Western women and 61.9%–86.4% of Korean women have a dense mammographic breast composition (22-25). In our study, the dense breast composition ratio in Turkish women was calculated to be 36.2%, which was comparable to the lower end of the range for that of Western women.

Warren et al. (14) reported an MGD of 3 mGy for small breasts and a range of 5–10 mGy for large breasts. Further, Young and Oduko (26) studied the radiation dose received during the breast-screening program on 25,409 women living in the United Kingdom. According to their findings, 1.8% of the population has large breast tissue (breast thickness >90 mm), and women with large breasts have 1.7 times the radiation exposure compared to the general population (26). According to the regression analysis performed in our study, breast thickness was the most powerful parameter determining MGD level. Breast thickness increases as a result of increased breast volume. In our study, breast diameters in two axes, breast thickness, and breast volume were significantly different between women exposed to a low dose (<3 mGy) and those exposed to a high dose (>3 mGy). Given that the women in our study had larger breast volume than women of other ethnicities, it is possible that the relatively high dose detected was due to the larger breast volume.

High MGD is associated with "dense" mammographic breast composition (27). When compared to European and North American women, Asian women have smaller but more dense breast patterns (28). In the study of Baek et al. (17), Korean women were found to be exposed to higher MGD due to their small but denser breast pattern. However, in our study, the nondense group had higher MGD values than the dense group. Furthermore, univariate regression analysis revealed a negative correlation between breast density and MGD. However, women with dense breast patterns had significantly smaller breast volume than the nondense group. Therefore, higher MGD in the nondense group of our study population was most likely associated with higher breast volume in these women. This is supported by the fact that when the volume parameter was disabled, the multivariate regression analysis revealed a significant association between breast density and increased MGD.

Mammographic compression reduces superposition and thickness of breast tissue while maintaining homogeneity, and it also decreases radiation exposure (29-32). However, pain is a significant problem of compression, especially in patients who have had breast surgery (33). According to the Norwegian breast cancer screening program guidelines, the compression force should be between 108 and 177 N. It has been reported that compressing the breast tissue after a certain point causes discomfort in the patient rather than a decrease in breast thickness (34). In our study, the mean breast compression force was 127.13 ± 30.89 N, and there was a negative relationship between compression force and MGD. This can be explained by a reduction in the required dose caused by a decrease in breast thickness as a result of increased compressive force. In a study evaluating the relationship between breast compression and MGD in Asian women by Lau et al. (35), the mean compression pressure was reported to be 122.2 ± 34.5 N, which was close to the value in our study.

Our results showed that patients with a history of breast-conserving surgery required a higher MGD. We believe this was due to increased tissue density, caused by postoperative edema, skin thickening, surgical scar tissue, and existing surgical clips (36, 37).

We had some limitations: it was a single-center study. As a result, multicenter studies are needed to evaluate more objectively. MGD reflects the dose delivered by the machine, not the dose received by the breast. Therefore, the dose to which the breast is exposed may be reduced.

In conclusion, although the risk of cancer from mammography is extremely low, dose optimization is critical due to the repeated radiation exposures during screening programs. Women with larger breast volumes are subjected to higher doses of radiation. Moreover, screening programs and radiation doses can be individualized to women who are young, have larger breast volume, and have had breast-conserving surgery.

Ethics Committee Approval: This study was approved by Ondokuz Mayıs University Faculty of Medicine (no: B.30.2.ODM.0.20.08/634, date: 02.08.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: A.İ.S., A.V.P.; Design: A.İ.S., A.V.P.; Data Collection and/or Processing: A.İ.S., M.Ö., A.V.P.; Analysis and/or Interpretation: A.İ.S., M.Ö., A.V.P.; Literature Review: A.İ.S., A.V.P.; Writing: A.İ.S., A.V.P.; Critical Review: İ.S., A.V.P.

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Original Article

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Effects of Primary Tumor Resection on Metastatic Breast Cancer Survival and the Predictive Power of Neutrophil: Lymphocyte Ratio on Prognosis

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ABSTRACT

Objective: The aim was to investigate the effect of primary tumor resection (PTR) on survival in metastatic breast cancer patients and to assess the power of the neutrophil-to-lymphocyte ratio (NLR) regarding the prediction of prognosis in this patient group.

Materials and Methods: Female patients diagnosed with and starting treatment for metastatic breast cancer from 2003 to 2016 in the general surgery and oncology clinics at a single center were retrospectively reviewed. Pre-treatment NLR value and survival situations were evaluated.

Results: A total of 117 patients were enrolled. The disease-specific survival (DSS) of the patients was 41.4 months. When stratified into PTR and systemic treatment (ST) groups, there was no difference in the survival (p = 0.054); 43.5 months in the PTR group vs 30.7 months in the ST group. When hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative subgroups were analyzed, DSS was significantly longer (p = 0.02) in the PTR group (55.4 months) compared to the ST group (41.8 months). Finally, in patients with an NLR of <2.3, DSS was significantly longer (p = 0.03) in the PTR group (56.1 months) compared to the ST group (25.2 months).

Conclusion: These results suggest that DSS can be increased with PTR in selected patients with a diagnosis of metastatic breast cancer. NLR may be useful in selecting patients for appropraite treatment modality.

Keywords: Metastatic breast cancer, primary tumor resection, neutrophil-to-lymphocyte ratio, survival

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Key Points

- DSS was 43.5 months in the PTR group and 30.7 months in the ST group. Survival difference between the groups was not significant.
- In the HR-positive and HER2-negative subgroups, PTR was associated with longer DSS.
- In the NLR <2.3 subgroup, PTR was associated with longer DSS.
- PTR increased DSS rates in selected patient subgroups with metastatic breast cancer. NLR can be used as an effective tool in patient selection.

Introduction

Breast cancer is the most commonly diagnosed cancer in women and the most frequent reason for female cancer-related deaths in the world (1). In Turkey, the incidence of female breast cancer is 43.8/100,000 women, and 6% of all patients diagnosed with breast cancer have been reported to have metastasis (2). Metastatic breast cancer is considered an incurable disease, and patients are usually provided palliative care. Nevertheless, advances in systemic treatment (ST) have significantly improved the control of metastatic diseases, thus offering prolonged survival. In this context, the role of primary tumor resection (PTR) in survival has, therefore, become a matter worth investigating. According to current practice, surgery is limited to symptomatic support in the treatment of metastatic breast cancer, but recent studies have suggested that survival and life quality can be increased in patients undergoing PTR and subsequently treated with an appropriate ST course (3, 4).

The search for new inflammatory markers for various diseases has been investigated for some time. Of particular interest is the physiological response of leucocytes to stress, a phenomenon that causes an increase in the neutrophil count and a concomitant relative decrease in lymphocytes.

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Based on this physiological mechanism, the neutrophil-to-lymphocyte ratio (NLR) has been proposed as a simple inflammatory marker (5). NLR has been studied as a biomarker in various tumor types and some studies have investigated the relationship between NLR and survival for metastatic breast cancer patients (6).

The aim of this study was to investigate the effect of PTR on survival in metastatic breast cancer patients and to assess the power of the NLR in terms of predicting prognosis in this patient group. In this way, it was hoped to demonstrate the effectiveness of the NLR in determining patients with metastatic breast cancer who would benefit most from primary tumor surgery.

Materials and Methods

After securing approval from the ethics committee, the records of all patients who were diagnosed with and started treatment for metastatic breast cancer from 2003 to 2016 in our center were retrospectively reviewed. All eligible patients had received no treatment prior to their admission. The patients were stratified into two groups: the PTR group, who underwent PTR followed by systemic treatment (ST), and the ST group, who only received ST.

Patient information was gathered from the hospital information management system (SARUS DBMS, EES Ltd. Şti, Ankara, Turkey) data hosted by clinical archives using File Maker Pro 7 (Claris International Inc., Santa Clara, CA, USA). Other data were obtained from the Death Declaration System (DDS) of the Turkish Ministry of Health (www.obs.saglik.gov.tr). The patients who died due to the disease and the dates of death were determined from the DDS. Patients who died for different reasons and those who underwent surgery for metastasis other than primary tumor were excluded from the study.

For all patients in the study, age at the time of diagnosis of stage IV breast cancer, gender, menopause status, time of initial diagnosis, histopathology results, positivity or not for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2), metastasis status, and time of complete blood count test at initial diagnosis data has been recorded.

The diagnosis of metastatic disease was made prior to treatment initiation by radiological, laboratory and pathological examinations, including ultrasound, positron emission tomography-computed tomography (PET CT), bone scintigraphy, tomography, and biopsy. Surgical procedures were performed for palliative purposes and were classified as follows: breast-conserving surgery, including resection of the primary tumor with tumor negative surgical margin; modified radical mastectomy; and simple mastectomy.

Systemic therapies were administered by patient-specific multidisciplinary decision. Disease-specific survival (DSS) was documented by calculating the time period from initial diagnosis to time of death, as recorded in the DDS, expressed as months. Data gathering was completed by November 2018, and the last follow up visit was chosen as the end-point for data collection in those patients who were still alive at the end of the data collection period.

For the other aim of the study, the complete blood count acquired prior to the initiation of treatment was evaluated. Neutrophil and lymphocyte counts and the NLR at first admission were also calculated for each patient.

Statistical analyses were performed using SPSS version 20 (IBM Inc., Armonk, NY, USA). An investigation of survival with univariate analyses was performed using the log rank test. Cox regression analysis was used via the retroactive selection method for investigating individual factors for survival prediction in multivariate analysis. Survival rates were calculated using the Kaplan-Meier method (Figures 1-3). The log rank test was used for evaluating the effect of the median value of the NLR on survival. Receiver operating (ROC) curves were generated, and the area under the curves was calculated to assess the extent to which changes in NLRs were capable of distinguishing 5-year disease-specific survival (DSS). Youden's index was utilized to determine the appropriate cut-off value for NLRs. Calculations with <5% Type 1 error were accepted as statistically significant.

Results

A total of 117 female patients with metastatic breast cancer, with a median (range) age of 54 (26–86) years were enrolled. Among these patients, 38 (32.5%) were premenopausal and 79 (67.5%) were postmenopausal. DSS for the whole cohort was 41.4 months. Median age was 60 years in the ST group and 50 years in the PTR group. The primary tumor was surgically excised in 55 patients (47%) and not treated surgically in 62 patients (53%). When the metastatic areas of primary tumor were investigated, it was found that 52 (44.4%) patients had bone metastasis only, 27 (23.1%) had visceral metastasis, and 38 (32.5%) had both bone and visceral metastasis (Table 1).

Overall survival (OS) durations were: 47.2 months in patients with bone metastasis only, 40.2 months in patients with visceral metastasis, and 23.8 months in patients with both bone and visceral metastasis. OS was significantly higher in patients who only had bone metastasis ($p = 0.032$).

Cox regression analysis revealed a statistically significant relationship between DSS and hormone receptor (HR) status and the NLR ($p<0.05$), whereas there were no relations with age ($p = 0.86$), menopause status ($p = 0.77$), surgery status ($p = 0.15$), or metastatic status ($p = 0.22$). Following multivariate analysis, the NLR and HR status continued to exhibit a statistically significant relation with DSS ($p = 0.03$ and $p = 0.02$, respectively).

Survival was 43.5 months in the PTR group and 30.7 months in the ST group. DSS was not significantly different between the two groups ($p = 0.054$).

There were 64 patients with HR-positive/HER2-negative metastasis and the DSS was 55.4 months in the PTR group ($n = 27$) and 41.8 months in the ST group ($n = 37$), which was statistically significant ($p = 0.02$). When the NLR was evaluated for the whole cohort, the median value was found to be 2.3. In patients with an NLR of <2.3, survival was 56.1 months in the PTR group and 25.2 months in the ST group. This survival difference between the two groups was statistically significant in favor of the PTR group ($p = 0.03$) (Table 2).

Discussion and Conclusion

This study demonstrated that PTR followed by ST may provide better DSS compared to ST in patients with metastatic breast cancer, but only in selected patients. Although survival in the PTR group was longer than in the ST group, no statistically significant difference was found between the two groups in terms of DSS. However, subgroup analysis revealed that PTR had a positive effect on survival in patients

with HR-positive/HER2-negative metastasis. Furthermore, in patients with an NLR of <2.3, survival of the PTR group was longer than in the ST group (p = 0.03).

Since Rapiti et al. (7) published the results of an important study in 2006 that reported that PTR reduced cancer-related deaths in patients with metastatic breast cancer, this procedure has been of interest to clinicians managing this patient group. Since 2006, many retrospective and a few prospective studies have been conducted. However, PTR in metastatic breast cancer patients remains controversial.

In a recently published, comprehensive meta-analysis, the effectiveness of locoregional therapy (LRT) in patients with *de novo* stage IV breast cancer was investigated. Meta-analysis results from 216,066 patients revealed that LRT can reduce mortality by 31.8%. Furthermore, it has been reported that surgery can specifically reduce mortality by 36.2% (8). Studies comparing OS results also reported that PTR is associated with longer OS (9-11).

In the retrospective study conducted by Babiera et al. (12), although single-site metastasis and *HER2/Neu* gene mutation were negative, they found no statistically significant difference in survival, although a longer survival trend was reported. That study further showed that PTR was associated with increased metastasis-progression-free survival. Meanwhile, in a study on the relationship between metastasis and survival, Fields et al. (13) reported that PTR in metastatic breast cancer patients reduced the incidence of death, not only in patients with bone metastases but also in those with metastases at other sites. In our study, we found no relation between metastatic site and DSS but this result may be due to the effect of the sample size or the classification of metastasis status.

Table 1. Demographic data

		PTR Group	ST Group	Total
Age		50	60	54
Menopause status	Premenopausal	21 (18%)	17 (14.5%)	38 (32.5%)
	Postmenopausal	34 (29%)	45 (38.5%)	79 (67.5%)
Hormone receptor status	HR+	35 (30%)	51 (43.5%)	86 (73.5%)
	HR–	20 (17%)	11 (9.5%)	31 (26.5%)
HER2 receptor status	HER2+	14 (12%)	18 (15.3%)	32 (27.3%)
	HER2–	41 (35%)	44 (37.7%)	85 (72.7%)
Metastasis sites	Bone-only	25 (21.4%)	27 (23.1%)	52 (44.5%)
	Visceral only	17 (14.5%)	10 (8.5%)	27 (23%)
	Lung	9	4	13
	Liver	4	5	9
	Lung, liver	0	1	1
	Mediastinal	4	0	4
	Bone and visceral	13 (11.1%)	25 (21.4%)	38 (32.5%)
	Lung, bone	1	12	13
	Lung, brain, bone	0	1	1
	Lung, liver, bone	2	4	6
	Lung, pancreas, bone	1	0	1
	Brain, bone	1	2	3
	Brain, liver, bone	0	1	1
	Liver, bone	8	4	12
	Liver, mediastinal, bone	0	1	1
Type of surgery	MRM	46 (39.3%)	-	55 (47%)
	Simple mastectomy	7 (6%)	-	55
	BCS	2 (1.7%)	-	55
Systemic therapies	Chemotherapy	40 (34.2%)	43 (36.8%)	83 (71%)
	Endocrine therapy	6 (5.2%)	5 (4.3%)	1 1(9.5%)
	Chemotherapy plus endocrine therapy	2 (1.7%)	1 (0.8%)	3 (2.5%)
	Missing	7 (6%)	13(11%)	20 (17%)

PTR: Primary tumor resection; ST: Systemic treatment; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; MRM: Modified radical mastectomy; BCS: Breast conserving surgery

A prospective randomized study by Badwe et al. (14) compared PTR with ST in the treatment of metastatic breast cancer patients and examined OS using a sample of 350 metastatic breast cancer patients between 2005 and 2013. They reported no difference in OS between the PTR and ST groups. Moreover, through subgroup analyses, they found that menopause, metastatic areas, estrogen and progesterone receptor or HER2 status did not make a significant difference to OS. However, there are important factors affecting the results in this study. The patients, in contrast to our study, were metastatic breast cancer patients who had previously undergone chemotherapy and responded to treatment before being included in the study and then randomized. Furthermore, although 107 (31%) of the 350 patients in their study had HER2-positive disease, only 8% of these patients were able to receive HER2-targeted therapy due to financial constraints (14). The presence of these factors may have had a significant impact on treatment efficacy and survival, and this should be kept in mind when comparing survival outcomes.

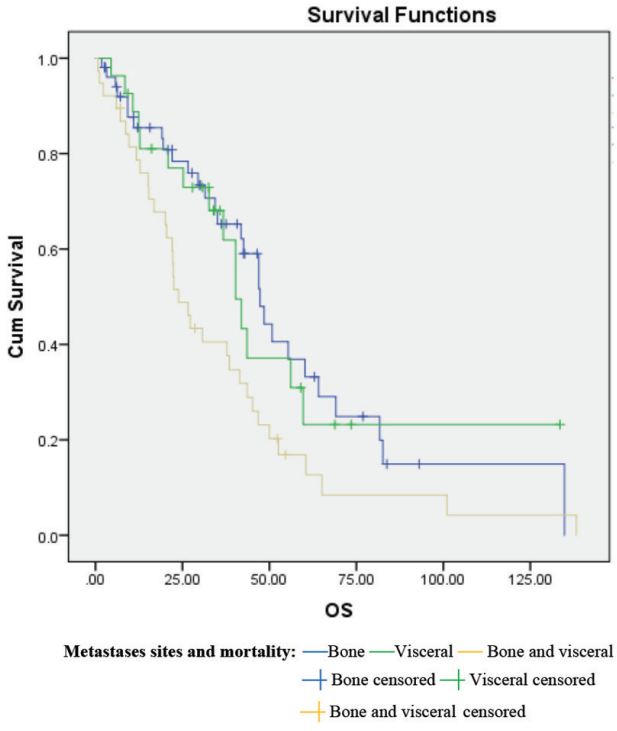

Figure 1. Survival difference between metastatic sites

OS: Overall survival; Cum: Cummulative

Table 2. Statistically significant parameters

	PTR	ST	p
NLR <2.3 (n = 49)	26	23	
DSS (month)	56.1	25.2	**0.03**
ER/PR (+), HER2 (-) (n = 64)	27	37	
DSS (month)	55.4	41.8	**0.02**

Significant p-values are shown in bold and italic.

PTR: Primary tumor resection; ST: Systemic treatment; DSS: Disease-specific survival; NLR: Neutrophil-to-lymphocyte; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; n: Number

The other prospective study, the MF07-01 trial, was designed by Soran et al. (15). This was a multicenter, phase III, randomized controlled study whose results were first published in 2016 and then in 2018 after a 5-year follow-up (16). A total of 274 metastatic breast cancer patients were randomized into two groups: one received ST after LRT and the other received ST alone, after which they were evaluated in terms of OS. Patients did not receive any treatment before being included in the study. The 5-year follow-up results revealed that 41.6% of the LRT group and 24.2% of the ST group were alive. In the LRT group, the risk of death was 34% lower than that in the ST group. In subgroup analysis, OS was significantly higher in patients with HR-positive/

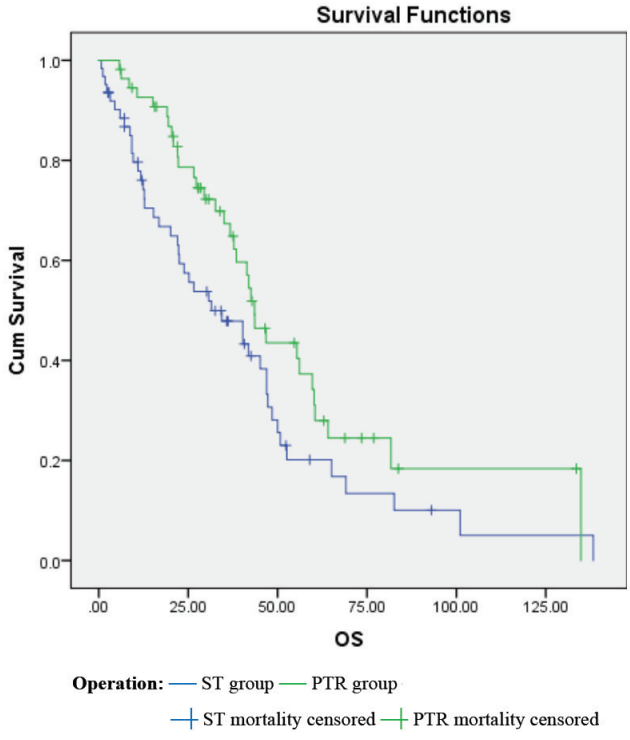

Figure 2. Survival difference between study groups

OS: Overall survival; Cum: Cummulative

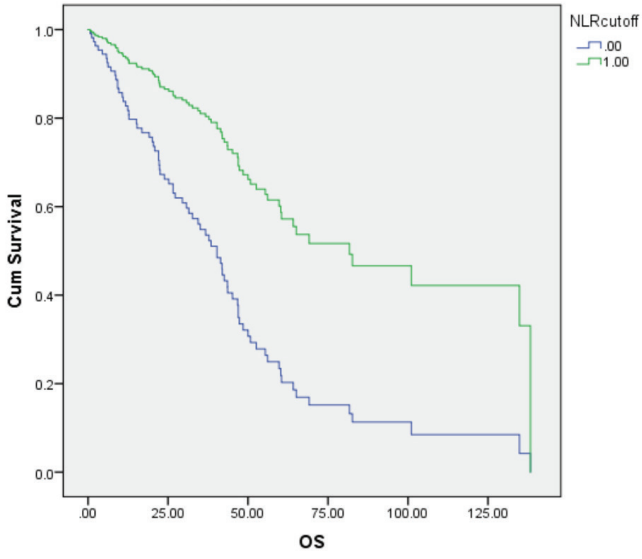

Figure 3. Survival difference between NLR cut-off values

OS: Overall survival; Cum: Cummulative; NLR: Neutrophil-to-lymphocyte

HER2/Neu-negative, bone-only metastasis who were under 55 years of age in the LRT group compared to the ST group. Patients in the LRT group with bone-only metastasis had a survival outcome that was 14 months longer than that in the ST group (15).

To the best of our knowledge, our study is the first to evaluate the effect of PTR on survival and then examine the predictive significance of the NLR in metastatic breast cancer patients. In the NLR <2.3 subgroup, DSS was significantly longer in the PTR group compared with the ST group. Many studies have shown that NLR can be of prognostic value in breast cancer, similar to other cancers. However, most studies on NLR and its value in breast cancer did not specifically examine metastatic breast cancer.

Our study differs from the literature in that it specifically examines the prognostic value of NLR in metastatic breast cancer patients. A systematic review and meta-analysis by Ethier et al. (16) reported that a high NLR has been shown to have a negative effect on OS and disease-free survival, and has been identified as an easily accessible prognostic marker. It has also been reported that neutrophils inhibit the immune system and suppress the activity of lymphocytes and the T-cell response; thus, tumor growth may increase. Furthermore, high NLR can be considered an indicator of increased inflammation, which may also result in immunosuppressive effects and lymphocyte inhibition (16). Another report stated that NLR may be used as an independent prognostic factor for OS in metastatic breast cancer patients (17). Takuwa et al. (18) retrospectively examined the results of 171 metastatic breast cancer patients and showed a strong association between a high NLR and poor prognosis. Similarly, in a meta-analysis of 18 studies, Liu et al. (19) investigated the prognostic value of the NLR before breast cancer treatment and showed a correlation between a high NLR and poor prognosis in breast cancer patients.

A recent retrospective study by Iimori et al. (20) of 34 stage IV breast cancer patients undergoing endocrine therapy showed that a low NLR was associated with a reduction in treatment failure rates, progression-free survival and an increase in OS. Multivariate analysis results showed that treatment response and a low NLR were independent factors for a better prognosis, suggesting that the NLR can be used as a predictive marker of endocrine treatment response in stage IV breast cancer patients (20). In the observational studies of Azad et al. (21), published in 2012, all stages of breast cancer in patients diagnosed and treated between 2004 and 2006 were evaluated for NLR. They found that those with an NLR of >3.3 had the the highest first- and fifth-year mortality rates, whereas those with an NLR of <1.8 had the lowest mortality rate. Thus, an NLR of >3.3 was shown to be an independent predictor of mortality (21). In our study, performing PTR in patients with NLR values below 2.3 significantly increased OS.

Our study has some limitations that should be noted. Primarily, this work was a retrospective, single-center study. Thus, it was subject to various limitations encountered in retrospective studies, such as the lack of regular records of adjuvant therapy regimens, which explains why the chosen surgical method was selected. The importance of PTR in metastatic breast cancer can be understood more clearly with the recent widespread, multicenter, prospective studies that continue to collect data. It was important in our study to have an equal number of study groups over a long period of time in order to follow multidisciplinary treatments and investigate the effect of PTR on survival in metastatic breast cancer patients. This allowed us to determine the efficacy of using NLR in conducting appropriate patient selection and, subsequently, to recommend this practice.

In conclusion, the results of our study using ST following PTR in the treatment of metastatic breast cancer patients significantly increased survival in HR-positive/HER2-negative patients compared to ST only, with longer survival in patients with an NLR of <2.3, thus contributing to the literature on treatments for these patients. We believe that PTR may be an important treatment option in metastatic breast cancer patients and that NLR, as an indicator of systemic inflammation, can be a useful criterion in the selection and delivery of optimal therapy. However, in patients with stage IV breast cancer, further research is needed to evaluate the effect of patient selection on survival after PTR.

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Turkey, Antalya Training and Research Hospital with the decision number 2/007 dated 24/01/2019.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed

Authorship Contributions

Conception: Y.Ç., U.R.G., B.D., N.H.B., Ş.G.; Design: Y.Ç., U.R.G., B.D., N.H.B., Ş.G.; Data Collection and/or Processing: Y.Ç., U.R.G., B.D., N.H.B., Ş.G.; Analysis and/or Interpretation: Y.Ç., U.R.G., B.D., N.H.B., Ş.G.; Writing: Y.Ç., U.R.G., B.D., N.H.B., Ş.G.

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Original Article

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Breast Hamartoma: Clinical, Radiological, and Histopathological Evaluation

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ABSTRACT

Objective: Breast hamartomas are rare, benign, and slow-growing breast tumors that can be definitively diagnosed by combining the results of clinical, radiological, and histopathological examination. This study aimed to evaluate the clinical, radiological, and histopathological features of hamartomas and summarize our clinical approach to hamartomas.

Materials and Methods: Patients diagnosed with breast hamartoma between 2010 and 2020 in our clinic were retrospectively analyzed. Demographic information, clinical examination, radiological findings, histopathological features, changes during follow-up, and follow-up data were obtained and analyzed.

Results: Of the 1,429 patients operated on in our clinic for benign breast diseases between January 2010 and March 2020, 39 (2.7%) were diagnosed with breast hamartomas with histopathological examination. All patients were women with a median age of 37 (19–62) years. Most of the patients (64%) were in the premenopausal period. Radiological examinations were conducted using mammography (66%), breast ultrasonography (100%), and breast magnetic resonance imaging (48%). Biopsy was performed in 14 preoperative patients, and nine (64%) patients were diagnosed with hamartoma. All patients were operated on; 37 patients underwent a lumpectomy, and two had a mastectomy. No patients had hamartoma recurrence during an average follow-up period of 39 months.

Conclusion: Hamartomas are similar to other benign breast pathologies. Definitive diagnosis can be achieved by combining the results of clinical, radiological, and histopathological examination. Given its similar composition to normal breast tissue, hamartoma has a low rate of malignancy. Definitive diagnosis and appropriate surgical treatment are required.

Keywords: Breast, hamartoma, diagnostic imaging, surgery

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Key Points

- Breast hamartoma is a rare, slow-growing breast lesion.
- Obtaining a definitive diagnosis with a single imaging method is challenging.
- Although hamartoma has benign histological characteristics, rare malignancies should not be overlooked.

Introduction

Pryn first identified breast hamartoma as "mastoma" in 1928 (1). Various cases have been reported as adenolipoma, fibroadenolipoma, or lipofibroadenoma (2). Breast hamartoma was first defined as "hamartoma" in 1971 by Arrigoni et al. (3) and was included in the World Health Organization classification in 1981 (2).

Different tissues such as milk ducts, lobules, adipose and fibrous tissue, smooth muscle, and hyaline cartilage are present in breast hamartoma (4). A breast hamartoma is an extremely rare, benign, and slow-growing breast lesion that occurs more commonly in women than men and in the perimenopausal period than other ages. It accounts for 0.7% of benign breast lesions in women (5). Although their size is between 2 cm and 5 cm on average, hamartomas can occasionally grow much larger (6). In most case series, the age range of patients with breast hamartomas is 13–88, with an average of 45 years (2, 7).

Common clinical presentation of breast hamartomas is as a painless, mobile, palpable mass in the breast or anisomastia. However, breast hamartomas may not always be easily distinguished on physical examination because of small size and/or similarity to breast tissue (7, 8).

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Hamartoma diagnosis can be confirmed through mammography, ultrasonography (USG), magnetic resonance imaging (MRI), fine-needle aspiration biopsy (FNAB), and core biopsy.

In mammography screenings, hamartoma diagnosis incidence is reportedly 8% (2). On USG, hamartomas present different heterogeneous echo-patterns depending on the percentages of adipose and glandular components. Therefore, diagnosis is challenging (9). In cases of conflicting radiological and clinical findings, MRI can be used for differential diagnosis. In MRI, lesions are usually surrounded by a well-circumscribed smooth capsule and are denser than breast tissue (10).

Hamartoma is generally a benign disease but may rarely be present with breast malignancy (11, 12). An excisional biopsy is usually required to differentiate a hamartoma from other benign breast lesions, such as fibroadenoma, lipoma, and cystosarcoma phyllodes (13).

Clinical diagnosis in breast hamartomas can only be confirmed by combining physical examination, radiological imaging, and histological examination findings because of the lack of cytological and histological distinctive structural features (7).

We aimed to define the clinicopathological features of hamartomas and summarize our clinical approach to hamartoma over the 10-year period of experience in our clinic.

Materials and Methods

Files of patients who had surgery for benign breast disease in our clinic between January 2010 and March 2020 were analyzed retrospectively. Patients who were diagnosed with breast hamartomas histopathologically, either through breast biopsy or postoperative histopathological examination were included in the study.

The patients' demographic data, medical history, reason for presentation and complaints, radiological findings, biopsy results, applied treatment method and operation method, histopathology results, and follow-up period were recorded. Radiological data were from mammography, breast USG, and breast MRI. Biopsy was used for histopathological diagnosis (fine-needle aspiration, core, radiology-assisted stereotactic marking), and the results were recorded. Treatment method (surgery, follow-up without surgery), surgery type (mastectomy, lumpectomy, and oncoplastic surgery), postoperative pathology results, and postoperative follow-up period of the patients were obtained.

Descriptive statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 25.0 (IBM Inc., Chicago, IL., USA). The study was submitted to Mersin University Clinical Research Ethics Committee, and ethics committee approval (Ethics committee number: 2020/611-11) was obtained for the study.

Result

Of the 1,429 patients undergoing surgery for benign breast disease, 39 (2.7%) were diagnosed with breast hamartoma. The patients were women, and the median age was 40 (21–62) years. Of the 39 patients, 25 (64%) were in the premenopausal period and 14 (36%) were in the postmenopausal period. Clinical presentations at the admittance included (self) palpable painless mobile mass in 31 (79%) patients and newly detected mass during follow-up in eight (21%) patients. The newly detected masses were asymptomatic. In addition, 23 (59%) of the masses were located in the right breast, and 16 (41%) were located in the left breast (Table 1).

Mammography imaging was not suitable because 13 patients were younger than 35. USG was performed in seven of the patients, of whom six also underwent MRI. In four patients, hamartoma was diagnosed with mammography. All patients had USG. The remaining 26 patients were older than 37, and they had mammography. MRI and USG were requested for 13 of the 26 patients; in the 13 other patients, USG and mammography were regarded as sufficient before the operation (Table 1).

Mammography was performed in 26 patients. According to the Breast Imaging-Reporting and Data System (BI-RADS), 13 patients were evaluated as BI-RADS II, 11 patients as BI-RADS III, and two patients BI-RADS IV. Microcalcification was detected in two (8%) patients, asymmetric density increments in five (19%), and nodular opacity in 14 (54%).

Table 1. Demographic, clinical, radiological, surgical, and pathological data of the pçatients

	n	%
Age (years)	40 (21–62)	
Gender		
Female	39	100
Male	0	0
Premenopausal	25	64
Postmenopausal	14	36
Laterality of lesion		
Right	23	59
Left	16	16
Presenting symptoms		
Painless mass	31	79
Incidental	8	21
Preoperative diagnosis	14	36
Core biopsy	14	36
Hamartoma	9	64
Fibroadenoma	3	21
Adenolipoma	2	15
Radiological modality		
Ultrasonography	39	100
Mammography	26	67
Magnetic resonance imaging	19	49
Surgical technique		
Lumpectomy	37	95
Mastectomy	2	5
Tumor size (mm)	23 (8–45)	

n: Number

Breast USG findings yielded a smooth-contoured appearance in all patients, solid appearance in three patients, and heterogeneous echogenicity in 29 patients. Nineteen patients had breast MRI.

MRI findings were as follows. While 19 patients had masses with smooth borders, 13 patients had heterogeneous masses, six had pure solid masses, nine had masses with thick-walled borders, and none had masses with irregular borders or cystic structures. Hamartoma was suggested as a preliminary diagnosis in 13 (68%) after MRI. Common characteristics of patients who required MRI were evaluated and it was found that they tended to be older than the other patients, and their mass sizes were smaller (Figure 1). Suspicious lesions were not detected in the axilla of any of the patients with radiological examinations. The success of imaging methods in detecting breast hamartoma in patients undergoing imaging was 30% in mammography, 18% in USG, and 68% in MRI.

Preoperative core biopsy was performed in 14 (35.9%) patients but not in the remaining 25 patients. Core biopsy was the preferred biopsy type, and FNAB was not used in any patients. Biopsy results yielded the following preliminary diagnoses: hamartoma in nine patients, adenolipoma in two patients, and fibroadenoma in three patients (Table 1). The postoperative pathology result in all patients with and without biopsy was breast hamartoma. Surgery was performed in all patients because of the increase in breast size during follow-up, the high mass/breast volume ratio, or the asymmetrical appearance of the breasts.

All patients underwent surgery. Lumpectomy was performed in 37 (94.9%) of the patients and simple mastectomy in two. Six of 37 (16.2%) patients underwent lumpectomy using radio-guided stereotactic marking because of the small sizes of the masses. Mastectomy was preferred in two patients because of the high mass/breast volume ratio.

Following histopathological examination, the median mass size was 23 (8–45) mm. A pathology-radiology agreement was obtained for the size. The lobular structure, fibrous stromal structure, adipose tissue, smooth muscle fibers, and normal breast tissue were clustered in a scattered location within the mass lesion on histopathological examination. The mean follow-up period of the patients was 39 months, and no recurrence or breast malignancy was detected during follow-up.

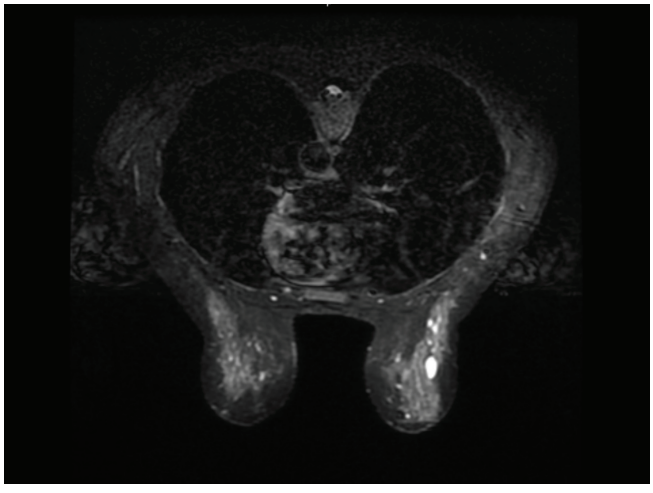

Figure 1. Minimal hyperintense lesion in the upper outer quadrant of the left breast, 11 × 8 mm in size, well-circumscribed, and homogeneous, in T1W hypointense STIR

STIR: Short tau inversion recovery

Discussion and Conclusion

Breast hamartomas are well-circumscribed, benign lesions consisting of glandular tissue, epithelial elements, fibrous tissue, and adipose tissue, which may be present in ordinary or varying proportions (14). Hamartomas are rare, slow-growing lesions with an average diameter of 2–5 cm but can sometimes grow to large sizes (6). They are common in middle-aged women during the perimenopausal period. Hamartomas rarely occur in ectopic breast tissue located in the axillary or inguinal region and are again rarely detected in males (15).

In situ and infiltrative carcinomas may occur inside or adjacent to hamartomas despite being histologically benign (16, 17). Given their small size, hamartomas are challenging to diagnose through a physical examination. The diagnosis is achieved with the widespread use of breast screening methods including biopsy and various imaging methods (7).

The clinical diagnosis of hamartoma is based on the combined findings of mammography, sonography, and histological analysis. Combining the diagnostic methods is much better than the use of any single method, which might lead to misdiagnosis (7).

No specific finding has been described in imaging methods. Given their difference in composition from breast tissue, hamartomas may have different radiological findings. Hamartomas are mammary lesions that can show different opacities on mammography, round or ovoid shape, and sharply limited or smooth contours; they can also be heterogeneous or easily separated from normal breast tissue (18). In the present study, four (10%) patients had a preliminary diagnosis of hamartoma with mammography alone.

In contrast to mammography, USG can provide detailed information about the borders, nature, content, mobility, and homogeneity of the breast lesion. Although USG has relative advantages to mammography, cross-sectional examinations such as MRI are required in patients with a history of surgery and high breast volume to diagnose breast hamartoma accurately (19). A previous study reported that breast MRI was more successful than USG and mammography in the radiological diagnosis of breast hamartoma (20). The results from our study support this finding.

The characteristics of breast hamartoma on MRI examination are as follows: smooth, intense, heterogeneous appearance, and an appearance similar to adipose tissue inside. Given its cross-sectional nature, breast MRI during the diagnosis and classification of hamartoma is a more advantageous imaging method than mammography and USG. It allows distinction of the mass from the normal breast tissue and accurate evaluation of the lesion's borders and structure (10). Testempassi et al. (20) evaluated the MRIs of patients diagnosed with breast hamartoma and found a correlation between the MRI findings and the macroscopic appearance of the lesion. Erdem et al. (15) employed MRI in women who were not able to undergo mammography because of breastfeeding or pregnancy and found that MRI can verify the diagnosis by providing additional information after USG. However, MRI may be inadequate in reaching a definite diagnosis of breast hamartoma in some cases. Ko et al. (21) highlighted the issue of MRI findings being similar to malignancy because of the distribution of different tissue components within the

hamartoma, and further examination may be required to achieve a differential diagnosis.

Breast hamartomas consist of breast canals, lobules, fibrous stroma, adipose tissue, and varying amounts of smooth muscle (4). On histopathological examinations of samples taken from our cohort, all structures defined within normal breast tissue had heterogeneous distributions at varying rates.

Hamartomas contain normal breast tissue cytologically and histologically and have a heterogeneous tissue distribution. Thus, diagnosis is limited to fine-needle aspiration and core biopsy accompanied by USG. By comparison, surgical resection is more useful for identifying hamartomas and allows the examination of all tissue components (22). Surgical treatment is recommended for patients with suspicion of hamartoma or with a firm diagnosis of hamartoma (9). In our series, 14 patients were biopsied and nine (64%) patients were diagnosed preoperatively with hamartoma, whereas five (36%) patients were diagnosed with non-hamartoma. Previous studies reported that breast hamartomas cannot be followed up without surgery in patients with small-sized hamartomas with histopathological diagnosis (23, 24).

Breast hamartomas are not premalignant. However, given their glandular breast tissue, breast hamartomas can rarely undergo malignant changes similar to normal breast tissue. Therefore, achieving a definitive histopathological diagnosis is crucial. The incidence of malignancy in normal breast tissue within the hamartoma is as low as 0.1%. A previous study detected lobular carcinoma in situ and invasive carcinomas by performing excisional biopsy after obtaining mammography results suggesting possible malignancy due to irregular microcalcifications and tissue changes (25).

Hamartomas are usually smooth-bordered, mobile, non-invasive lesions on the chest wall and skin. They should be removed with as minor a surgical intervention as possible. However, eradicating the lesion with a robust surgical margin is also essential because of the potential for recurrence and, rarely, possible malignancy foci within the lesion (9). Breast hamartomas may occur in masses that do not radiologically suggest a breast hamartoma and are not indicated for biopsy.

Ethics Committee Approval: The study was submitted to Mersin University Clinical Research Ethics Committee, and ethics committee approval (no: 2020/611-11) was obtained for the study.

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Authorship Contributions

Conception: D.T.; Design: A.D.; Supervision: A.D.; Materials: D.T.; Data Collection and/or Processing: B.A.; Analysis and/or Interpretation: M.B.; Literature Review: M.B.; Writing: D.T., B.A.; Critical Review: A.D.

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Original Article

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Analysis of Knowledge About Male Breast Cancer Among Higher Education Male Students

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ABSTRACT

Objective: Breast cancer is the most common cancer among women, both in Brazil and worldwide. Breast cancer can also affects men but this constitutes only 1% of cases and is thus considered rare, and for this reason is little studied. Statistics indicate an increase in its incidence with an estimate of new cases in recent years. This study aims to analyze the knowledge of higher education students in relation to breast cancer in men. the knowledge of higher education students in relation to breast cancer in men.

Materials and Methods: exploratory study with a quantitative approach. 299 male students participated in the study. Data collection took place through semi-structured questionnaires, completed by students from pure science, human sciences and health at a higher education institution.

Results: Regardless of the area of undergraduate study, 65.9% of the volunteers reported not knowing about breast cancer in men. Regarding predisposing factors for the development of breast cancer, 77.3% reported not knowing about these while 68.9% reported not knowing about breast self-examination. However, 67.6% believe that breast cancer in men can be prevented. Worryingly, 62.5% reported that they only seek medical assistance when becoming ill.

Conclusion: Evidence from this study suggests that higher level undergraduates have limited knowledge about breast cancer in men. Only one third knew that male breast cancer was possible. Even smaller proportions knew of the predisposing factors for breast cancer, how to perform self-examination and about diagnosis. These latter factors, when combined with a tendency to seek medical help only when ill, suggests a short-fall in health knowledge which should be corrected.

Keywords: Breast cancer, masculine, health promotion, men's health

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Key Points

- Higher education students show limited knowledge about breast cancer in men.
- Health care for men needs more attention.
- Young adults in professional training areas other than health care have limited understanding of breast cancer in men.

Introduction

Breast cancer (CA) is a very heterogeneous disease, with a wide variety of clinical and prognostic developments. Globally, breast CA is the fifth greatest cause of death from cancer - totaling 684,996 deaths - considering both sexes and all ages (1). Even when considering non-melanoma skin CA, female breast CA still ranks first in the estimated number of prevalent cases (5 years) worldwide for all ages. For men, the disease is rare, and the lifetime risk of breast CA is approximately 1:1000, with this risk being 1:8 for women (2). In 2018, about 2,550 men were diagnosed with breast CA in the United States and it accounted for 480 deaths. In comparison, there were approximately 266,120 new cases of women with breast CA and approximately 40,920 deaths (3).

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In Brazil, data from the National Cancer Institute José Alencar Gomes da Silva (INCA) estimate that 66,280 new cases of breast CA appear each year between 2020 and 2022 (4). Currently, little is known about the incidence of breast CA in men, few records are found concerning such pathology, and studies, due to the low prevalence, often do not receive incentives. Thus, it is not even possible to find estimated incidence/mortality rates in the GLOBOCAN (2020) reports (1). In Brazil, however, according to a study done in 2018, among the 17,763 deaths from breast CA, 17,572 were female and 189 male (5).

The most common histological type in women is epithelial cell carcinoma, which is divided into *in situ* and invasive. The most common carcinomas are ductal and lobular carcinomas, with luminal subtypes A and B being the most frequent and with the best prognosis (6-9). Concerning breast tumors in men, these subdivisions have no relevant impact, but it is known through research of gene expression that there may be genetic aberrations and molecular types not seen in women, thus worsening their prognosis (10). Several risk factors contribute to the development of male and female breast CA. According to INCA, with data from 2019, age over 50 is considered the most important among the risk factors for both sexes. Another important factor is related to the family history of CA in first-degree relatives, where the chances of development increase by 2.5 times (11). Amongst genetic factors, it is important to highlight mutations in the breast *CA* genes, and those in BRCA2 are closely associated with high-risk tumors, with worse prognosis, unlike the BRCA1 type mutations, that indicate lower rates of morbidity and mortality. In men the estimates for the development of male breast CA range from 1% to 5% for men with BRCA1 mutations and from 5% to 10% for men with BRCA2 mutations (12).

According to the data published by Carvalho Neto et al. (11), both men and women who drink more than 10g/day of alcohol have a 16% increased risk of developing breast CA. Other predisposing risk factors include exposure to radiation, administration of estrogen, and diseases associated with hyperestrogenism, such as cirrhosis. Obesity can also increase the risk of breast CA in men, possibly due to hormonal mechanisms. There is data suggesting that black men are at greater risk than non-Hispanic white men (13). Testosterone levels also dictate an important increase in the risk of developing the disease, as men have 20 times more androgenic hormone compared to postmenopausal women (14). Klinefelter syndrome, characterized by hypogonadism and low testosterone levels, an anomaly generated by a prototype XXY sex chromosome appears to convey a much increased risk of male breast CA. According to a study by Swedish Cancer Registry, the estimated risk of breast CA among men with Klinefelter syndrome is increased by up to 50 times, compared to unaffected men (15).

There are controversies regarding the prevention and screening of male breast CA. Some authors claim that such malignancies can be prevented through adequate nutritional care and physical activities, but that, in addition to these habits, the best from of prevention is the early diagnosis of the disease, which, as in women, when done in the early stages, substantially increases the chances of curative treatment (16).

This diagnosis, unfortunately, does not happen frequently, since it is not a prevalent disease in men, because they are unaware of the possibility of acquiring it, of being ignored by public policies, and because of the prejudice and stigmatization that characterize breast CA as a disease of women. Furthermore, there are no national or international guidelines from health agencies to guide health professionals on how to properly prevent male breast cancer, making the condition an undernoticed public health issue (17). As men have less breast tissue than women, nodules suggestive of a tumor are more easily noticed, but they spread more easily and quickly, causing them to be noticed in already advanced conditions (18).

Management of male breast CA is the same as for female CA. Therapeutic interventions include surgery, radiotherapy and systemic therapies, which include chemotherapy and endocrine treatments (19).

The aim of this study was to investigate the extent of knowledge about male breast CA among men in higher education, and also to compare the degree of knowledge about this subject among students of different subjects including human science, pure science and health science, at the Higher Education Institution of Uberaba Faculty of Human Talents.

Materials and Methods

The basic function of a good research project is to facilitate a robust comparison between the different variables of the groups of subjects included in the study. Thus, in order to seek reliable results, this cross-sectional study was adopted with an observational descriptive character. The study was carried out via a questionnaire completed by undergraduate students studying health science, pure science and humanities fields at the Faculty of Human Talents (FACTHUS), located in the city of Uberaba, Minas Gerais, Brazil.

Eligible subjects included all male undergraduate students in these subjects. Male students were randomly selected from the FACTHUS population. Inclusion criteria were male students enrolled in this faculty and who agreed to complete the questionnaire. Exclusion criteria were those who were outside the pre-established study population and those who were chosen at random but refused to participate.

Three questionnaires were used. The first collected sociodemographic data including marital status, age, maternal education, family income and the area of the undergraduate course. The second questionnaire assessed life habits, including the age of sexual initiation, use of drugs, dietary supplements and steroid drugs, as well as alcohol and tobacco consumption. The third questionnaire investigated the extent of knowledge about breast CA in men, including general knowledge of male breast CA, if treatment is available, predisposing factor for developing breast CA in men, genetics and heredity issues, if the respondent was aware of family cases, aspects of prevention and the habit of conducting routine medical consultations.

The statistical analysis was carried out using Excel 2013 for Windows (Microsoft - EUA). Data was analyzed using SPSS, version 20 (IBM Inc., Armonk, NY, USA). The Shapiro-Wilk Test was used to verify the normal distribution of the quantitative variables. The continuous variables, which present normal distribution, were expressed in mean ± standard error of mean, for the multiple comparisons, the ANOVA test and Tukey's test were used. Student's t-test was used for single comparisons. Variables that did not have normal distribution were expressed in median and range, for the multiple comparisons, the Kruskal-Wallis and Dunn's tests were used. For single comparisons, Mann-Whitney's test was used. For the comparisons of frequencies

and percentages, the chi-square test was used. The significance level was set at 5% ($\alpha = 0.05$).

This project was submitted to the Research Ethics Committee with Human Beings of the FACTHUS under registration number 05/2018, as well as the use of the free and informed consent term to carry out the project and apply the questionnaires to people as required. Resolution 466/2012 of the National Health Council on ethical issues in research with human participants, from the Ministry of Health of the Federative Republic of Brazil.

Results

The sample consisted of 299 male undergraduate students aged between 17 and 50 years. The evaluated students were from the areas of humanities, pure science and health sciences. The proportions of the cohort by education area were: 56.2% from pure science; 26.1% from humanities; and 17.7% from health sciences. The sociodemographic data of the participants is shown in Table 1. It shows the sample distribution in relation to the median age of 24.0, with a range of 33. Regarding marital status, most of the sample (75.9%) was single, while the most common maternal education level was high school/technical education (41.8%). The majority of respondents (68.2%) reported a family income of at least two minimum wages.

Regarding lifestyle habits, respondents reported that the onset of sexual activity was on average at 14.2 years of age, with a minimum age of 9 and a maximum of 19 (Table 2). In relation to the use of drugs, supplements and steroids 71.2 % report no use. Regarding alcohol and cigarette consumption, 57.2% were users.

In this sample of male higher education students there was a worrying deficit in knowledge about male breast CA (Table 3). Almost two-thirds (65.9%) were unaware that male breast cancer exists. In terms of treatment of male breast CA, 66.9% thought that it was possible to successfully treat the disease while 32.1% thought that there was no cure. Regarding predisposing factors in the development of breast cancer, most respondents (77.3%) thought that there were no predisposing factors.

In this cohort, 58.2% thought that male breast cancer had a hereditary element and 52.2% reported no history of breast cancer in their families. Regarding breast self-examination, 68.9% said they had no knowledge of how to self examine, and 76.6% of participants reported not knowing the signs and symptoms of male breast cancer.

In terms of breast cancer prevention, 67.6% reported having knowledge of appropriate preventative measures while 23.7% answered they had no knowledge. Of the 299 participants, 62.5% report that they only go to a medical appointment when they become ill.

Comparing the mean ages of the students studying different subject areas showed that students of pure sciences tended to be significantly older ($p<0.0001$; Table 4). These students were significantly more likely to be married (29.8%; $p = 0.01$) but for the three subject areas most male students were single: pure science 69.6% single; humanities 83.3% single; and health sciences 84.9% were single.

Most participants reported that their mothers had achieved high school/technical education (Table 4). The proportion of mothers with elementary education was higher in the students from the humanities (26.9%), compared to graduate courses, the percentage of parents is higher in the health course 32.1% ($p = 0.006$). Students from the pure sciences tended to have greater family income (>2 minimum wages) than students from the other two subject areas (72% vs 64.1% and 62.3%). Students from the humanities were more likely to have a family income below one minimum salary (9%) compared to either the students from pure sciences (2.4%) or health sciences (1.9%).

Table 1. Distribution of the sample in relation to age, marital status, maternal education, family income and area of the undergraduate course

Variables	n (%)
Median age (range), years	24 (33)
Marital status	
Single	227 (75.9)
Married	70 (23.4)
No data	2 (0.7)
Maternal education	
Fundamental	66 (20.7)
Medium / Technical	125 (41.8)
Graduation	57 (19.1)
Postgraduate studies	17 (5.7)
No data	38 (12.7)
Family income	
Up to 1 salary	12 (4.0)
Between 1 and 2 Salaries	58 (19.4)
Above 2 wages	204 (68.2)
No data	25 (8.4)
Undergraduate area	
Pure Sciences	168 (56.2)
Humanities	78 (26.1)
Health Sciences	53 (17.7)

Table 2. Distribution of the sample in relation to life habits

Questions	
Beginning of sexual activity (years)	**Mean (min-max)** 14.2 (9-19)
	n (%)
Use of drugs, supplements and steroids	
Yes	83 (27.8)
No	203 (71.2)
No data	3 (1.0)
Alcohol and cigarette consumption	
Yes	171 (57.2)
Not	128 (42.8)

Across the different groups of students the reported age of initiating sexual activity varied significantly (Table 5). Reported use of drugs and supplements was low in each group, with the rates being 14.1% in the humanities, rising to 30.2% in the health sciences and 33.3% in the pure sciences. This pattern was different and significantly different between the groups for use of alcohol and tobacco with health sciences students reporting the most widespread use (77.4%) followed by the humanities (60.3%) and the lowest reported usage was in the pure sciences students (49.4%).

Table 3. Distribution of the sample in relation to knowledge about Male Breast Cancer

Questions	Answers
What is male breast cancer	**n (%)**
Yes	102 (34.1)
No	197 (65.9)
Breast cancer can be cured	
Yes	200 (66.9)
No	96 (32.0)
No data	3 (1.0)
Influencing factors in the development of breast cancer	
Yes	66 (22.1)
No	231 (77.3)
No data	2 (0.7)
Hereditary	
Yes	174 (58.2)
No	122 (48.8)
No data	3 (1.0)
Family history of breast cancer	
Yes	141 (47.2)
No	156 (52.2)
No data	2 (0.7)
Knowledge about self-examination	
Yes	79 (26.4)
No	206 (68.9)
No data	14 (407)
Signs and symptons	
Yes	60 (20.1)
No	229 (76.6)
No data	10 (3.3)
Every tumor is cancer	
Yes	142 (49.2)
No	132 (44.1)
No data	20 (6.7)
Breast cancer can be prevented	
Yes	202 (67.6)
No	71 (23.7)
No data	26 (8.7)
Medical consultation	
When sick	187 (62.5)
Annually	88 (29.4)
No data	24 (8.0)

When asked about knowledge of Male Breast Cancer, 30.4% of respondents in pure science, 37.2% in the humanities and 41.5% in the health sciences knew of male breast cancer, results that were not different ($p = 0.263$). Similarly knowledge of the heredity and prevention of breast cancer were also not statistically significant (Table 6). With regard to breast cancer having a cure, 84.9% of health sciences students knew that it was possible, while this proportion fell to 79.5% in the humanities and 55.4% in the pure sciences. In terms of predisposing factors for the development of breast cancer most students had no knowledge, with less than a third of health sciences and humanities students understanding that predisposing factors exist; significantly fewer pure sciences students knew of the existence of these factors ($p = 0.005$).

More than half of the health sciences and pure sciences students reported a family history of breast cancer (54.7% and 51.8%, respectively). Only a minority of students knew about self-examination; 19.6%, 34.6% and 35.8% in the pure sciences, humanities and health sciences student groups respectively. With regard to the signs and symptoms of breast cancer, the three areas showed that most students did not have knowledge of this (Table 6). When asked if every breast tumor is considered a cancer, most students of pure science (61.9%) responded "yes" while significantly fewer in the health sciences and humanities thought this was true (37.7% and 29.5%, respectively; $p<0.0001$). Finally, with regard to medical consultations, most students reported that they only seek to consult when they are ill, with 73.8% of pure sciences students, 57.7% of humanities students and 34% of health sciences students giving this response.

Discussion and Conclusion

Our main results show that most volunteers reported not knowing about breast cancer in men, regardless of the area of study, pure sciences, humanities or health sciences. Regarding the influential factors for the development of breast cancer, most reported not knowing about these factors. Also, the male respondents in this study reported not knowing about breast self-examination, but they believed that there are ways to prevent breast cancer. However, most respondents only sought medical help when unwell.

Greater knowledge about the pathology, dissemination of information through the media and high awareness of female breast CA in primary health care services means that female breast tumors tend to be discovered in less advanced stages. This is not happening with male breast CA, but a similar programme would be important to reduce the psychosocial suffering of those who have the diagnosis, in addition to disseminating knowledge. (19).

This study confirms earlier findings, which showed that men have little knowledge about male breast CA (20). According to the National Institute of Cancer, the incidence and prevalence of male breast cancer in Brazil is low, and due to this, there is little scientific and general interest in the subject. In addition, the fact that the literature on breast cancer is mostly aimed at the disease in women contributes to misinformation among men. For example, breast cancer prevention

campaigns and instructions on how to perform self-examination are directed at the female population, as seen in the October Rose, which focuses on the fight against breast cancer and encouraging the participation of the population in combating this disease (21).

Most of the interviewed participants demonstrated that they were unaware of what male breast cancer is, as well as being unaware of the signs and symptoms and predisposing factors, confirming a lack of general knowledge, even in students of the health sciences. The same was observed by Thomas, when 28 men with no personal history of breast cancer, and with at least one relative of maternal blood with the disease were interviewed (19). Approximately 80% were unaware of the possibility that they could develop the disease, and despite being at high risk, all participants reported that the family unit never discussed the subject. Still, the majority reported that they did not know how to identify signs and symptoms of the condition, except for nodules in the breast.

Table 4. Distribution of the sample in relation to age, marital status, maternal education, family income in the different areas of knowledge

Variables	Exact sciences	Human sciences	Health sciences	p-value
Mean age (SEM)	26.7 (0.56)	24.0 (0.53)*	23.6 (0.48)*	**0.0001**
Marital status, n (%)				
Single	117 (69.6)	65 (83.3)*	45 (84.9)*	
Married	50 (29.8)	12 (15.4)	8 (15.1)	**0.010**
No data	1 (0.6)	1 (0.8)	0 (0.0)	
Maternal education, n (%)				
Fundamental	31 (18.5)	21 (26.9)	10 (18.9)	
Medium/Technical	69 (41.1)	34 (43.6)	22 (41.5)	
Graduation	25 (14.9)	15 (19.2)	17 (32.1)#	**0.006**
Postgraduate studies	13 (7.7)	1 (1.3)	3 (5.7)	
No data	30 (17.9)	7 (9.0)	1 (1.9)	
Family income, n (%)				
Up to 1 salary	4 (2.4)	7 (9.0)	1 (1.9)	
Between 1 and 2 salaries	20 (11.9)	19 (24.4)	19 (35.8)#	**0.0001**
Above 2 wages	121 (72.0)	50 (64.1)	33 (62.3)	
No data	23 (13.7)	2 (2.6)	0 (0.0)	

*p<0.05 vs volunteers from exact courses.
#p<0.05 vs volunteers from exact and human courses.
SEM: Standard error of mean, n: Number

Table 5. Distribution of the sample in relation to life habits in different areas of knowledge

Questions	Exact sciences	Human sciences	Health sciences	p-value
Beginning of sexual activity mean (SEM) years	13.7 (0.21)	15.2 (0.22)*	14.6 (0.32)	**0.0001**
Use of drugs, supplements and steroids, n (%)				
Yes	56 (33.3)	11 (14.1)$	16 (30.2)	
No	109 (64.9)	67 (85.9)	37 (69.8)	**0.012**
No data	3 (1.8)	0 (0.0)	0 (0.0)	
Alcohol and cigarette consumption, n (%)				
Yes	83 (49.4)	47 (60.3)	41 (77.4)*	**0.001**
No	85 (50.6)	31 (39.7)	12 (22.6)	

*p<0.05 vs volunteers from exact courses.
$p<0.05 vs volunteers in the exact and health courses.
SEM: Standard error of mean, n: Number

Table 6. Distribution of the sample in relation to the knowledge about male breast cancer in the different areas of knowledge

Questions	Exact sciences	Human sciences	Health sciences	p-value
What is male breast cancer, n (%)				
Yes	51 (30.4)	29 (37.2)	22 (41.5)	0.263
No	117 (69.6)	49 (62.8)	31 (58.5)	
Breast cancer can be cured, n (%)				
Yes	93 (55.4)	62 (79.5)*	45 (84.9)*	**0.0001**
No	74 (44.0)	15 (19.2)	7 (13.2)	
No data	1 (0.6)	1 (1.3)	1 (1.9)	
Influencing factors in the development of breast cancer, n (%)				
Yes	25 (14.9)	24 (30.8)*	17 (32.1)*	**0.005**
No	143 (85.1)	53 (67.9)	35 (66.0)	
No data	0 (0.0)	1 (1.3)	1 (1.9)	
Hereditary, n (%)				
Yes	103 (61.3)	44 (56.4)	27 (50.9)	0.658
No	64 (38.1)	33 (42.3)	25 (47.2)	
No data	1 (0.6)	1 (1.3)	1 (1.9)	
Family history of breast cancer, n (%)				
Yes	87 (51.8)	25 (32.1)$^{\$}$	29 (54.7)	**0.019**
No	79 (47.0)	53 (67.9)	24 (45.3)	
No data	2 (1.2)	0 (0.0)	0 (0.0)	
Knowledge about self-examination, n (%)				
Yes	33 (19.6)	27 (34.6)*	19 (35.8)*	**0.0001**
No	121 (72.0)	51 (65.4)	34 (64.2)	
No data	14 (8.3)	0 (0.0)	0 (0.0)	
Signs and symptons, n (%)				
Yes	27 (16.1)	16 (20.5)	17 (32.1)*	**0.032**
No	132 (78.6)	61 (78.2)	36 (67.9)	
No data	9 (5.4)	1 (1.3)	0 (0.0)	
Every tumor is cancer, n (%)				
Yes	104 (61.9)	23 (29.5)*	20 (37.7)*	**0.0001**
No	56 (33.3)	46 (59.0)	30 (56.6)	
No data	8 (4.8)	9 (11.5)	3 (5.7)	
Breast cancer can be prevented, n (%)				
Yes	121 (72.0)	44 (56.4)	37 (69.8)	0.181
No	35 (20.8)	25 (32.1)	11 (20.8)	
No data	12 (7.1)	9 (11.5)	5 (9.4)	
Medical consultation, n (%)				
When sick	124 (73.8)	45 (57.7)*	18 (34.0)*	**0.0001**
Annually	34 (20.2)	24 (30.8)	30 (56.6)	
No data	10 (6.0)	9 (11.5)	5 (9.4)	

*p <0.05 vs volunteers from exact courses.
$^{\#}$p <0.05 vs volunteers from exact and human courses.
$^{\$}$p <0.05 vs volunteers in the exact and health courses.
n: Number

Contrary to expectations, despite the majority not having knowledge about the disease, most believe there is a cure for it, which could reflect respondents' knowledge of female breast cancer, suggesting an effective message from campaigns targeted at women. Similarly, more than 55% of respondents believed that there was a hereditary element in breast CA. It is possible to speculate that respondents in our study are basing their responses on information about female breast CA which has stressed a combination of environmental, hormonal and genetic factors in pathogenesis (13). Data from the Generations Study has shown there is a higher incidence of breast cancer in women who had first-degree relatives with the disease (22). A large cohort study from the United Kingdom of 110,000 women reported that the risk of breast cancer increased considerably based on the number of family cases in terms of age and the national incidence levels of this disease (23).

Still, in our subjects, most were unaware of the existence of self-examination, and most did not usually go to medical consultations until actually becoming unwell. Once again, this reflects the targeting of campaigns to the female audience, and the scarcity of stimulus for men to protect themselves, as demonstrated in the studies of Alves et al. (24) and Gomes et al. (25), who claimed that men identified and externalized their needs less, as well as the need for assistance and, therefore, seek health services less when compared to women.

The interviewees were grouped according to the area of higher education in pure sciences, humanities and health sciences, in order to carry out analyzes and comparisons between groups. Thus, it was expected that knowledge about male breast cancer would be greater among health sciences students. However, the results showed that knowledge was similar between groups. Still, when analyzing alcohol and cigarette consumption among students, it was higher among health students (77.4%), despite these being known risk factors for several pathologies, such as cardiovascular diseases (26). Our data present similar findings to that of Ferraz et al. in which they evaluated 284 undergraduates in medicine, law, and civil engineering, and found a higher prevalence of alcohol and tobacco use among medical students (27).

Finally, an elegant study conducted by Özaydın et al. (28) reported that men who followed women with breast cancer during treatment, still did not have sufficient and accurate knowledge of the disease. These authors correlated higher levels of knowledge about breast cancer with more positive attitudes during the care of women. Thus, the authors suggested that breast cancer awareness activities should include men, in order to increase their knowledge and change their attitudes in a more positive way. Our analysis suggest that there is a directly proportional relationship between maternal education and knowledge of breast cancer, so that the children of better educated women tended to have greater knowledge of the condition. Similar findings have been reported previously when greater knowledge of the relationship between Human Papiloma virus and cervical or penile cancer and also Pap smear in women was identified (29-31).

As a limitation of the study, the authors emphasize that because it is a survey that used a self-completion questionnaire, with no influence from the researchers, it is possible that the volunteers did not understand the questions correctly, and therefore answered incorrectly. Another fact is that by possible knowledge about breast cancer in women, the volunteers may have been influenced to answer the questions about knowing about male breast cancer and whether breast cancer would be curable. Thus, this is made as a possible bias of acquisition, but does not invalidate the evidence that the male population in question needs support in health education, especially breast cancer in men.

In Conclusion these results showed that respondents in this study had limited knowledge about breast cancer in men, as well as its risk factors, forms of self-care and diagnosis, and a deficit in health care follow-up.

Considering the increase in the number of late diagnoses of male breast cancer, and mostly in stages of poor prognosis, these findings suggest that it is important to counter the lack of information about the disease and its signs and symptoms while also providing information concerning the possibility of screening and potential cures. It will be important to undertake further studies concerning men's knowledge of male breast CA, in other and larger populations. In addition, we suggest a need for on-going surveys in order to monitor the effect of better public health information about the condition and to emphasize the importance of early diagnosis, screening and the potential benefits of prompt treatment.

Ethics Committee Approval: This project was submitted to the Research Ethics Committee with Human Beings of the FACTHUS under registration number 05/2018, as well as the use of the free and informed consent term to carry out the project and apply the questionnaires to people as required. Resolution 466/2012 of the National Health Council on ethical issues in research with human participants, from the Ministry of Health of the Federative Republic of Brazil.

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Authorship Contributions

Conception: D.R.A., A.L.B.V., J.C.A.; Design: D.R.A., A.L.B.V., J.C.A.; Data Collection and/or Processing: D.R.A., E.H.F., D.K., R.M.S., V.F.M.C., P.P.G.D.R.F., B.S.R.A., Í.M.M.M., M.R.O., A.L.B.V., J.C.A.; Analysis and/or Interpretation: D.R.A., E.H.F., D.K., R.M.S., V.F.M.C., P.P.G.D.R.F., B.S.R.A., Í.M.M.M., M.R.O., A.L.B.V., J.C.A.; Writing: D.R.A., E.H.F., D.K., R.M.S., V.F.M.C., P.P.G.D.R.F., B.S.R.A., Í.M.M.M., M.R.O., A.L.B.V., J.C.A.

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Original Article

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The Expression of Galectin-3 in Tumor and Cancer-Associated Fibroblasts in Invasive Micropapillary Breast Carcinomas: Relationship with Clinicopathologic Parameters

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ABSTRACT

Objective: Galectin-3 affects tumor progression and cell surface polarization by expressing from the tumor and cancer-associated fibroblasts (CAFs). Therefore, it may have a role on micropapillary carcinomas (IMPC), which have characteristic morphological features. The aim was to investigate the expression levels of Galectin-3 within tumor and peritumoral CAFs in IMPC, and to compare with expression in invasive ductal carcinomas (IDC).

Materials and Methods: Hematoxylin and Eosin-stained preparations of resection materials examined between 2010-2016 were re-evaluated. Thirty-four IMPC cases and 34 IDC cases with similar molecular subtype distribution to IMPC were compared. Galectin-3 levels were evaluated with a calculated H-score in tumor and semi-quantitatively in CAFs.

Results: While tumoral Galectin-3 expression levels were higher in IMPCs compared to IDCs, there was no difference for Galectin-3 expression in CAFs between the two histologic types. However, there was no significant relationship between tumoral Galectin-3 expression and clinicopathological parameters in IMPCs. When the subjects were divided into two groups, depending on their Galectin-3 status regardless of histological types, the loss of Galectin-3 expression in tumor was found to be related to larger tumor size/advanced pT stage and a greater number of metastatic nodes. Additionally, expression of Galectin-3 in CAFs was found to be associated with distant metastasis.

Conclusion: IMPC showed prominent Galectin-3 expression in tumor compared to IDC. However, independent from the histological type, whereas the loss of Galectin-3 expression in tumor showed an association with larger tumor size and higher number of metastatic axillary lymph nodes, the presence of Galectin-3 expression in CAFs showed an association with distant metastasis.

Keywords: Breast, cancer-associated fibroblast, galectin-3, invasive breast cancer, micropapillary carcinoma

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Key Points

- Tumoral Galectin-3 expression was found higher in invasive micropapillary carcinomas (IMPCs) compared to invasive ductal carcinomas (IDCs).
- In IMPCs, there was no relationship between Galectin-3 expression and clinicopathological parameters.
- Independent from the histologic type of breast cancer, loss of Galectin-3 expression in tumor showed an association with larger size of tumor and a greater number of metastatic axillary lymph nodes.

Introduction

The morphological features of invasive micropapillary carcinoma (IMPC) were defined by Fisher in 1980 as an exfoliative appearance in papillary breast carcinomas (1). The term "micropapillary carcinoma" was first used by Siriankgul in 1993 for breast IMPCs (2). Since then, IMPC has been described in many locations, such as lung, bladder, and salivary glands (3).

IMPC is composed of small groups of tumor cells with no fibrovascular core that may mimic lymphovascular invasion. These groups of cells show a characteristic reverse polarization described as 'inside-out' pattern (4). In other words, the apical sides of the tumor cells are closest to the stroma rather than the luminal surface (5). This feature can be demonstrated by the presence of positive immunostaining for EMA (MUC1) on the periphery of tumor cell groups. In addition to that, microvilli observed by electron microscopic examination on the outer surface of tumor

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cell clusters support reverse polarization (6). This appearance suggests that tumor cells in micropapillary carcinoma have a higher mobility and thus are more likely to invade adjacent tissues than tumor cells in ordinary invasive breast carcinoma. Importantly, it has also been thought that microvilli-like structures can help in establishing relations with endothelial cells (4).

Cancer is a neoplastic mass in which malignant epithelial cells interact with the stromal microenvironment. This microenvironment facilitates or inhibit tumor formation and/or progression. Cancer-associated fibroblasts (CAFs) constitute the major cell group within this microenvironment (7). Based on the contribution of tumor stroma to tumor invasion and metastasis, many drugs targeting CAFs have been tried and promising results have been obtained (8). CAFs also are responsible for resistance to chemotherapeutic drugs in most tumors (8).

Galectins belong to a family of carbohydrate-binding proteins that show a high affinity for β-galactosides. Galectin-3, which is the only member of the chimeric galectin group, is also the most studied member of the Galectin family (9). Since Galectin-3 can demonstrate a wide distribution, both inside and outside the cell, its functions are roughly grouped into intracellular and extracellular activities (10). Intracellular functions include anti-apoptotic effect, regulation of intracellular signal transduction, gene expression, and mRNA regulation (10). Extracellular functions include the regulation of cell adhesion, angiogenesis, and immune regulation (10). All these functions associated with Galectin-3 are important features at every stage of the tumorigenesis process, from local invasion to metastasis. In recent years, it has been shown that Galectin-3 can also be expressed by CAFs, affecting all these mechanisms (11, 12). For this reason, Galectin-3-focused therapies are on the agenda in targeted treatment studies for a range of solid cancers, and it has been reported that it may have the potential to be a useful marker in preventing resistance to some chemotherapeutic drugs (13, 14).

In this study, in patients with IMPC, which exhibits an unusual morphology and organization of tumor cells and its relation to the stroma and is usually accompanied by lymphovascular invasion and axillary lymph node metastasis, we aimed to investigate: 1) Galectin-3 immunostaining properties in tumor cells and the surrounding stromal fibroblasts, and to compare them with IDC evincing a similar molecular phenotype; and 2) to reveal the relationship between Galectin-3 expression status and clinicopathological parameters and survival.

Materials and Methods

Hematoxylin and eosin (H&E) stained sections of surgical excision materials belonging to 850 cases evaluated for breast carcinoma between 2010-2016 were retrieved from the archives of our clinic. All slides were re-examined under a light microscope. Cases containing at least a 10% micropapillary component in an invasive tumor were identified. Micropapillary morphology was confirmed by EMA (MUC1) immunohistochemical staining in all cases.

The clinical information concerning the relevant patients was gathered, either through direct contact with the managing physicians of the multidisciplinary working group and/or in some cases from the hospital's intranet system. Patients who had received neoadjuvant therapy and those with metastasis at the time of diagnosis were excluded from the study. Accordingly, IMPC cases were included. In order to compare the Galectin-3 immunohistochemical staining characteristics in IMPC cases, the same number of IDC cases (non-IMPC group) with the same molecular phenotype distribution as the IMPC group were identified consecutively.

An immunohistochemical study was performed using the streptavidin-biotin method. All of the tissues were fixed with a 10% neutral buffered formalin. For each case, the tumor blocks were selected that best represented the content and histological composition of the tumor and comprised minimal necrosis and hemorrhage. Non-tumoral breast parenchyma was used as the internal control. The immunohistochemical staining procedure was applied using a BenchMark ULTRA Ventana device.

For Galectin-3 (Cell Marque, 9C4 clone, 1/75 dilution), cytoplasmic and/or membranous staining in normal breast luminal epithelial cells in areas adjacent to the tumor was considered as the positive internal control. For invasive tumor cells, the staining density was evaluated as none, minimal, medium or strong and subsequently scored as 0, 1, 2 or 3, respectively. (Figure 1a-d). The extent of staining was evaluated as the proportion of the stained area. As a result of multiplying these two values with each other, a value of 0 to 300 (H-score) was found where "0" indicated the absence of staining, and “300” representing strongly intense diffuse staining across all tumor tissues. All cases except those having an H-score value of 0 were considered positive for Galectin-3 immunohistochemical staining. For CAFs, staining intensity was evaluated as follows: 0 (0%), 1 (<10%), 2 (10%–50%), 3 (>50%) and scored ina similar fashion to Galectin-3 staining in tumor cells (0, 1, 2 or 3). Group 0 was considered negative, Groups 1, 2 and 3 were considered positive (Figure 2a-b).

P53 (Ventana, DO9 clone, 1/250 dilution) immunohistochemical expression was accepted as ‘positive’ for nuclear staining in 50% or more of tumor cells, and as ‘negative’ in staining less than 50%.

Mean ± standard deviation, and median (minimum and maximum range) values were used as descriptive statistics to define continuous variables and frequency distribution rates, and percentages were used to describe categorical variables. Kolmogorov-Smirnov normality tests were employed to determine the normal distribution of continuous variables. Paired comparisons between groups were investigated using independent samples of t-tests and chi-square tests. Associations between variables were determined via Pearson moment correlation coefficients. Survival analysis was carried out using Kaplan-Meier and Log Rank tests. A value of $p<0.05$ was accepted to indicate statistical significance. IBM SPSS, version 20 (IBM Inc., Armonk, NY, USA) was used for the analysis of all data.

Ethical approval for this study was obtained from the Ethics Committee of İstanbul Training and Research Hospital (reference no: 963).

Results

In total 34 IMPC cases were included and compared with 34 cases of IDC. The clinicopathological features of all cases are summarized in Table 1.

The Galectin-3 staining properties of the tumor cells and CAFs of the IMPC group are summarized in Table 2. The level of Galectin-3 expression in tumor cells was significantly higher in the IMPC group than in the IDC group ($p<0.05$). However, no significant difference

was found for Galectin-3 expression level in the CAFs between the groups (p>0.05) (Table 2).

There was no significant association between Galectin-3 expression within the invasive tumor cells of the IMPC and other clinicopathological parameters (p>0.05). However, the mean tumor size (3.53 ± 2.13 cm) tended to be larger in cases with negative Galectin-3 expression in tumor cells than those with positive Galectin-3 expression (2.42 ± 1.12 cm) (p = 0.059). Additionally, the relationship between Galectin-3 expression and the pT stage approached significance (χ^2 (2) = 5.832; p = 0.05). Thus, while advanced pT stages were associated with the loss of Galectin-3 expression in the tumor, early pT stage was associated with the presence of Galectin-3 expression in the tumor.

All 68 cases, both IMPC and IDC, were divided into two groups, either Galectin-3 positive or negative, and the relationship between Galectin-3 expression and other clinicopathological parameters was evaluated (Table 3-4). The mean tumor size was significantly greater in patients with no staining for Galectin-3 in tumor cells than those with positive staining (p<0.05). Consistent with this, patients in the negative Galectin-3 staining group had a significantly higher pT stage and a higher number of metastatic axillary lymph nodes (p<0.05). No other significant differences were identified between the positive or negative staining groups and clinicopathologic parameters (Table 3). Additionally, when patients were stratified by positive or negative Galectin-3 staining in CAFs, no significant differences in clinicopathological features were found (Table 4).

The median (range) follow-up period of all cases was 79 (1–113) months. During follow-up, 14 (20.6%) patients died and distant metastases were detected in 15 (22.1%) patients. The Galectin-3 staining properties in the cases with distant metastasis and/or patients who died due to breast cancer are summarized in Table 5.

When examined with the Kaplan-Meier method, disease-free survival (DFS) and overall survival (OS) rates were higher in patients with

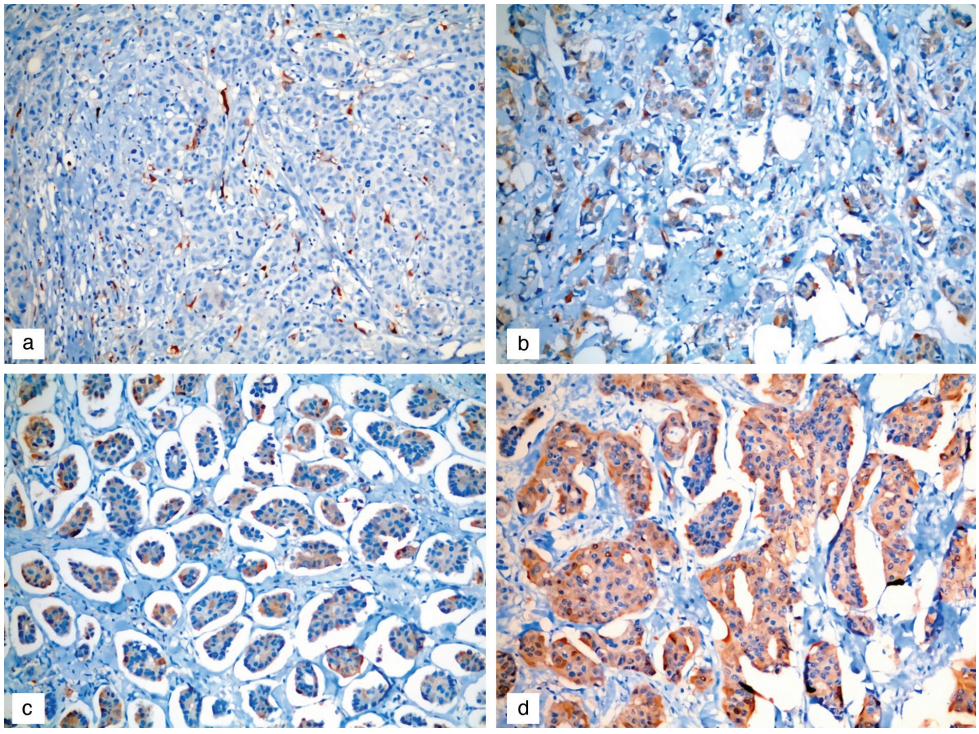

Figure 1. Immunostaining for Galectin-3 in tumor cells; **a)** Invasive tumor cells (Invasive ductal carcinoma) showing negative immunostaining for Galectin-3 (Score 0). Some of the inflammatory cells were seen as positive - internal control; **b)** Invasive micropapillary carcinoma showing weak cytoplasmic staining (Score 1); **c)** moderate degree of staining (IMPC) (Score 2); **d)** severe degree of staining (IDC) (Score 3)

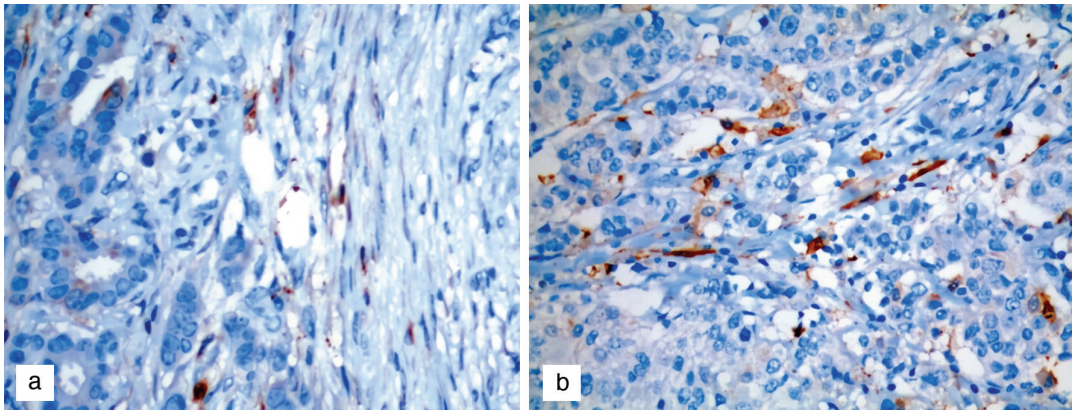

Figure 2. Galectin-3 immunostaining within CAF's, **a)** weak staining, **b)** strong staining

Table 1. Clinicopathologic features of the cases in IMPC and IDC groups

		Histologic type	
		IMPC (n = 34)	**IDC (n = 34)**
Age (min–max) mean ± SD		(34–80) 56 ± 11.73	(29–80) 54.26 ± 12.73
Gender	Female	32	34
	Male	2	0
Side	Right	20	18
	Left	14	16
Tumor Galectin-3	Negative	15	24
	Positive	19	10
CAF Galectin-3	Negative	10	9
	Positive	24	25
Nuclear Grade	2	11	15
	3	23	19
Histologic Grade	1	0	1
	2	19	19
	3	15	14
Tumor size (cm) (min–max) mean ± SD		(1–8) 2.91 ± 1.71	(1–6) 2.76 ± 1.44
pT stage	1	12	15
	2	18	16
	3	4	3
Angiolymphatic invasion	Absent	10	13
	Present	24	21
Perineural invasion	Absent	30	26
	Present	4	8
Multifocality	Absent	26	27
	Present	8	7
Multicentricity	Absent	28	28
	Present	6	6
***In situ* component**	Absent	6	8
	Present	28	26
Microcalcification	Absent	11	14
	Present	23	20
Number of positive nodes (min–max) mean ± SD		(0–20) 5.18 ± 6.29	(0–33) 6.59 ± 8.60
pN stage	0	8	8
	1	11	8
	2	6	10
	3	8	8
Extranodal extension	Absent	9	10
	Present	15	16
Ki-67 index (%) (min–max) mean ± SD		(5–90) 30.76 ± 18.68	(5–90) 29.5 ± 19.94

Table 1. Continued

		Histologic type	
		IMPC (n = 34)	IDC (n = 34)
Ki-67*	<20%	7	8
	>20%	26	18
Mutant p53	Absent	15	8
	Present	8	0
Molecular subtype	A	6	6
	B	22	22
	TN	2	2
	HER2	4	4
Adjuvant chemotherapy	Absent	2	3
	Present	32	31
Hormonotherapy	Absent	7	5
	Present	27	29
Radiotherapy	Absent	4	6
	Present	30	28
Metastasis	Absent	28	25
	Present	6	9
DFS		(1–105)	(4–113)
(min–max) mean ± SD		55.09 ± 24.81	77.5 ± 33.56
OS		(1–105)	(4–113)
(min–max) mean ± SD		61.26 ± 21.88	87.15 ± 26.4
Survival	Alive	29	25
	Exitus	5	9

IMPC: Invasive micropapillary carcinoma, IDC: Invasive ductal carcinomas, CAF: Cancer-associated fibroblasts, DFS: disease free survival, OS: overall survival, SD: Standard deviation, HER2: Human epidermal growth factor receptor 2, TN: Triple-negative, Ki-67 immunhistochemical staining was available for 33 cases in IMPC group, and for 26 cases in IDC group, n: Number

Table 2. Association of Galectin-3 expression with histologic type

		IMPC	IDC	p-value
Tumor Galectin-3	Positive (n; %)	19 (55.9%)	10 (29.4%)	**0.049**
	Negative (n; %)	15 (44.1%)	24 (70.6%)	
CAF Galectin-3	Positive (n; %)	24 (70.6%)	25 (73.5%)	1
	Negative (n; %)	10 (29.4%)	9 (26.5%)	

IMPC: Invasive micropapillary carcinoma, IDC: Invasive ductal carcinomas, CAF: Cancer-associated fibroblasts, n: Number

Galectin-3 positive staining in tumor cells compared to negative cases, but this difference did not reach statistical significance using Log-Rank tests. However, DFS and OS rates were higher in patients with no Galectin-3 expression in CAFs but once again, this difference did not reach statistical significance.

Discussion and Conclusion

IMPC of the breast usually exhibits axillary lymph node involvement at the time of diagnosis. In this study, we investigated the levels of Galectin-3 expression, both in tumor cells and CAFs in IMPCs and sought to ascertain any differences in Galectin-3 expression in IMPCs compared to IDC (non-IMPC) tumors. Accordingly, the level of Galectin-3 expression in invasive tumor cells was significantly higher in the IMPC group than in the IDC group. No significant correlation was found between Galectin-3 expression levels and clinicopathological parameters in the IMPC group. However, loss of Galectin-3 expression in tumor cells in IMPC yielded a result close to significance with larger tumor size and more advanced pT stages. Then, all cases, regardless of

Table 3. Distribution of clinicopathological parameters in groups of tumor with and without Galectin-3 expression

	Tumor Galectin-3 (-) (n)	Tumor Galectin- 3 (+) (n)	p-value
Age (mean ± SD)	54.82 ± 13.12	55.55 ± 11.01	0.81
Side			
Right	21	17	0.89
Left	18	12	
Nuclear Grade			
2	14	12	0.83
3	25	17	
Histologic Grade			
1	1	0	
2	21	17	0.66
3	17	12	
Tumor size (cm) (mean ± SD)	3.15 ± 1.83	2.41 ± 1.02	**0.038***
pT stage			
1	13	14	
2	17	15	**0.046***
3	7	0	
Angiolymphatic invasion			
Absent	14	9	0.87
Present	25	20	
Perineural invasion			
Absent	30	26	0.30
Present	9	3	
Multifocality			
Absent	31	22	0.95
Present	8	7	
Multicentrisity			
Absent	30	26	0.30
Present	9	3	
***In situ* component**			
Absent	9	5	0.77
Present	30	24	
Microcalcification			
Absent	15	10	0.93
Present	24	19	
Number of positive nodes (mean ± SD)	7.45 ± 8.89	3.86 ± 4.65	**0.037***
pN stage			
0	9	7	
1	7	12	0.14
2	10	6	
3	12	4	

Table 3. Continued

	Tumor Galectin-3 (-) (n)	Tumor Galectin- 3 (+) (n)	p-value
Extranodal extension			
Absent	11	8	1
Present	19	12	
Ki-67 index (%) (mean ± SD)	28.47 ± 16.58	32.91 ± 22.60	0.39
Ki-67			
<20%	9	6	1
>20%	27	17	
Mutant p53			
Absent	14	9	0.18
Present	2	6	
Molecular subtype			
A	6	6	0.41
B	28	16	
TN	1	3	
HER2	4	4	
Adjuvant chemotherapy			
Absent	4	1	0.55
Present	35	28	
Hormonotherapy			
Absent	6	6	0.81
Present	33	23	
Radiotherapy			
Absent	8	2	0.22
Present	31	27	
Metastasis			
Absent	30	23	1
Present	9	6	
Survival			
alive	29	25	0.37
exitus	10	4	

*mutant p53 defines positive nucleer staining in more than 50% of the invasive tumor cells, and was evaluated in 23 cases with IMPC and 8 cases with IDC.
SD: Standard deviation, n: Number, IMPC: Invasive micropapillary carcinoma, IDC: Invasive ductal carcinomas

histological type, were divided into two groups according to whether the tumor cells displayed Galectin-3 expression or not. On analysis in cases with no Galectin-3 expression in tumor cells there was a significant association with larger tumor size, more advanced T stage, and a greater number of metastatic lymph nodes compared to those with Galectin-3 expression.

Only a few studies have investigated the relationship between Galectin-3 expression with histological type in breast carcinomas (15, 16). In one of these studies, invasive tubular carcinomas and IDC cases in the pT1 stage were compared for immunohistochemical expression of Galectin-3 in tumor cells (15). Widespread cytoplasmic and/or nuclear Galectin-3 immune expression was detected in full-thickness sections of tumors, in invasive tubular carcinomas, compared to histological grade 1 IDCs. In the other study, an H-score was calculated by considering the cytoplasmic and/or nuclear staining in tumor cells in full-thickness sections from 218 cases with IDC and 25 cases with invasive lobular carcinoma (16). The authors reported that Galectin-3 nuclear expression was more common in invasive lobular carcinomas compared to IDC cases. To the best of our knowledge, only a single study has investigated Galectin-3 expression in IMPC as a special histological subtype (17). In this study, the relationship between tumor cells and with the stroma in the pancreas and periampullary region IMPCs was evaluated with immunohistochemical staining for E-cadherin and Galectin-3, and diffuse and strongly intense cytoplasmic staining was detected in invasive tumor cells in all cases. The researchers reported that Galectin-3 may be a marker for tumor

Table 4. Distribution of clinicopathological parameters in CAF Galectin-3 negative and positive groups of tumor

	CAF Galectin-3 (-) (n)	CAF Galectin-3 (+) (n)	p-value
Age (mean ± SD)	53.26 ± 13.39	55.86 ± 11.75	0.43
Side			
Right	12	26	0.63
Left	7	23	
Nuclear Grade			
2	7	19	1
3	12	30	
Histologic Grade			
1	0	1	
2	12	26	0.65
3	7	27	
Tumor size (cm) (mean ± SD)	2.89 ± 1.52	2.81 ± 1.60	0.85
pT stage			
1	7	20	
2	10	24	0.95
3	2	25	
Angiolymphatic invasion			
Absent	5	18	0.60
Present	14	31	
Perineural invasion			
Absent	15	41	0.92
Present	4	8	
Multifocality			
Absent	16	37	0.65
Present	3	12	
Multicentrisity			
Absent	17	39	0.54
Present	2	10	
***In situ* component**			
Absent	4	10	1
Present	15	39	
Microcalcification			
Absent	8	17	0.77
Present	11	32	
Number of positive nodes (mean ± SD)	5.26 ± 6.67	6.15 ± 7.99	0.67
pN stage			
0	8	8	
1	2	17	
2	4	12	0.08
3	5	11	

Table 4. Continued

	CAF Galectin-3 (-) (n)	CAF Galectin-3 (+) (n)	p-value
Extranodal extension			
Absent	2	17	0.34
Present	8	23	
Ki-67 index (%) (mean ± SD)	25.36 ± 19.71	31.71 ± 17.86	0.28
Ki-67			
<20%	6	9	0.17
>20%	8	36	
Mutant p53			
Absent	6	17	0.76
Present	1	7	
Molecular subtype			
A	5	7	0.30
B	9	35	
TN	2	2	
HER2	3	5	
Adjuvant chemotherapy			
Absent	1	4	1
Present	18	45	
Hormonotherapy			
Absent	3	9	1
Present	16	40	
Radiotherapy			
Absent	5	5	0.19
Present	14	44	
Metastasis			
Absent	16	37	0.65
Present	3	12	
Survival			
Alive	17	37	0.34
Exitus	2	12	

CAF: Cancer-associated fibroblast, SD: Standard deviation, n: Number

progression and metastasis in other pancreatic tumor types, based on Galectin-3 positivity detected in tumor cells in micropapillary carcinoma, a subtype of pancreatic neoplasia with a high grade and high metastatic potential. In our study, Galectin-3 immunostaining in tumor cells was significantly higher in the IMPC group than in the IDC group. However, we did not find a significant relationship between Galectin-3 positivity seen in tumor cells within IMPC and clinicopathological parameters. This suggests that Galectin-3 may play a role in micropapillary morphology, as Galectin-3 has been reported to affect cell surface polarization (18).

There are conflicting findings in studies evaluating the relationship between Galectin-3 expression in tumor cells and clinicopathological parameters in breast carcinomas. In the study of Ilmer et al., among all 87 patients with breast cancer who received chemotherapy and axillary lymph node metastases, lymphovascular invasion was detected less frequently in those with higher Galectin-3 expression (H-score level ≥150). However, no relationship was found between Galectin-3 expression level and age, ER/PR/CerbB2 expression status, the number of positive lymph nodes, stage, and histological grade (19). In the study of Zhang et al., examining positive cytoplasmic and/or nuclear Galectin-3 expression in full-thickness sections containing tumor, increased Galectin-3 expression was correlated with young age, increased tumor size, higher histological grade, a greater number of metastatic lymph nodes, and triple-negative molecular subtype (13). In our study, contrary to this finding, we found larger tumor size, more advanced T stage, and a greater number of metastatic lymph nodes in cases where Galectin-3 expression was not detected in tumor cells. However, other studies have not detected a relationship between tumor

Table 5. Analysis of the cases in terms of distant metastasis and survival according to Galectin-3 expression status

		Tumor Galectin-3		CAF Galectin-3	
		(-) n/%	(+) n/%	(-) n/%	(+) n/%
Exitus cases* (n = 14; 20.6%)		10 (71.4%)	4 (28.6%)	2 (14.2%)	12 (85.8%)
Median time, month (exitus cases*)		42.5	63.5	41.5	54
Metastatic cases (n = 15; 22.1%)		9 (60%)	6 (40%)	3 (20%)	12 (80%)
Median time, month (metastasis)		34	36	65	32.5
Metastasis site**	Bone	7	-	-	7
	Brain	2	2	1	3
	Lung	1	2	-	3
	Liver	2	1	1	2
	Neck lymph nodes	-	1	-	1
	Mediastinum	1	-	1	-

CAF: Cancer-associated fibroblasts, *the patients who died because of breast cancer (exitus), **metastasis was determined at one or more sites
n: Number

size, T-stage and Galectin-3 expression (16, 20). In another study that included 116 breast cancer patients where staining intensity of ≥30% in tumor cells was considered as Galectin-3 positivity, Galectin-3 positivity was associated with increased lymphovascular invasion and a higher rate of PR expression (20). Many studies in the literature have investigated the relationship between Galectin-3 expression in tumor cells and prognosis. Some have found an association between Galectin-3 expression levels in tumor cells and good (19, 20) or poor prognosis (21), while others were unable to detect any correlation between Galectin-3 expression levels in tumor cells and prognosis (13, 16, 22). In a study, conducted with a large patient population (n = 1086), immunhistochemical expression of Galectin-3 in tumor cells was not associated with survival, while a significant correlation was found with drug resistance. These authors suggested that treatment models targeted at Galectin-3 may be useful in preventing resistance to chemotherapeutic drugs (13).

A limited number of studies have evaluated the relationship between the expression of Galectin-3 in stroma and the clinicopathological parameters in breast carcinomas. In a study involving 273 breast cancer patients, higher histological grade, and more advanced pN stage were reported in patients with Galectin-3 expression in stromal fibroblasts (16). In the same study, cases with Galectin-3 expression in stromal fibroblasts were found to be associated with worse prognosis, whereas no significant relationship between Galectin-3 expression in tumor cells and survival rates was detected (16). Logullo et al. examined the immunhistochemical expression of Galectin-3 in tumor cells and stromal fibroblasts in 92 early-stage breast carcinoma cases (22). In approximately half of the cases, tumor cells stained positively with Galectin-3 (cytoplasmic staining), while in more than half of them staining of the stromal (nuclear quality) component was observed. These authors speculated that the intracellular localization of Galectin-3 may vary, depending on the tumorigenicity of the cell. In the same study, the immune expression of Galectin-3 in tumor cells or stroma was not associated with DFS and OS. However, it was not explicitly stated which cellular component in the stroma was stained with Galectin-3. In our study, we did not find a significant difference in the level of Galectin-3 expressed in CAFs between a histological subtype of IMPC cases and IDC cases. In addition, considering all the cases, regardless of histological type, we did not find a significant difference in terms of DFS and OS between patients with and without CAF Galectin-3 expression. However, cases with distant metastasis and/or patients who had died showed higher rates of Galectin-3 positivity in CAFs.

Some experimental studies have suggested that the loss of Galectin-3 expression in tumor cells increased the metastatic potential of the tumor to regions such as lymph nodes and bone marrow (23), while decreased Galectin-3 expression in stroma affected the adhesion molecules in the tumor microenvironment and increased the metastatic potential of tumor cells (24). However, to our knowledge, no study has investigated the relationship between Galectin-3 expression and the region of metastasis in breast carcinomas in humans. In the current study, in the cases with distant metastases, tumor cells were negative for Galectin-3 in 60% of the cases, while CAFs were positive for Galectin-3 in 80% of the cases. Similarly, in patients who had died from breast cancer, tumor cells were negative for Galectin-3 in 71.4% while CAFs were positive for Galectin-3 in 85.8%. Bone was the most common site for metastasis in our study. Indeed, in all cases with bone metastasis (n = 7), Galectin-3 expression was absent in the tumor cells, but present in the CAFs.

Our study compared a specific histological type (IMPC) with IDC patients in terms of immunhistochemical expression of Galectin-3 in a limited number of patient populations who underwent a median of 79 months clinical follow-up. The limitations of this study are the low number of patients and the low level of H-score that was considered positive for Galectin-3 in tumor cells.

In this study, loss of Galectin-3 expression in tumor cells was found to be associated with aggressive clinical parameters, including larger tumor size, advanced pT stage and a higher number of metastatic nodes, and this relationship appeared to be independent of the histological tumor type.

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Original Article

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Indocyanine Green Fluorescence-Guided Sentinel Node Biopsy in Breast Cancer Within a North African Population: A Retrospective Study

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ABSTRACT

Objective: Radio isotopes and blue dyes alone or in combination are the most commonly used tracer agents in sentinel node (SN) biopsy for early breast cancer. Recent studies have found fluorescence method using indocyanine green (ICG) as a promising technology with fewer disadvantages.

Materials and Methods: Retrospective analysis of our database that included patients with clinically node-negative breast cancer scheduled for breast surgery and SN biopsy between 2016 and January 2021. Patients who underwent detection using fluorescence-ICG were included in this study.

Results: A total of 47 patients were included. Median age was 50 (range: 24–78) years. Mean tumor size was 3.4 ± 1.5 cm. All patients received ICG injection and 11 received a combination of ICG and blue dye. Forty-five successful SN identifications with ICG were performed and 99 nodes retrieved. Eleven procedures were undertaken after initial systemic therapy. Twenty-four patients had at least one positive SN for malignancy. Mean follow up was 29.2 months and no axillary recurrence was noted during the study period.

Conclusion: ICG appears to be a feasible and accurate method for SN biopsy with high identification rate. This is the first study of ICG in sentinel node biopsy in a North African population.

Keywords: Breast cancer, indocyanine green, sentinel lymph node biopsy, surgery

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Key Points

- Sentinel node is a standard of care for early breast cancer patients.
- Radio Isotopes alone or combined with blue dye are the most commonly used tracer agents but have several clinical limitations.
- This study is the first to report fluorescence guided sentinel node biopsy in a North African setting and confirms it as a promising technology.

Introduction

Sentinel node (SN) technique in breast cancer was first describe in 1994 by Giuliano et al. (1) and Krag et al. (2). The aim of the technique is to identify patients who can be spared axillary clearance. Since than the procedure has become a standard approach for breast cancer patients with clinically node-negative disease (3). Radio isotopes (RI) alone or in combination with blue dyes (BD) are the most commonly used tracers. A combination of different tracers is recommended to increase identification rates and decrease false negative rates (3). Despite consistent identification rates higher than 90% (4), published data (5) report several clinical limitations with these tracers including hypersensitivity, potential radioactivity exposure with high volume activity, the need for specially arranged specimen transportation for pathology, and regular on-site contamination tests. This increases the already high cost further. These drawbacks have led to the development of alternative tracers, such as super-paramagnetic iron oxide nanoparticles (6) and contrast-enhanced ultrasound (7). Numerous cohort studies and clinical trials from Asia (7, 8), Europe (9), and the US (10) have suggested the use of indo-cyanine green (ICG) as a promising candidate for tracer in this technique.

To the best of our knowledge, and after an extensive literature search, no study reported the use of ICG fluorescence-guided SN biopsy in breast cancer in North Africa and this study represents the first cohort of ICG fluorescence application within this setting.

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Materials and Methods

We performed a retrospective review of our prospective, maintained database that included breast cancer planned for SN biopsy at the F. Hached University teaching hospital (Sousse, Tunisia). Data between April 2016 and January 2021 were reviewed. Only non-pregnant or lactating adult female patients without palpable clinical nodes and considered suitable for such procedure at multidisciplinary meetings were included. We excluded from our analysis the first ten cases as these were considered to consitute the "learning curve" (11). A single operator (SH) carried out all the procedures.

Under general anesthesia, 5 mL at 2.5 mg/mL of Infracyanine (Laboratoire SERB; France) were injected circumferentially around the areola. Two mL of patent blue-V dye (Laboratoire Guerbet, Aulney-Sous-Bois, France) were injected in combination in the cohort of patients undergoing the procedure after primary chemotherapy. This was followed by a breast massage to facilitate absorption into the lymph vessels. Then the surgical lights were turned off and images were obtained under near-infrared light using a first-generation near infra-red (NIR) device (12). The course of subcutaneous lymphatic drainage pathway fluorescence was followed up to where it became indistinct as the lymphatics entered deeper in the axilla and an incision was performed at that place. Lymphatic duct identification using the NIR camera allowed localization and removal of the sentinel lymph node(s). Further fluorescent imaging was performed to identify potential residual signal in the axilla and such signal-sites were removed. Following ICG assisted-dissection, blue-stained nodes were excised, if any. After SN biopsy, conservative surgery or mastectomy was performed according to indication and axillary dissection was performed according to international guidelines.

Statistical analysis and ethical approval

Baseline patient's and tumor characteristics, and identification rate of the SN with ICG and with dye, when used, were recorded. Data were entered and analyzed in Excel then analyzed using PSPP v 1.2.0-3. The continuous variables are presented as mean ± standard deviation and categorical variables are presented as count and percentages, unless specified.

The study was performed in accordance with the Declaration of Helsinki. All patients provided informed consent following a detailed explanation of the procedures that they may undergo. Institutional ethical review board approval was obtained (F. Hached University teaching Hospital 01/02/2015 and Faculty of Medicine of Sousse-CEFMS82), the study itself was also retrospectively registered as NCT04879680 (clinicaltrial.gov).

Results

During the study period, and after exclusion of the first ten cases, 47 patients who underwent SN biopsy using the above-mentioned technique were included. Median age at time of surgery was 50 years (range: 24–78 years). A total of 45 successful SN procedures were performed (identification rate = 95.7%). Median removed nodes per patient was 2 (range: 1–4). In two patients, the procedure failed and they underwent axillary clearance that was, in both cases, pathologically positive.

Thirty-six patients (76.5%) received upfront operation while others received primary systemic therapy. ICG-blue dye combination was used for this last group of patients and, in this subgroup, identification rate was 100% with ICG (11/11) and 81.9 % with blue dye (9/11). Patients and tumor characteristics are described in Table 1.

Twenty-six patients underwent axillary dissection (24 positive SN and two failed procedures). The remaining 21 patients with negative SN on frozen section were confirmed thereafter. Importantly, in 11 of the 24 positive SN cases (45.8%), SN was a solitary, pathologically positive node on axillary clearance. Median follow-up time was 30 (1–51) months while median follow-up time for the subgroup of patients with negative SN was 28 (1–51) months and no axillary recurrence was noted in this group during the study period.

Discussion and Conclusion

With an equivalent overall survival, disease-free survival, and regional control, sentinel lymph node biopsy has become the standard of care for patients with early breast cancer and clinically negative axillary lymph nodes (3) and has gradually replaced axillary dissection indications. Several drawbacks have been reported with conventional methods, such as Isotope and dye, and this has led to the development of new tracers. In the super-paramagnetic iron oxide nanoparticles (6) (SPIO) procedure, magnetic nanoparticles are injected and the SN is subsequently detected by a hand-held magnetometer. This technique has shown promising results (13) but its major drawback is interference of iron with possible postoperative breast MRI. Contrast-enhanced ultrasound using microbubbles is also a recently developed technique (7). The contrast agent is cheap but the results remain suboptimal and highly operator dependent when compared to other tracers (7). The development and introduction of a fluorescence technique as a new method of SN detection has allowed a number of these disadvantages to be overcome.

Numerous studies, including clinical trials, evaluating ICG as a tracer for SN have been published worldwide (7-10) but to the best of our understanding, this study represents the first in a North

Table 1. Patients and tumor characteristics, (n = 47)

Mean age, years, (range)	50.1	(24–78)
Mean body mass index, kg/m² (± SD)	22.7	(± 3.1)
Left side tumor	28	(58.6%)
Tumor size (cm) before surgery (± SD)	3.1	(± 1.5)
Multifocal tumor	8	(17%)
Tumor location		
Upper outer quadrant	19	(41.3%)
Upper inner quadrant	7	(15.2%)
Lower inner quadrant	9	(19.5%)
Lower outer quadrant	6	(10.8%)
Central	6	(13%)
Molecular type		
Luminal A	7	(14.8%)
Luminal B	7	(14.8%)
HER2 enriched	20	(42.5%)
Triple negative	13	(29.7%)

SD: Standard deviation, n: Number

African population. After a short, technique-specific, learning curve as performed by others (11), we found a 95.7% identification rate, similar to those reported in the literature, which ranges between 93% and 100% (14, 15).

The body of information from the current data suggests that using ICG as a tracer allows real-time visualization of lymphatic channels, provides a high identification rate with a low dose of tracer and has an excellent safety profile in clinical use (16). Two recent, comprehensive meta-analyses (14, 15) addressed the question of whether ICG can act as a better tracer agent compared with conventional techniques. ICG alone is a better tracer agent compared with BD and/or RI alone and is not inferior compared to BD and RI in combination (14, 15). Yin et al. (15) concluded that ICG was a suitable alternative to traditional tracers to detect SN in patients with breast cancer while Kedrzycki et al. (14) recommended that "hospitals using RI and or BD could consider changing their practice to ICG". Some studies suggested that the rapid spread of ICG and high sensitivity of fluorescence detection devices lead to a greater number of dissected SN with ICG fluorescence when compared to RI and/or blue dye. (17-19). We retrieved a mean of 2.2 nodes per procedure and our data do not support this but our sample size was limited.

Age over 60 and high body mass index (BMI) were suggested to negatively affect identification rate (14) but results of the different studies are conflicting. In our study, both cases in whom identification failed were less than 60 years and both had a BMI of 25. None of these two patients received neoadjuvant chemotherapy and both had positive macrometastatic nodes at axillary clearance. Whether node invasion by lymphatic channel obstruction is a risk factor for identification failure is a matter of debate and needs further studies.

Eleven patients in our study group received neoadjuvant chemotherapy prior to SN. They received combined ICG-blue dye technique and SN localization was successful with ICG in all patients in this subgroup. This is in accordance with recent studies that show promising results of this tracer combination after neoadjuvant chemotherapy with an identification rate ranging from 83% to 100% (20-22) and very low false-negative rates (22).

Cost-effectiveness of ICG is a matter for debate. Near Infrared camera devices are expensive (basic models start at 19,000 Euros) but Indocyanine green tracer prices range from 18 Euros in India (Aurogreen®) to 124 Euros for Infracyanine® that we used in our study. Once opened the vial should be used within eight hours, and the amount is sufficient for two procedures. Thus in high volume units the procedure will be more cost effective than in smaller units and may even compare with Patent Blue®.

Limitations of our study include selection bias, absence of direct comparison with conventional tracer, and absence of systematic axillary clearance for the entire cohort to assess the false-negative rate. However, in our study, 45.8% of patients had a solitary sentinel node with negative axillary clearance. This is a clear positive quality indicator and in accordance with previously published data (9).

No recurrence occurred in our study, but the median follow-up was relatively short (30 months). A recent long-term follow-up study by Wang et al. (22) confirmed that the ICG-BD combination was safe. In 687 early breast cancer patients who underwent the procedure with histologically negative SN, 0.64% recurred after a median follow-up of 5.6 years.

This study is the first cohort in whom ICG fluorescence was used for SN in breast cancer in a North African setting and includes a reasonable sized cohort with a single operator. The high identification rate of the technique in the present study is in accordance with recent comprehensive meta-analysis and confirms its potential to become the standard of care in this indication.

Ethics Committee Approval: Institutional ethical review board approval was obtained (F. Hached University teaching Hospital 01/02/2015 and Faculty of Medicine of Sousse- CEFMS82), the study itself was also retrospectively registered as NCT04879680 (clinicaltrial.gov).

Informed Consent: All patients provided informed consent following a detailed explanation of the procedures that they may undergo.

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Authorship Contributions

Surgical and Medical Practices: S.H., Concept: S.H., A.A., A.K., S.C., O.K., S.B., M.B., H.K., Design: S.H., A.A., A.K., S.C., O.K., S.B., M.B., H.K., Data Collections and/or Processing: A.A., A.K., S.C., O.K., Analysis and/or Interpretation: S.H., A.A., A.K., S.C., O.K., S.B., M.B., H.K., Literature Search: A.A., A.K., S.C., O.K., S.B., M.B., H.K., Writing: S.H., A.A., A.K., S.C., O.K., S.B., M.B., H.K.,

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Original Article

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Neo-Adjuvant Chemotherapy in Luminal, Node Positive Breast Cancer: Characteristics, Treatment and Oncological Outcomes: A Single Center's Experience

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ABSTRACT

Objective: Neo-adjuvant chemotherapy (NAC) is the treatment of choice for patients with locally advanced breast cancer (BC). In luminal-like BC, the decision to administer NAC remains controversial. The purpose of this study was to describe the clinical characteristics, treatment, and oncological outcomes of luminal-like, node positive, BC patients treated with NAC, and to identify independent predictive factors for treatment.

Materials and Methods: All consecutive patients with luminal-like, node positive BC who underwent NAC were retrospectively reviewed. Pathologic complete response (pCR) was defined as no invasive or *in situ* residual tumor in both breast and axillary nodes (ypT0N0).

Results: A total of 205 luminal-like, node positive BC patients underwent NAC. Overall, 34 (16.6%) patients showed pCR, 86 (42.0%) patients underwent breast-conserving surgery (BCS), 119 (58.0%) patients underwent mastectomy, 130 (63.4%) patients underwent axillary lymph node dissection (ALND) without prior sentinel lymph node biopsy (SLNB), and 75 (36.6%) patients underwent breast surgery plus SLNB. Pathologic CR to NAC (29.1% vs 7.6% if no pCR, odds ratio = 2.866, 95% confidence interval = 1.296-6.341, p = 0.009) was found to significantly increase the probability to receive BCS. There was no significant difference in terms of disease-free and overall survival between patients with luminal-like, node positive BC receiving BCS or mastectomy (p = 0.596, p = 0.134, respectively), and ALND or SLNB only (p = 0.661, p = 0.856, respectively).

Conclusion: Luminal-like, node positive BC presents low pCR rates after NAC. Pre-operative chemotherapy increases the rate of BCS. Pathologic CR has emerged as an independent predictive factor for BCS. In patients with axillary pCR, SLNB is an acceptable procedure not associated with worse oncological outcomes.

Keywords: Chemotherapy, breast cancer, breast-conserving surgery, mastectomy, lymph nodes, dissection

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Key Points

- Despite favorable long-term survival, luminal-like breast cancer is relatively resistant to neo-adjuvant chemotherapy and pathologic complete response is less likely to occur. Therefore, the decision to administer pre-operative chemotherapy remains controversial.
- Although pathologic complete response should not be used as a surrogate endpoint for improved survival, in luminal-like, node positive breast cancer, it has emerged as an independent predictive factor for breast conserving surgery.
- The use of neo-adjuvant chemotherapy in luminal-like, node positive breast cancer allows the performance and increases the rate of breast conserving surgery in patients previously requiring mastectomy.
- In luminal-like, node positive breast cancer patients with axillary pathologic complete response, sentinel lymph node biopsy is a safe and acceptable procedure not associated with worse oncological outcomes.

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Introduction

The therapeutic algorithm for invasive breast cancer (BC) includes three different treatment modalities: surgery, systemic therapy, and radiation therapy. Traditionally, systemic therapy has been administered to BC patients after surgery, in the adjuvant setting (1). However, the potential role of neo-adjuvant chemotherapy (NAC) – i.e. systemic therapy started before surgery – began to gain importance in breast oncology, and it has been regarded as an equally safe and effective option when compared to adjuvant therapy (2-4). Nowadays, NAC is the treatment of choice for patients with locally advanced BC (5, 6). In this setting, the intent of NAC is to expand surgical options and to improve survival (7). Moreover, indication for NAC has been extended to patients with large, operable BC in order to allow and to increase the rate of breast conserving surgery (BCS), thus avoiding mastectomy (8, 9). The next clinical dilemma concerns the optimal management of BC patients with clinically node positive axilla. Recently, the role of NAC as a means of down-staging the axilla has been investigated, both to avoid the complications of axillary lymph node dissection (ALND) and as a source of prognostic information. Axillary pathologic complete response (pCR) is observed in 20%–42% of node positive patients (10-12) and is associated with a more favourable survival (12, 13). It appears rational to conclude that aggressive surgical treatment with ALND might be omitted in patients with axillary pCR (14, 15). However, the increasing use of NAC has raised doubts about the optimal approach to the axilla, including accuracy and timing of sentinel lymph node biopsy (SLNB). Furthermore, NAC has been considered a standard therapy only in triple negative (TN) and human epidermal growth factor receptor 2 (HER2) enriched disease, with pCR being more pronounced in these biological sub-types (16). In luminal-like BC, NAC is less effective, achieving lower pCR rates compared to the previously cited more aggressive sub-types, despite high conversion rate from mastectomy to BCS (17, 18). Therefore, the decision to administer NAC to luminal-like BC patients remains controversial. The purpose of this study was to describe the clinical characteristics, treatment, and oncological outcomes of luminal-like, node positive BC patients treated with NAC, and to identify independent predictive factors for treatment, resulting in either BCS or mastectomy.

Materials and Methods

Study design and patient management

All consecutive patients with luminal-like, node positive BC who underwent NAC at the Breast Unit of Humanitas Clinical and Research Center (Milan, Italy) between January 2008 and December 2019 were retrospectively reviewed. All patients underwent pre-operative staging with bilateral breast and axillary ultrasound (US). Pre-operative mammography or magnetic resonance imaging (MRI) of the breast was not mandatory, although, they were performed in the majority of the patients. Diagnosis of invasive BC with node metastasis was histologically confirmed in all patients by core needle biopsy in both breast and axilla. A multidisciplinary tumor board composed of breast surgeons, oncologists, radiotherapists, radiologists, plastic surgeons, and pathologists discussed the management of every patient. Indication for NAC was: locally advanced, >2 cm diameter, luminal-like BC with histologically confirmed axillary metastasis. Assessment of response to NAC was performed after each cycle with clinical examination. After three months of NAC, each patient underwent a second bilateral breast and axillary US. All patients underwent post-NAC response evaluation by one or a combination of the following radiological examinations: bilateral breast and axillary US, MRI of the breast, or total-body positron emission tomography. All patients underwent either BCS or mastectomy. Indication for conserving surgery or mastectomy was given by the breast surgeon after NAC tumor response evaluation. Conversion rate from mastectomy to BCS was analyzed retrospectively. Regarding the management of the axilla, before 2015, all patients underwent breast surgery plus ALND directly without SLNB. Between 2015 and 2018, all clinically node negative patients underwent breast surgery plus SLNB and in case of sentinel node negativity, ALND was omitted. From December 2018, patients begun to be enrolled in the NEONOD2 prospective clinical trial (19) and in case of micro-metastatic sentinel node, ALND was omitted. The following exclusion criteria were used: patients not treated with NAC; other BC sub-types (TN or HER2 enriched disease); clinical tumor diameter ≤2 cm or not measurable tumor before NAC; patients who did not complete pre-operative staging with both breast and axillary US; patients who did not undergo core needle biopsy of both breast and axilla or post-NAC radiological response evaluation; patients with other prior malignancies; and follow-up <12 months. Taxane-based adjuvant chemotherapy was administered to patients who did not achieve pCR and did not complete both anthracycline and taxane-containing regimen before surgery. Adjuvant endocrine treatment was administered to all patients after surgery and adjuvant radiotherapy was recommended for all patients who underwent BCS. Follow-up was performed every six months, including physical examination, routine biochemistry, mammography, and breast and axilla US. Abdominal US and chest X-ray was prescribed annually. Each patient gave informed consent for the operation and for clinical data acquisition.

Definitions

In 2011, the St. Gallen expert consensus panel adopted a sub-type-based approach for the treatment of early BC using levels of estrogen receptor (ER), progesterone receptor (PgR), Ki67, and HER2 expression (20). In our study and in line with the 2013 St. Gallen update (21), luminal A-like BC was defined as ER positive, PgR positive (cut-point ≥20%), HER2 negative, Ki67 'low' <14%, whereas luminal B-like BC was defined as ER positive, PgR negative or low (cut-point <20%), HER2 negative, Ki67 'high' ≥14%. Additionally, luminal B-like BC was defined as ER-positive, highly proliferating disease with high histological tumor grade (G3) (22, 23). However, none of these classification systems could produce a strong consensus in sub-dividing luminal-like BC (24). Despite ER being bimodally expressed, thus creating an important cut-off point, proliferation-related genes are expressed along a unimodal continuum, making it extremely difficult to apply a significant cut-off point (25). HER2 status was assessed by immunohistochemistry and defined as negative if the score was 0/1+, equivocal if the score was 2+, or positive if the score was 3+. Equivocal cases were further assessed by fluorescent *in situ* hybridization, according to the recommendations of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) (26). Tumor staging was defined according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) cancer staging system (AJCC Cancer Staging Manual, 8^{h} edition) (27). Tumor response rate to NAC was defined as the calculated percent rate of breast tumor and axillary node size reduction between baseline and after systemic therapy. The tumor response rate was calculated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (28). Pathologic CR was defined as no invasive or non-invasive residual tumor in both breast and axillary

nodes (ypT0 N0), excluding patients with pathological stage ypTis. Disease-free survival (DFS) was defined as the period from the date of surgery to the date of any tumor progression, including loco-regional recurrence or distant metastasis. Overall survival (OS) was defined as the time interval from surgery to death from any cause or last follow-up.

Statistical analysis

Patients were selected from the institutional prospectively maintained database and retrospectively analyzed. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The Kaplan-Meier method was used to estimate the recurrence and survival probabilities and the log-rank test was used to compare two different groups of axillary treatment (SLNB-only vs ALND). Last follow-up was updated up to December 1st, 2020. Follow-up was ≥12 months in all luminal-like, node positive BC patients and no patient was lost to follow-up. The multivariate analysis was performed using a logistic regression model to identify independent predictors of treatment for luminal-like, node positive BC. The multivariate analysis included any variable associated with the result at the univariate analysis (inclusion cut-off value $p<0.10$). Statistical significance was set at $p<0.050$. Data analyses and figures were performed with IBM SPSS, version 25.0 (IBM Inc., Armonk, NY, USA).

Results

Patients' characteristics

Between January 2008 and December 2019, 5,739 patients with luminal-like BC underwent surgical treatment at the Breast Unit of Humanitas Clinical and Research Center (Milan, Italy). Of these patients, 205 luminal-like, node positive patients underwent NAC before surgery, of whom 124 (2.2%) and 81 (1.4%) were luminal A-like and luminal B-like, respectively. The mean age of the patients was 54.8 years (range, 30-77), and 136 (66.3%) patients were post-menopausal. Bilateral mammography and MRI of the breast were performed in 191 (93.2%) and 89 (43.4%) patients, respectively. Before NAC, the mean diameter of breast tumor was 32 mm (range, 21-80), 148 (72.2%) patients were affected by cT2 BC, and 47 (22.9%) and 20 (9.8%) patients were affected by multifocal and multicentric tumors, respectively. Regarding NAC treatment protocol, 69 (33.7%) patients received only anthracycline for four cycles, while 136 (66.3%) patients received both anthracycline and taxanes. After NAC, the mean diameter of the breast tumor was 22 mm (range, 0-75). Out of these 205 patients, 34 (16.6%) showed pCR. Characteristics of these patients are summarized in Table 1.

Treatment of the breast and axilla

Overall, 86 (42.0%) patients underwent BCS, while 119 (58.0%) patients underwent mastectomy. Thirty-three (16.1%) patients who were initially candidates for mastectomy, were subsequently treated with BCS. Regarding the management of the axilla, 130 (63.4%) patients underwent breast surgery plus ALND without SLNB, and 75 (36.6%) underwent breast surgery plus SLNB. Of the latter group, 41 (54.7%) had positive sentinel node and underwent subsequent ALND, while eight (10.7%) patients and 26 (34.6%) patients had micro-metastatic and negative sentinel node, respectively and thus ALND was omitted. Regarding adjuvant treatment, 16 (7.8%) patients and 182 (88.8%) patients underwent post-operative systemic therapy and radiotherapy, respectively. On multivariate analysis, one independent factor of treatment of luminal-like, node positive BC was identified.

Table 1. Characteristics of 205 patients with luminal, node positive breast cancer treated with neo-adjuvant chemotherapy

Characteristics	Number (%)/mean (SD)
Patients	
Age (years)	
Post-menopausal	54.8 (11.9)
Pre-operative staging	136 (66.3%)
Mammography	191 (93.2%)
US*	205 (100%)
Biopsy°	205 (100%)
MRI	89 (43.4%)
Dimension pre-NAC (mm)	32 (17.1)
Stage pre-NAC	
- cT2	148 (72.2%)
- cT3	35 (17.1%)
- cT4	22 (10.7%)
-cN1	205 (100%)
NAC with anthracycline only	69 (33.7%)
NAC with anthracycline and taxanes	136 (66.3%)
Tumor	
Multifocal	47 (22.9%)
Multicentric	20 (9.8%)
Sub-type	
- Luminal A-like	124 (60.5%)
- Luminal B-like	81 (39.5%)
Histotype	
- Ductal	188 (91.7%)
- Lobular	11 (5.4%)
- Mucinous	6 (2.9%)
Grade G3	56 (27.3%)
Vascular invasion	74 (36.1%)
Single nodule	151 (73.7%)
pCR to NAC	34 (16.6%)
Dimension post-NAC (mm)	22 (18.9)
Stage post-NAC	
- ypT0	34 (16.6%)
- ypT1a	14 (6.8%)
- ypT1b	23 (11.2%)
- ypT1c	42 (20.5%)
- ypT2	78 (38.1%)
- ypT3	14 (6.8%)
- ypN0	44 (21.5%)
ypNmi	8 (3.9%)
- ypN1	47 (22.9%)
- ypN2	77 (37.6%)
- ypN3	29 (14.1%)

Table 1. Continued

Characteristics	Number (%)/mean (SD)
Surgical treatment	
- BCS	86 (42.0%)
- Mastectomy	119 (58.0%)
- SLNB not followed by ALND	34 (16.6%)
- SLNB followed by ALND	171 (83.4%)
Post-operative treatment	
- CHT	16 (7.8%)
- Radiotherapy	182 (88.8%)
- Endocrine	205 (100%)

SD: Standard deviation, US*: Breast and axillary ultrasound, Biopsy°: Breast and axillary ultrasound-guided biopsy, MRI: Magnetic resonance imaging, NAC: Neo-adjuvant chemotherapy, CHT: Chemotherapy, pCR: Pathological in-breast and axillary response to neo-adjuvant chemotherapy, BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection

Pathologic CR to NAC (29.1% vs 7.6% if pCR to NAC, odds ratio (OR) = 2.866, 95% confidence interval (95% CI) = 1.296-6.341, p = 0.009) was found to significantly increase the probability to receive BCS for luminal-like, node positive BC. Treatment details, univariate and multivariate analyses are summarized in Tables 1 and 2.

Oncological outcomes

After a mean follow-up of 53 months, 18/205 (8.8%) patients developed recurrence. In the BCS group, 4/86 (4.7%) and 6/86 (7.0%) had loco-regional recurrence and distant metastases, respectively. In the mastectomy group, 2/119 (1.7%) and 6/119 (5.0%) had loco-regional recurrence and distant metastases, respectively. All the patients in the BCS group who had loco-regional recurrence underwent salvage mastectomy. Patients with distant metastases were treated with systemic therapy. Overall, 15/205 (7.3%) patients died; 12 patients suffered a BC related death, while three patients died for other reasons. Moreover, the oncological outcomes of conservative and radical breast and axillary treatment were analyzed and compared. There was no significant difference in terms of DFS and OS between patients with luminal-like, node positive BC receiving BCS or mastectomy (p = 0.596, p = 0.134, respectively), and ALND or SLNB only (p = 0.661, p = 0.856, respectively) after NAC. Oncological outcomes are summarized in Table 3 and Figures 1 and 2.

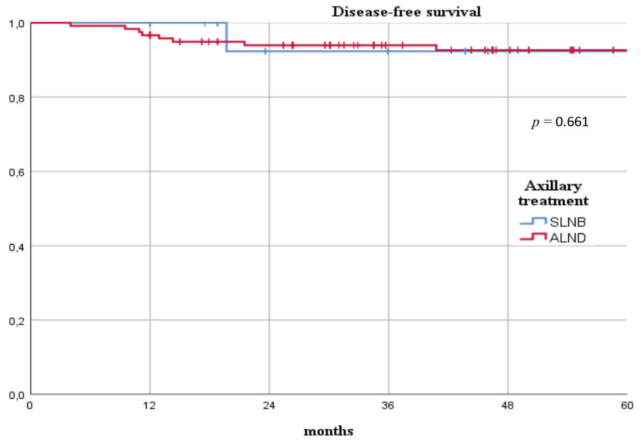

Figure 1. Disease-free survival of luminal, node positive breast cancer patients treated with neo-adjuvant chemotherapy according to axillary treatment

This figure depicts the recurrence curves of luminal, node positive breast cancer patients according to axillary treatment after neo-adjuvant chemotherapy.

ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy only

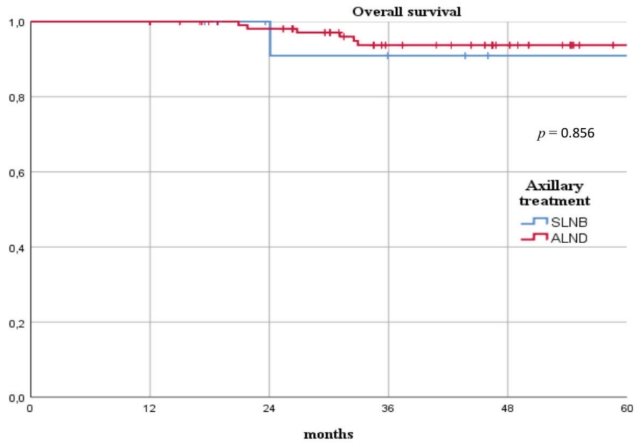

Figure 2. Overall survival of luminal, node positive breast cancer patients treated with neo-adjuvant chemotherapy according to axillary treatment

This figure depicts the survival curves of luminal, node positive breast cancer patients according to axillary treatment after neo-adjuvant chemotherapy.

ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy only

Discussion and Conclusion

The ability of NAC to evaluate the *in vivo* chemo-sensitivity of primary BC has emerged as a major prognostic tool in understanding individual patient outcome. Pathologic CR has been associated with improved long-term oncological outcomes in virtually every study and has emerged as a surrogate endpoint for survival in several NAC trials (29). However, the prognosis and responses to NAC differ according to the biological sub-type of BC. Generally, patients with luminal-like BC show good long-term oncological results, whereas those with TN and HER2-enriched disease have poor outcomes (16). Interestingly, it appears that the most aggressive biologic and tumor-related factors (high grade, high Ki-67, ER negativity) are more closely associated with achieving pCR. On the other hand, luminal-like BC is relatively resistant to NAC and pCR is less likely to occur, despite favorable long-term survival. A meta-analysis of 30 studies including 11,695 patients evaluating pCR after NAC found an overall pooled estimate of pCR of 19.2% (30). The probability of achieving pCR was seven times higher for HER2-enriched disease and five times higher for TN disease when compared to luminal-like BC. While pCR rates may be low in luminal-like sub-type, survival outcomes remain good, mainly because of favorable biological characteristics and benefits from adjuvant endocrine treatment. In 2012, a pooled analysis of 6,377 patients treated with anthracycline and taxane-based NAC showed that, in luminal-like BC, pCR did not have predictive power in terms of DFS and OS (18). Our study confirms the low pCR rate (16.6%) after NAC in luminal-like sub-type, and even though pCR

Table 2. Predictors of treatment (breast conserving surgery versus mastectomy) in luminal, node positive breast cancer patients treated with neo-adjuvant chemotherapy

Characteristics	BCS (n = 86) Tot. (%)	Mastectomy (n = 119) Tot. (%)	Univariate analysis	Multivariable analysis
			p-value	p-value OR (95% CI)
Demographic				
Age (years)				
- <55	47 (54.7%)	78 (65.6%)	0.165	-
- ≥55	39 (45.3%)	41 (34.4%)	-	
Post-menopausal				
- Yes	60 (69.8%)	76 (63.9%)	0.736	-
- No	26 (30.2%)	43 (36.1%)	-	
Pre-operative staging				
Stage pre-NAC				
- cT2	64 (74.4%)	84 (70.6%)	0.752	-
- cT3-4	22 (25.6%)	35 (29.4%)	-	
NAC				
- Anthracycline and taxanes	61 (70.9%)	75 (63.0%)	0.248	-
- Anthracycline only	25 (29.1%)	44 (37.0%)	-	
Tumor histotype				
- Ductal	79 (91.9%)	109 (91.6%)	0.872	-
- Lobular	5 (5.8%)	6 (5.0%)	-	
- Mucinous	2 (2.3%)	4 (3.4%)	-	
Vascular invasion				
- Yes	36 (41.9%)	38 (31.9%)	0.193	-
- No	50 (58.1%)	81 (68.1%)	-	
Single nodule				
- Yes	71 (82.6%)	80 (67.2%)	0.002[a]	0.221 0.628 (0.298-1.324)
- No	15 (17.4%)	39 (32.8%)	-	-
pCR to NAC				
- Yes	25 (29.1%)	9 (7.6%)	0.001[a]	0.009[a] 2.866 (1.296-6.341)
- No	61 (70.9%)	110 (92.4%)	-	-

BCS: Breast conserving surgery, n: Number, Tot.: Total, OR: Odds ratio, CI: Confidence interval, NAC: Neo-adjuvant chemotherapy, pCR: Pathological in-breast and axillary response to neo-adjuvant chemotherapy, [a]: Statistically significant

should not be used as a surrogate endpoint for improved survival in this setting, it has emerged as an independent predictive factor for breast conservation.

Neo-adjuvant chemotherapy is the treatment of choice for patients with large, operable BC. Its main effects include: decreasing the size and cellularity of the tumor; reducing the surgical resection range; and increasing the rate of BCS conversion, thus improving the cosmetic outcomes and quality of life. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial evaluated the facilitation of breast conservation in the NAC setting, and found increased rates of breast conservation in the NAC arm (67.8% vs 59.8%) (4). Additionally, results of the European Organization Research and Treatment of Cancer (EORTC) Trial 10902 showed a significant reduction in clinical tumor diameter to less than 2 cm from 14% at primary diagnosis to 47% after NAC, with a BCS conversion rate of 23% (31). In our study we retrospectively reviewed patients' and tumor characteristics, including: dimension, multifocality, and multicentricity and their surgical indication before NAC. The use of pre-operative systemic treatment allowed the performance of conserving surgery in 33 additional patients previously requiring mastectomy, increasing the rate of BCS by 16.1%.

Traditionally, all patients who presented with clinically node positive BC were recommended complete ALND, in order to eradicate the nodal basin of any lymph node disease, reducing the risk of loco-regional recurrence, and providing full pathologic nodal staging. Complete ALND remains an acceptable option for some patients with axillary metastases identified at the time of diagnosis. However, for patients receiving NAC, there is an increasing body of evidence supporting a more conservative axillary approach in patients with good clinical response. The American College of Surgeon Oncology Group (ACOSOG) Z1071 trial reported that approximately 65% of patients with HER2-enriched disease, 50% of patients with TN disease, and 21% of patients with luminal-

Table 3. Comparison of disease-free and overall survival of luminal, node positive breast cancer patients undergoing conservative or radical breast and axillary treatment after neo-adjuvant chemotherapy

Outcomes	BCS (n = 86)	Mastectomy (n = 119)	p-value	ALND (n = 171)	SLNB (n = 34)	p-value
	Mean (SD)			Mean (SD)		
DFS rate						
- 1-year	95.1%	98.8%		96.7%	100%	0.661
- 3-year	93.2%	94.7%	0.596	94.0%	92.3%	
- 5-year	92.6%	92.9%		92.6%	92.3%	
OS rate						
- 1-year	100%	100%		100%	100%	
- 3-year	90.7%	95.3%	0.134	93.7%	90.9%	0.856
- 5-year	90.7%	95.3%		93.7%	90.9%	

BCS: Breast conserving surgery, n: Number, ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy only, SD: Standard deviation, DFS: Disease-free survival, OS: Overall survival

like BC had pCR in the axilla (32). The benefits to avoiding unnecessary ALND for patients with strong response to NAC are clear, with a substantial reduction of the morbidity associated with the procedure, which may include paresthesias, pain, wound infection, seromas, and lymphedema. In our study, we showed that there was no significant difference in terms of DFS and OS between patients with luminal-like, node positive BC receiving ALND or SLNB only after NAC.

It is necessary to underline that our study has some limitations. Firstly, this is a single center study, subject to limitations due to its retrospective design, using observational data collected at a specific moment. Secondly, the evaluation of conversion from mastectomy to BCS was performed retrospectively. Despite these limitations, this study also presents several strong points. Definitions were clearly stated and strict inclusion criteria were used for the selection of a homogeneous group of luminal-like, node positive BC. All patients underwent pre-operative radiological staging, core needle biopsy in both breast and axilla, and post-NAC radiological response evaluation. Moreover, no patient was lost to follow-up.

In conclusion, our study confirms the low pCR rate after NAC in luminal-like, node positive BC. Pre-operative systemic treatment increases the rate of BCS. Although pCR should not be used as a surrogate endpoint for improved survival in luminal-like BC, it has emerged as an independent predictive factor for BCS. Additionally, in patients with axillary pCR, SLNB is a safe and acceptable procedure not associated with worse oncological outcomes.

Ethics Committee Approval: The present study complied with the guidelines for human studies. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The Institutional Review Board of Humanitas University Research Ethics Committee approved this retrospective study (no: H20-12-NAC, date: 12.12.2020).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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Radiological Underestimation of Tumor Size Influences the Success Rate of Re-Excision after Breast-conserving Surgery

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ABSTRACT

Objective: Failure to achieve adequate margins after breast-conserving surgery often leads to re-excision, either by repeat breast-conserving surgery (BCS) or by mastectomy. Despite the high frequency of this problem, the success rate of achieving adequate margins by repeat BCS is not well documented. The objective of this study was to determine the success rate of repeat BCS and identify the factors influencing that rate.

Materials and Methods: A retrospective review was performed of all women undergoing repeat BCS for inadequate margins after initial BCS in our breast unit between 2013 and 2019. Univariate and multivariate analyses were carried out to identify the factors influencing how often adequate margins were achieved after repeat BCS.

Results: One hundred fifty-four patients underwent repeat BCS after initially inadequate margins, of which adequate margins were achieved in 82%. Patients with successful repeat BCS had smaller tumors, had less underestimation of tumor size on imaging, and were less likely to have had cavity shaves taken at their initial BCS. A tumor size more than 50% larger than predicted by imaging was independently associated with failure of repeat BCS in multivariate analysis (odds ratio: 3.6, 95% CI: 1.41–9.20, p = 0.007). Underestimation of tumor size by imaging was commoner and more extensive in patients with larger tumors and those with ductal carcinoma in situ.

Conclusion: Re-excision by cavity shaves has a high success rate and should be offered to all patients who are deemed suitable for the procedure. Patients whose tumors are more than 50% larger than predicted by imaging should be counseled about the higher risk of failure.

Keywords: Breast-conserving surgery, breast imaging, breast neoplasms, margins of excision, re-excision

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Key Points

- In patients in whom initial breast-conserving surgery has not achieved adequate margins, repeat breast-conserving surgery is successful in 82% of cases.
- Underestimation of tumor size by imaging reduces the probability that repeat breast-conserving surgery will be successful.
- Underestimation of tumor size by imaging is commoner in patients with larger tumors and ductal carcinoma *in situ*.

Introduction

Breast-conserving surgery (BCS) is now firmly established as the standard of care for early breast cancer where feasible, with long-term follow-up demonstrating oncological safety (1). With ever-improving adjuvant treatment and understanding of tumor biology, local recurrence rates after BCS are low. Re-excision rates, on the other hand, despite improvement in recent years, remain high (2). With BCS performed on 180,000 women in the USA each year and a significant number of those requiring further surgery to obtain adequate margins, re-excision is clearly an area where improvements could have a significant impact on healthcare delivery (3).

For women requiring re-excision, a decision needs to be made on whether to perform repeat BCS, with further shaves of tissue removed at the inadequate margins, or proceed to mastectomy. Mastectomy guarantees that surgical treatment is complete and delivers an extremely high rate of margin clearance but is associated with an increased risk of short- and long-term morbidity and poorer body image (4, 5). Repeat BCS, on the other hand, allows the opportunity for conservation of the breast, although persistent inadequate margins may lead to a third or even a fourth operation, with increased operative risk, increased cost, poorer cosmesis, and a possible delay in adjuvant treatment (6-8). The decision on the type of re-excision is based primarily on the chance of repeat BCS successfully achieving an adequate margin, although the expected cosmetic

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result, the woman's attitude toward the risk of additional surgery, her suitability for an oncoplastic technique, and her degree of aversion to undergoing mastectomy also play a role. Given how often re-excision is necessary, the evidence base addressing factors that affect the success rate of repeat BCS is small.

The aim of this study was to determine the success rate of repeat BCS in achieving adequate margins and to identify clinical factors available at the time when the decision on the method of re-excision is made that would allow us to more accurately define that rate for each individual patient, allowing better informed decision making by patients and their surgeons on the method of re-excision.

Materials and Methods

All patients undergoing initial BCS in our breast unit between January 2013 and October 2019 were identified from a prospectively compiled database. Those undergoing re-excision by repeat BCS were included in the study. The exclusion criteria were patients undergoing neoadjuvant chemotherapy; patients where the initial BCS was an excision biopsy for diagnosis; patients undergoing repeat BCS by an oncoplastic reduction technique; patients with phyllodes tumors; patients undergoing repeat surgery to the axilla only; and patients undergoing repeat surgery to the breast for multifocal disease, early recurrence, or surgical complications. Approval was given by the local research governance committee. Patients routinely underwent preoperative digital mammography using Hologic Selenia Dimensions (Hologic, Marlborough, MA, USA) and ultrasound using Toshiba Xario (Toshiba, Tokyo, Japan) equipment. Magnetic resonance imaging (MRI) was not used routinely but was employed in scenarios where it was felt likely to alter management, particularly in patients with lobular tumors or with a marked discrepancy in tumor size between the mammography and ultrasonography results. When used, MRI was performed with either GE Optima (GE Healthcare, Chicago, IL, USA) or Siemens Sola (Siemens, Munich, Germany), both 1.5 tesla wide bore with 16 and 18 channel coils, respectively.

The choice of initial surgical approach, either mastectomy or BCS, was made by the multidisciplinary team in conjunction with the patient, taking into account factors such as radiological prediction of tumor size, breast size, tumor biology, genetic status, and comorbidities. The decision on whether to perform re-excision in patients with inadequate margins, as well as whether to achieve this by mastectomy or repeat BCS, was also made by the multidisciplinary team in conjunction with the patient, taking into account factors such as the number of involved margins, pathological tumor size, and perceived cosmetic outcome.

The multidisciplinary team followed the United Kingdom guidelines for adequate margin distance in invasive and non-invasive disease. The minimum adequate margin decreased to 1 mm during the study period, with the policy of the multidisciplinary team also changing to mirror these guidelines. Patients with an unsatisfactory deep or superficial margin were not routinely re-excised if the initial excision was known to extend to the pectoral fascia or subcutaneous tissue. The technique of planned circumferential cavity shaving in addition to wide local excision was not used in this study. Unplanned targeted cavity shaves were taken during the initial BCS at the operating surgeon's discretion if it was felt that a particular margin was at risk of being involved, either because of visualization or palpation of the tumor at the edge of the wide local excision specimen or breast cavity, or because of concern on intraoperative specimen radiology. Intraoperative radiology was performed for all wire-localized excisions but not for excisions where the tumor was palpable. No intraoperative pathological assessment of margins was performed.

The potential factors predicting the success of BCS investigated were age at the time of initial surgery; radiological tumor size; presence of ductal carcinoma *in situ* (DCIS); presence of DCIS only; pathological tumor size; Bloom-Richardson-Elston grade; tumor type; multifocality; axillary lymph node involvement; number of involved radial margins; whether targeted cavity shaves were taken at initial surgery; presence of lymphovascular invasion; estrogen receptor (ER) status; and human epidermal growth factor receptor 2 (HER2) status.

Assessment of the maximum diameter of the radiological malignancy was made by a consultant breast radiologist while performing the breast ultrasound or reporting the images of the mammogram and, if performed, the MRI. The radiological tumor size was defined as the largest of these measurements, irrespective of modality. This measurement was chosen as it is likely to be the measurement used both to decide whether to perform BCS initially and to plan the size of the resection specimen removed if BCS is performed.

Pathological tumor size was defined as the greatest diameter of the whole tumor, including any DCIS, as measured by a consultant pathologist. If tumors were multifocal, the size of the largest focus was used. If any additional tumor was found in targeted cavity shaves at the initial BCS, this was added to the pathological tumor size. Additional tumor removed at the repeat BCS was not added to the pathological tumor size for the purpose of the results of this study as this information is not available at the time when the decision on the method of re-excision is made and so could not contribute to the aims of this study. It was, however, used in determining the total tumor size used in planning the patients' adjuvant treatment.

The pathological tumor size to radiological tumor size ratio (PRR) was used as a measure of the degree of radiological underestimation or overestimation of tumor size. This was calculated by dividing the pathological tumor size by the radiological tumor size. A higher PRR signifies a greater degree of radiological tumor size underestimation.

Patients with Paget's disease of the breast were excluded from analysis involving radiological tumor size. Patients with pure DCIS were excluded from analysis involving grade, ER status, HER2 status, and lymphovascular invasion as these are not routinely recorded in our institution for these patients. Pathology reports from the re-excision specimen were examined for the presence of any DCIS or invasive carcinoma and whether the re-excision had achieved adequate margins.

The authors state that the study protocol has been approved by the Northern Health and Social Care Trust research committee (decision number: NT20-274636-02 date: June 10th, 2020).

Statistical analysis

Statistical analysis was performed using SPSS (SPSS Statistics for Macintosh, Version 24.0; IBM Corp, Armonk, NY, USA). Continuous variables were assessed by the Student's t-test for parametric data and Mann-Whitney U and Kruskal-Wallis tests for non-parametric data, where appropriate. Categorical data was assessed by Pearson's chi-square test and Fisher's exact test, where appropriate. Univariate analysis was performed to assess the associations between potential predictive factors and whether repeat BCS achieved an adequate margin. Odds ratios (ORs) for failure of repeat BCS were calculated

for each variable. Variables found to affect the success of repeat BCS in univariate analysis, with a threshold of $p<0.10$, were included in a multivariate binary logistic regression analysis, with a significance threshold of $p<0.05$.

Strengthening the reporting of observational studies in epidemiology (STROBE) reporting guidelines were followed when reporting this study.

Results

One thousand one hundred thirty-four patients underwent initial BCS during the study period. Two hundred twenty (16.5%) of these underwent reoperation for inadequate margins. Sixty-six underwent mastectomy, leaving 154 patients undergoing repeat BCS. These 154 patients formed the study group. All patients had ultrasonography and mammography, and seven had MRI. Not all patients with a lobular element had preoperative MRI, as the core biopsy had suggested ductal carcinoma, but the final pathology confirmed mixed ductal and lobular carcinoma. The cohort's surgical treatment is shown in Figure 1. One hundred twenty-six patients (82%) had successful repeat BCS, 104 who had no residual disease and 22 who had residual disease but adequate excision margins. One patient had a successful third BCS, while 27 patients underwent mastectomy as a third procedure.

Thirty-two patients (21%), including one with Paget's disease of the breast, had pure DCIS and were excluded from analyses on ER and HER2 status, lymphovascular invasion, and grade. All 122 patients with invasive disease had lymph node excision, 16 by axillary clearance and 106 by sentinel node biopsy. The patient with Paget's disease also had sentinel node biopsy.

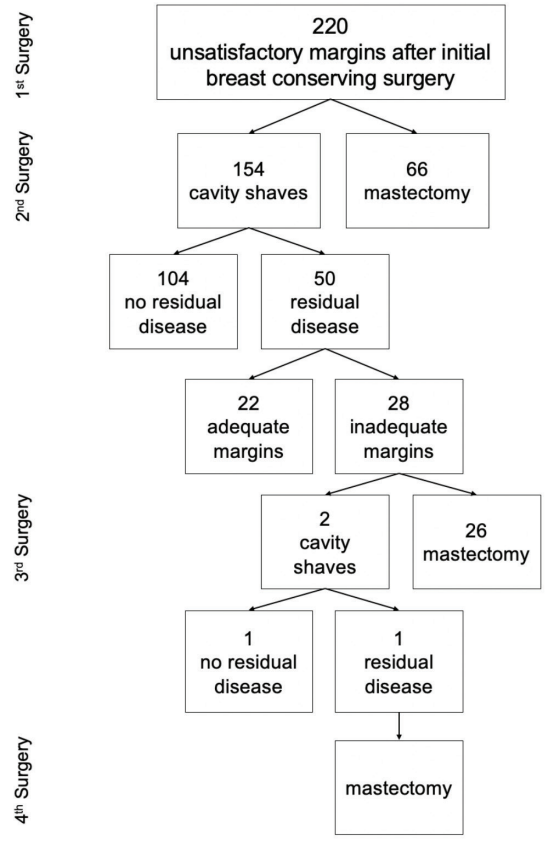

Figure 1. Study group assignment by surgical treatment. In all, 16.5% of patients had a second operation after initial BCS, 2.1% had a third operation, and 1 patient (0.07%) underwent a fourth

BCS: Breast-conserving surgery

Patient characteristics and pathological factors for the groups with successful and unsuccessful BCS are shown in Table 1. Patients with successful repeat BCS had smaller tumors and a lower PRR and were less likely to have had targeted cavity shaves taken at their initial BCS. They also tended to be of a lower grade, but this trend did not reach significance. The success rate of repeat BCS decreased as the degree of tumor size underestimation by radiology increased (Figure 2).

Ninety-four percent of patients with two or three of the factors predicting successful repeat BCS did have successful repeat BCS, whereas only 61% of patients with none of these factors had successful repeat BCS (OR for failure with no factors predicting success was 9.58, 95% CI: 2.94–31.21, $p = 0.0001$).

Univariate and multivariate analyses for failure of repeat BCS are shown in Table 2. Underestimation of tumor size by radiology, with a PRR of over 1.5, independently predicted failure of repeat BCS in multivariate analysis.

Underestimation of tumor size by radiology was commoner in patients whose specimens contained DCIS. The average PRR was 1.21 in patients with invasive disease only and 1.99 in patients with DCIS ($p = 0.00398$). Eighty-eight percent of patients with invasive disease had a PRR below 1.5, whereas only 54% of patients with DCIS did ($p = 0.00266$).

Underestimation of tumor size by radiology was more likely as the pathological tumor size increased (Figure 3). Targeted cavity shaves were more likely to have been taken at the initial BCS where the tumor size was underestimated by radiology ($p = 0.00988$, Figure 4).

Tumor size measurement was similar between mammography and ultrasonography (mean 15.5 mm vs 16.2 mm, $p = 0.271$). In the seven patients undergoing MRI, the mean MRI tumor measurement was larger than that in the cohort as a whole at 26.3 mm, but these seven patients also had larger tumor measurements on mammography (mean 26 mm, $p = 0.95$) and ultrasonography (mean 21 mm, $p = 0.41$).

There was no difference in the degree of underestimation of tumor size between mammography and ultrasonography, with a mean PRR of 1.91 for mammography and 1.92 for ultrasonography ($p = 0.60$).

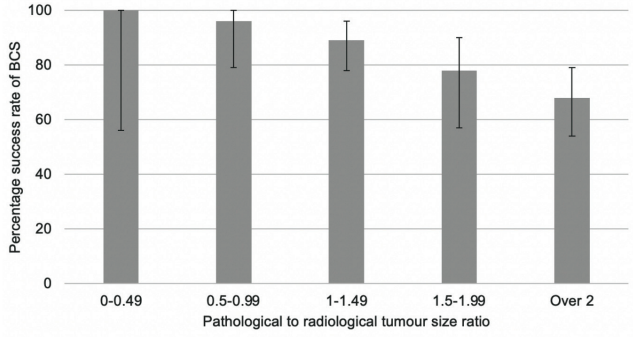

Figure 2. Success rate of repeat BCS by PRR. Repeat BCS was less likely to be successful in patients with a higher degree of tumor size underestimation by radiology

BCS: Breast-conserving surgery, PRR: Pathological tumor size to radiological tumor size ratio

In the small number of patients undergoing MRI, the mean PRR calculated on the basis of the MRI measurement was lower at 1.48, corresponding to a lesser degree of tumor size underestimation, but this was not significant (p = 0.234 vs mammogram and p = 0.238 vs ultrasound).

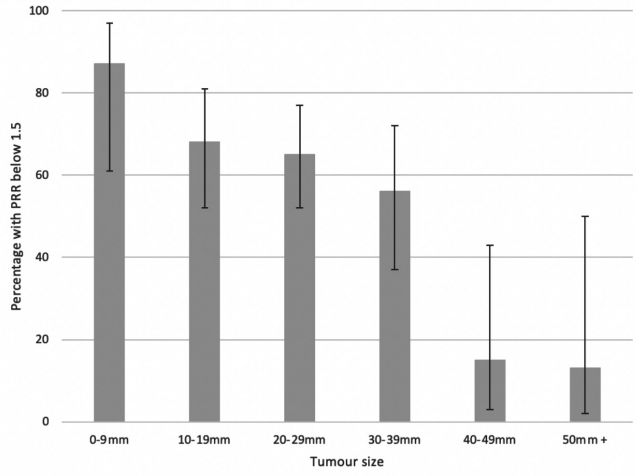

Figure 3. PRR by pathological tumor size. Patients with larger tumors were more likely to have tumor size underestimation by radiology

PRR: Pathological tumor size to radiological tumor size ratio

Discussion and Conclusion

This study focused on the common problem of re-excision after BCS, in particular the method of that re-excision. We found a high rate of success of repeat BCS but showed that underestimation of the tumor size by imaging independently predicted failure.

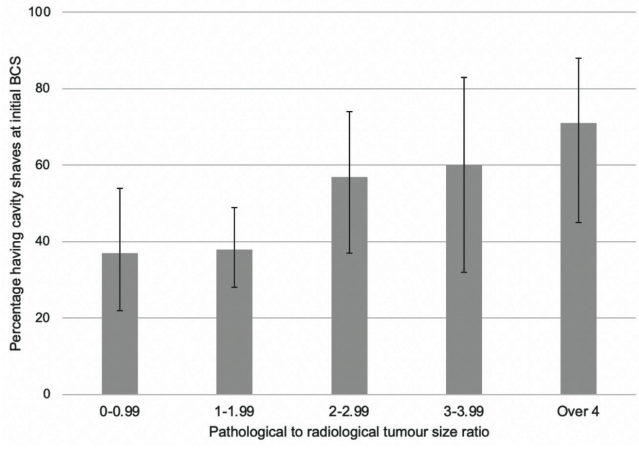

Figure 4. Rate of cavity shaves taken at initial BCS by PRR. Tumor size underestimation by radiology made it more likely that surgeons took unplanned targeted shaves at initial BCS

BCS: Breast-conserving surgery, PRR: Pathological tumor size to radiological tumor size ratio

Table 1. Comparison of patients with successful and unsuccessful repeat BCS

Factor	Successful 127 patients	Unsuccessful 27 patients	p-value
Mean age (range)	56 (32–83)	59 (46–79)	0.1172
Any DCIS present	105/127 (83%)	25/27 (93%)	0.2532
Pure DCIS	27/127 (21%)	5/27 (19%)	0.7499
Mean radiological tumor size (range)	16 mm (3–40)	14 mm (2–27)	0.3030
Mean pathological tumor size (range)	23 mm (2–75)	29 mm (6–50)	0.0274
Mean PRR (range)	1.72 (0.3–8)	2.56 (0.9–7)	0.0005
Multifocal tumor present	12/127 (9%)	3/27 (11%)	0.7194
IDC	91/100 (91%)	21/22 (95%)	0.6881
Mean specimen weight (range)	50 g (5–164)	51 g (11–140)	0.6312
Grade			
1	25/100 (25%)	2/22 (9%)	
2	47/100 (47%)	10/22 (45%)	0.1469
3	28/100 (28%)	10/22 (45%)	
ER positive	87/100 (87%)	19/22 (86%)	0.9361
HER2 negative	85/100 (85%)	17/22 (77%)	0.3754
LVI present	33/100 (33%)	6/22 (27%)	0.6020
Involved nodes present	32/101 (32%)	6/22 (27%)	0.6891
Mean number involved margins (range)	0.55 (0–2)	0.74 (0–2)	0.2713
Any involved margin	56/127 (44%)	15/27 (56%)	0.2780
Targeted shaves taken at initial surgery	52/127 (41%)	17/27 (63%)	0.0367

DCIS: Ductal carcinoma *in situ*, PRR: Pathological tumor size to radiological tumor size ratio, IDC: Infiltrating ductal carcinoma, ER: Estrogen receptor, HER2: Human epidermal growth factor receptor 2, LVI: Lymphovascular invasion

Table 2. Univariate and multivariate analysis of factors predicting failure of repeat BCS

Factor	Failure rate of BCS	Univariate analysis			Multivariate analysis		
		OR for BCS failure	95% CI	p-value	OR for BCS failure	95% CI	p-value
Age							
≥50	19%	1					
<50	14%	0.67	0.25–1.79	0.4201			
DCIS							
Present	8%	1					
Absent	19%	2.62	0.58–11.88	0.2532			
Pure DCIS							
Yes	18%	1					
No	16%	0.84	0.29–2.43	0.7518			
Tumor size							
<20 mm	9%	1					
≥20 mm	22%	2.67	0.95–7.53	0.0554	2.10	0.71–6.20	0.178
PRR							
≤1.5	8%	1					
>1.5	29%	4.34	1.71–11.03	0.0011	3.60	1.41–9.20	0.007
Multifocal tumor							
No	17%	1					
Yes	20%	1.20	0.31–4.57	0.7283			
Tumor type							
IDC	19%	1					
ILC or mixed	10%	0.48	0.06–4.01	0.6881			
Grade							
1	7%	1					
2	18%	2.66	0.54–13.09	0.3216			
3	26%	4.46	0.89–22.36	0.1020			
LVI							
Absent	19%	1					
Present	15%	0.76	0.27–2.13	0.6033			
Axillary nodes							
Not involved	19%	1					
Involved	16%	0.81	0.29–2.26	0.6892			
Any margin involved							
No	14%	1					
Yes	21%	1.58	0.69–3.66	0.2774			
Margins involved							
0	14%	1					
1	19%	1.41	0.56–3.54	0.4666			
2	26%	2.11	0.64–6.95	0.3024			
Any targeted shaves taken at initial BCS							
Yes	12%	1					
No	25%	2.45	1.04–5.78	0.0368	1.91	0.77–4.71	0.162

Table 2. Continued

Factor	Failure rate of BCS	Univariate analysis			Multivariate analysis		
		OR for BCS failure	95% CI	p-value	OR for BCS failure	95% CI	p-value
ER status							
Positive	18%	1					
Negative	19%	1.06	0.27–4.08	0.9361			
HER2 status							
Negative	17%	1					
Positive	25%	1.67	0.53–5.20	0.5242			

BCS: Breast-conserving surgery, OR: Odds ratio, CI: Confidence interval, DCIS: Ductal carcinoma *in situ*, PRR: Pathological tumor size to radiological tumor size ratio, IDC: Infiltrating ductal carcinoma, ILC: Infiltrating lobular carcinoma, LVI: Lymphovascular invasion, ER: Estrogen receptor, HER2: Human epidermal growth factor receptor 2

Re-excision is currently a widely debated topic in breast surgery. Substantial efforts have been made in recent times to reduce rates of re-excision. Novel surgical techniques, including intraoperative ultrasound, intraoperative cytology, in-theater specimen radiology, and circumferential cavity shaving, have been introduced to reduce margin involvement (9, 10). Much work has also been carried out investigating the size of the resection margin that gives the optimum balance between unnecessary re-excision and future local recurrence. While debate remains over what constitutes an adequate margin, with United Kingdom (UK) guidelines recommending a 1 mm margin for invasive disease, while United States (US) guidelines mandate only no tumor on ink, it is clear that avoiding involved margins is essential in reducing the tumor burden sufficiently so that the combination of surgery and adjuvant therapy can lead to extremely low local recurrence rates (11). The ideal scenario would clearly be to achieve this at initial BCS; however, if this is not achieved, re-excision still reduces local recurrence, although possibly not to the same level as if adequate margins were achieved at the initial BCS, particularly if the re-excision contains residual disease (12–14). Inaccurate targeting of re-excision may at least partially explain this. Particularly with mobilization of glandular flaps to fill the lumpectomy defect at initial BCS, the exact site of margin involvement may not be correctly identified at repeat BCS, potentially leaving residual disease in the breast despite a histologically clear re-excision specimen. The sharing of adverse prognostic indicators between the need for re-excision and local recurrence may also contribute. While local recurrence rates may be higher, overall survival in patients undergoing re-excision is no different to those having successful initial BCS, whether the re-excision is achieved by repeat BCS or mastectomy (15). Although re-excision rates are improving, with a meta-analysis finding a re-excision rate of 14% in recent studies, substantially lower than historic rates, the burden of re-excision remains high (2). Given how frequently the decision on the method of re-excision needs to be made, very few studies have looked at the rate of success of re-excision BCS or investigated the factors that influence it. Our study showed a success rate of re-excision BCS of 82%. It must be borne in mind that this was a group of patients considered appropriate candidates for repeat BCS, and 30% of patients with inadequate margins during the study period chose mastectomy as their method of first re-excision and so were not included in this study group. Fisher et al. also showed a success rate for repeat BCS of 82%, Morrow et al. (16) 93%, and Coopey et al. (17) 91% in registry-based cohort studies, the focus of which was not on factors influencing the success of repeat BCS (15–17). Houvenaeghel et al. (18) showed a success rate of repeat BCS of 87%, with patients under 50 and those with larger or multifocal tumors less likely to have successful repeat BCS. In a cohort of patients with invasive lobular carcinoma, Piper et al. found a success rate of repeat BCS of 74%, with higher success rates in those who were older and had fewer involved nodes. Patients whose repeat BCS was unsuccessful also had larger tumors in their study, but this did not reach significance (19).

This study did not investigate the type of re-excision to offer if repeat BCS did not achieve adequate margins. In our study, all but two patients in this situation underwent mastectomy. Our policy is to avoid more than three operations on the breast, if possible, based on concerns regarding excess tumor burden, delay to adjuvant therapy, and previous national guidance. Of the two patients who underwent a third BCS in our cohort, one achieved adequate margins, while the other underwent mastectomy as a fourth operation. Other series have addressed this situation, with Cellini et al. (20) showing a 61% success rate and Coopey et al. (17) a 67% success rate at third BCS and 25% at fourth BCS, with a 2% local recurrence rate in those patients at 64-month median follow-up.

Underestimation of tumor size by radiology is a well-recognized problem in the literature. It has previously been shown that radiological tumor size underestimation influences the success of initial BCS, with a greater degree of underestimation leading to a greater need for re-excision (21). Tumor size underestimation has also been shown to increase the probability of residual disease in the re-excision specimen (22). We showed that a pathological tumor size exceeding the radiological measurement by more than 50% independently predicted a higher failure rate of repeat BCS, to our knowledge the first study to demonstrate this in the literature. The rate of underestimation was generally high in this study as it included only patients who had failed initial BCS, a group known to have a higher rate of underestimation (21). The imaging modality may play a role in tumor size underestimation, having previously been shown to be commoner with ultrasonography than with mammography (23). Ultrasonography is operator dependent, and underestimation may be due to factors such as failure to measure the halo around the tumor or the tumor size exceeding the size of the transducer. In tumors with a significant component of DCIS, the tumor extent may be underestimated on ultrasound as the typical microcalcifications are less readily visible or measurable. Non-

calcified DCIS may lead to tumor underestimation on mammography (24–26). We found no difference in the degree of size underestimation between mammography and ultrasonography in this study, although we did find that underestimation of tumor size was commoner in patients with DCIS and also with larger tumors, findings echoed in other studies (25, 27). Radiological underestimation of tumor size has been shown to occur less often with MRI, although MRI can also lead to overestimation, possibly due to enhancement of background parenchyma (24, 28). We found that MRI underestimated tumor size to a lesser extent than mammography or ultrasound, although too few patients in this cohort underwent MRI to allow a useful comparison.

The pathological tumor type also influences the degree of radiological size underestimation. Lobular primaries are at higher risk of radiological underestimation, due to their diffuse growth pattern, with less distortion of the breast architecture and a lack of difference in density or echogenicity between the tumor and normal breast tissue. Lobular tumors are also more likely to exhibit irregular contours and more diffuse margins and have a higher likelihood of satellite foci (29). We did not find a higher rate of underestimation in lobular tumors, although they made up only 10 patients of our cohort.

We found that patients with a greater degree of radiological underestimation were more likely to have had targeted cavity shaves taken at the time of their initial BCS. We believe this is because the surgeon's initial excision is guided by the preoperative radiological tumor size, with a larger tumor than expected only being detected intraoperatively, by direct palpation, visualization, or intraoperative specimen radiology and leading to additional tissue being taken. To our knowledge, this is the first time this correlation has been reported in the literature.

A limitation of the study is that patients were from a single center, which limited the number of patients, and the treatment decisions made may not be replicated in other centers. We followed UK guidelines on an adequate margin distance of 1 mm, different to US and other European guidelines, which may make this study less applicable in countries following those guidelines. A further limitation is that we had no data on cosmetic outcomes for patients who had re-excision, relying on margin adequacy as the only marker for success of the repeat BCS.

Further work could explore the extent to which patients value particular factors, such as the risk of additional surgery, cosmesis, delay in adjuvant treatment, or potential avoidance of radiotherapy when making the decision on whether to have repeat BCS or to choose mastectomy.

In conclusion, re-excision by cavity shave has a high success rate and should be offered to all patients who are thought suitable. Patients whose tumors are more than 50% larger than was predicted on imaging should be counseled about the higher risk of failure with consideration given to larger excisions or oncoplastic techniques.

Ethics Committee Approval: The authors state that the study protocol has been approved by the Northern Health and Social Care Trust research committee (decision number: NT20-274636-02 date: June 10th, 2020).

Informed Consent: Patient-level consent was waived by the committee as no treatment decisions were altered by the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: D.S., J.A., B.M.; Concept: D.S., B.M.; Design: D.S., B.M.; Data Collection and/or Processing: D.S., J.A., B.M.; Literature Search: D.S., J.A., B.M.; Writing: D.S., J.A., B.M.

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

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Original Article

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Assessment of Leptomeningeal Carcinomatosis Diagnosis, Management and Outcomes in Patients with Solid Tumors Over a Decade of Experience

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ABSTRACT

Objective: Leptomeningeal carcinomatosis (LMC), a common complication of advanced malignancies, is associated with high morbidity and mortality, yet diagnosis and treatment decisions remain challenging. This study describes the diagnostic and treatment modalities for LMC and identifies factors associated with overall survival (OS).

Materials and Methods: We performed a single-institution retrospective study (registration #: OSU2016C0053) of 153 patients diagnosed with LMC treated at The Ohio State University, Comprehensive Cancer Center, (OSUCCC)-James between January 1, 2010 and December 31, 2015.

Results: Median age at diagnosis was 55.7 years, and 61% had Eastern Cooperative Oncology Group baseline performance status ≤1. Most common primary tumors were breast (43%), lung (26%), and cutaneous melanoma (10%). At presentation, most patients were stage III-IV (71%) with higher grade tumors (grade III: 46%). Metastases to bone (36%), brain (33%), and lung (12%) were the most common sites with a median of 0.5 years (range, 0-14.9 years) between the diagnosis of first metastasis and of LMC. 153 (100%) patients had MRI evidence of LMC. Of the 67 (44%) who underwent lumbar puncture (LP), 33 (22%) had positive cerebrospinal fluid (CSF) cytology. Most patients received radiotherapy for LMC (60%) and chemotherapy (93%) for either the primary disease or LMC. 28 patients received intrathecal chemotherapy, 22 of whom had a primary diagnosis of breast cancer. 98% died with median OS of all patients was 1.9 months (95% CI: 1.3-2.5 months).

Conclusion: Despite improved treatments and targeted therapies, outcomes of LMC remain extremely poor. Positive CSF cytology was associated with lower OS in patients who had cytology assessed and specifically in patients with breast cancer. CSF cytology serves as an important indicator for prognosis and helps aid in developing individualized therapeutic strategies for patients with LMC.

Keywords: Leptomeningeal carcinomatosis, breast cancer, metastasis, cerebrospinal fluid, magnetic resonance imaging

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Key Points

- LMC most commonly presents with late-stage cancers with cancers of the breast, lung and melanoma being the most common primary cancers.
- Diagnosis of LMC may be challenging and imaging with MRI brain and spine was most frequently used in our study as an aid in diagnosis and in some cases as the primary tool for diagnosis.
- CSF cytology is the gold standard for diagnosis but is not always technically possible to obtain as demonstrated by only 67 of 153 patients in this review having CSF sampled.

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- Prognosis was worse in patients with positive CSF cytology versus equivocal or negative cytology.
- Treatment of LMC either by intrathecal chemotherapy, radiation to the brain or spine, or systemic therapy was associated with an improvement in survival versus no treatment.

Introduction

Leptomeningeal carcinomatosis (LMC) is defined as metastatic involvement of the leptomeninges, subarachnoid space and cerebrospinal fluid (CSF) (1). Malignant tumor cells spread and disseminate to the subarachnoid space by hematogenous, perineural, lymphatic, or perivascular mechanisms or by direct extension from superficial brain metastases or bone metastases of the calvarium or spine (2-4). The incidence of LMC is increasing as patient survival improves with advances in the management of metastatic solid tumors and as magnetic resonance imaging (MRI) becomes more widely utilized (5, 6). LMC occurs in approximately 4%–15% of patients with malignant solid tumors, most commonly melanomas and malignancies of the breast, lung, and gastrointestinal organs (7-11). Signs and symptoms of LMC include headaches, vomiting, seizures, focal neurologic deficits, radicular neck and back pain, cerebellar dysfunction, altered mental status, cauda equina syndrome, dizziness, or syncope (12-14). The sensitivity and specificity of MRI in the diagnosis of LMC is difficult to estimate due to poor concordance with the gold standard diagnostic test of positive CSF cytology (15, 16). MRI with and without contrast is the initial and often the sole diagnostic tool for LMC (17). Definitive diagnosis of LMC depends on the presence of malignant cells in the CSF, but sensitivity is limited at about 50%–60% for the first lumbar puncture (LP) (6, 18, 19). If the first CSF analysis is negative, a second LP can increase sensitivity to 80%–85% (20). As a result of low sensitivity and patient intolerance one or more LPs, a probable diagnosis of LMC is made when MRI findings are present in the setting of systemic malignancy, even in the absence of positive CSF cytology (16).

Once diagnosed with probable or definitive LMC, median survival time for patients is 2–6 months with treatment (21-25). Most treatment recommendations are based on clinical experience or studies with a low level of evidence due to a lack of prospective, randomized trials for patients with LMC (26). Intrathecal chemotherapy is the direct instillation of chemotherapy into the subarachnoid space, making it a promising treatment strategy. Intra-CSF pharmacotherapy should be reserved mainly for patients with a positive cytology on LP given that clearance of CSF cytology is used as one indicator for efficacy of this treatment (27). This is usually provided via an Ommaya reservoir after adequate CSF flow is confirmed using ^{111}Indium-DTPA flow study.

Whole Brain Radiotherapy (WBRT) with whole spine irradiation can target the entire craniospinal axis and thus a larger area of disease burden in LMC, however its use is limited by significant myelotoxicity (26). Focal external beam radiation to areas of bulky leptomeningeal involvement of the spine causing CSF obstruction can be utilized to relieve symptoms and allow for the administration of intrathecal administration (26, 28). The survival benefit of the various radiation therapy modalities in LMC is unclear.

We conducted a retrospective study to assess the diagnosis, management and outcomes of leptomeningeal carcinomatosis at The Ohio State University.

Materials and Methods

Study design and data collection

This study was an IRB-approved (registration #: OSU2016C0053) retrospective chart review of clinical and histopathologic data from patients treated at The Ohio State University Comprehensive Cancer Center, (OSUCCC)-James that was initially approved on 05/04/2016 between January 1st, 2010 and December 31st, 2015. Eligible patients were identified by ICD-9 and ICD-10 codes (198.4/ C79.32, C79.49, respectively) and included patients who were diagnosed with leptomeningeal carcinomatosis or unspecified meningeal disease, as well as patients who were diagnosed with a malignant solid tumor, who had undergone a procedure indicative of leptomeningeal carcinomatosis according to current procedural terminology (CPT) codes. These procedures included insertion of cerebrospinal fluid drainage device or catheter, LP, intrathecal infusion or injection of a therapeutic or prophylactic substance, injection or infusion of cancer chemotherapeutic substance with destruction of blood brain barrier, or MRI imaging of the brain or spinal cord. Patients without LMC, patients with LMC secondary to leukemia, lymphoma, or primary central nervous system malignancies, patients with incomplete clinical data and those treated at other institutions were excluded. Per EANO-ESMO Clinical Practice Guidelines, MRI is the gold standard imaging tool for imaging suspected cases of LMC. Given the technical challenges of doing a lumbar puncture on some poor performance patients, we defined a case of LMC as having either positive CSF cytology or MRI imaging indicative of LMC. Of 469 medical records reviewed, 153 patients were determined eligible.

Data for the eligible patients were initially obtained from The Ohio State University Information Warehouse and uploaded into REDCap (29). Data missing from the initial query were populated using manual review of each patient's electronic medical record.

Outcome measures

The primary objectives of this study were to assess the overall survival (OS) of patients with LMC at the OSU-CCC James, and to examine if primary tumor characteristics, diagnostic information, management modalities (locoregional, systemic, or combined therapy) and demographic factors were associated with OS. We performed a specific subgroup analysis to assess treatment strategies and outcomes among LMC patients with primary breast cancer overall and each histologic subtype of breast cancer including hormone receptor positivity.

A change in treatment after LMC diagnosis was defined as a patient receiving any of the following new treatments or changes in initial therapy: focal radiation therapy to brain metastases, bulky sites of LMC burden or whole brain radiation therapy (WBRT); initiating IT chemotherapy, discontinuing previous systemic therapy, or initiating new systemic therapy. If a patient did not undergo any of the previously mentioned changes, they were considered as having no new treatment, even if continuing with any previous systemic therapy treatments or opting for supportive care alone.

Statistical analysis

Demographic and clinical characteristics were summarized using descriptive analysis reported as medians and interquartile range for continuous variables and frequencies and percents for categorical variables. Overall survival (OS) was defined as the time from the date of diagnosis to date of death due to any cause or last known follow-up. Patients were censored at the date last known to be alive. OS estimates were generated using Kaplan-Meier methods and compared using log-rank tests. All data analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) or Stata 14 (StataCorp LLC, College Station, TX). For comparison of continuous data of one variable between two groups, student's t-test was used. A two-sided p-value of <0.05 was considered significant in all analyses.

Results

Demographic features and clinical findings

A summary of demographic and clinical characteristics of eligible patients is displayed in Table 1. Eligible patients were predominately Caucasian (84%), with a median age at LMC diagnosis of 55.7 years (range: 25.0–84.9 years). The most common sites of primary tumor were breast, lung, and melanoma (43%, 26%, and 10%, respectively). Tumors associated with LMC were characterized by high grade histology (3% grade 1, 18% grade 2, and 46% grade 3), advanced stage disease at presentation (Stage I 7%, Stage II 17%, Stage III 25%, and Stage IV 46%), and nodal involvement (71%). In patients with metastases prior to LMC diagnosis, the most common sites were bone (36%), brain (33%), and lung (12%). The baseline Eastern Cooperative Oncology Group (ECOG) performance status at the time diagnosis of LMC was <1 in 61% ≥2 in 35% of patients.

Outcomes

Among this cohort, there were 150 (98%) observed deaths. The median OS was 1.9 months [95% confidence interval (CI): 1.3, 2.5]. The median time from primary cancer diagnosis to development of LMC was 2 years [interquartile range (IQR): 1–5.4 years]. The median time from initial metastatic disease to development of LMC was 0.5 years (IQR: 0–1.9 years) overall and was similar among primary cancer subtypes. Breast cancer was associated with the longest interval from metastasis to LMC of 0.7 years (IQR: 0.0–2.4 years), and lung cancer was associated with the shortest interval of 0.5 years (IQR: 0.0–0.8 years).

Differences were noted in the Kaplan-Meier estimates for OS between primary cancer diagnoses. The median OS in primary breast cancer was 2.4 months (95% CI: 1.2, 4.4), primary lung cancer was 1.3 months (95% CI: 0.9, 2.1), primary melanoma was 1.7 months (95% CI: 0.8, 3.5), and other primary cancers was 2.6 months (95% CI: 0.7, 3.5) (analysis of variance p = 0.012) (Figure 1). There was no difference detected in OS between ECOG performance status groups with a median OS of 2.0 months (95% CI: 1.5, 2.8) for patients with ECOG performance status 0–2 and 0.7 months (95% CI: 0.5, 3.2) for those with ECOG performance status 3 or 4 (p = 0.255).

Diagnostic findings

MRI of the brain and/or spine was performed in all patients (100%), and of those, 97% of patients had radiographic evidence of LMC. Figure 2 (a, b) shows an example of an MRI brain and lumbar spine with leptomeningeal enhancement consistent with LMC. Of the 67 patients who underwent LP, CSF cytology was positive in 49%,

Table 1. Demographic Summary

		Total (n = 153)
Age at LMC diagnosis	Median [IQR]	55.7 years [48, 62.5]
Race	White	128 (84%)
	Black	16 (10%)
	Other	9 (6%)
Site of primary cancer diagnosis		
Breast		66 (43%)
Lung		40 (26%)
Melanoma		16 (10%)
Head/Neck		8 (5%)
Renal		2 (1%)
Ovarian		3 (2%)
Prostate		4 (3%)
Other		14 (9%)
Initial stage at diagnosis		
I		10 (7%)
II		26 (17%)
III		38 (25%)
IV		71 (46%)
Unknown		8 (5%)
Histologic Grade		
I		4 (3%)
II		28 (18%)
III		71 (46%)
Unknown		50 (33%)
Biomarker status for breast primary (n = 66)		
Estrogen receptor		
Negative		24 (16%)
Positive		40 (26%)
Unknown		2 (1%)
Progesterone receptor		
Negative		30 (20%)
Positive		30 (20%)
Unknown		3 (2%)
HER2 status		
Negative		45 (29%)
Equivocal		2 (1%)
Positive		18 (12%)
Unknown		3 (2%)
Nodal involvement		
Yes		109 (71%)
No		36 (24%)
Unknown		8 (5%)

Table 1. Continued

	Total (n = 153)
ECOG performance status	
0	31 (20%)
1	62 (41%)
2	33 (22%)
3	17 (11%)
4	3 (2%)
Unknown	7 (5%)
Site of first metastasis	
Bone	55 (36%)
Brain	51 (33%)
Lung	18 (12%)
Liver	8 (5%)
Spinal Cord	1 (1%)
Other	17 (11%)
None	2 (1%)
Missing	1 (1%)

LMC: Leptomeningeal carcinomatosis, IQR: Interquartile range, HER2: Human epidermal growth factor receptor 2, CSF: cerebrospinal fluid, ECOG: Eastern Cooperative Oncology Group, n: Number

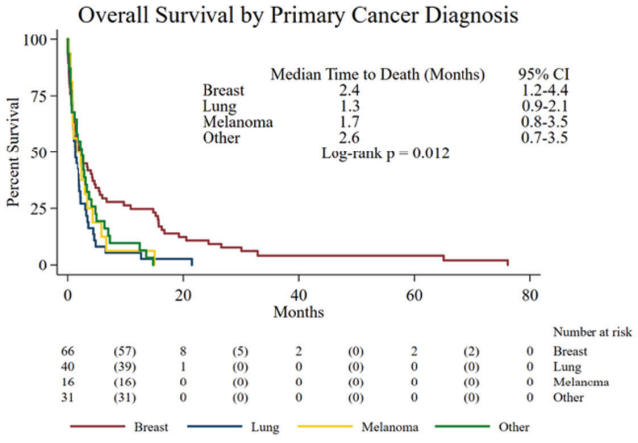

Figure 1. Kaplan-Meier survial curves showing the overall survival for patients with LMC secondary to breast cancer, lung cancer, melanoma, and other tumors

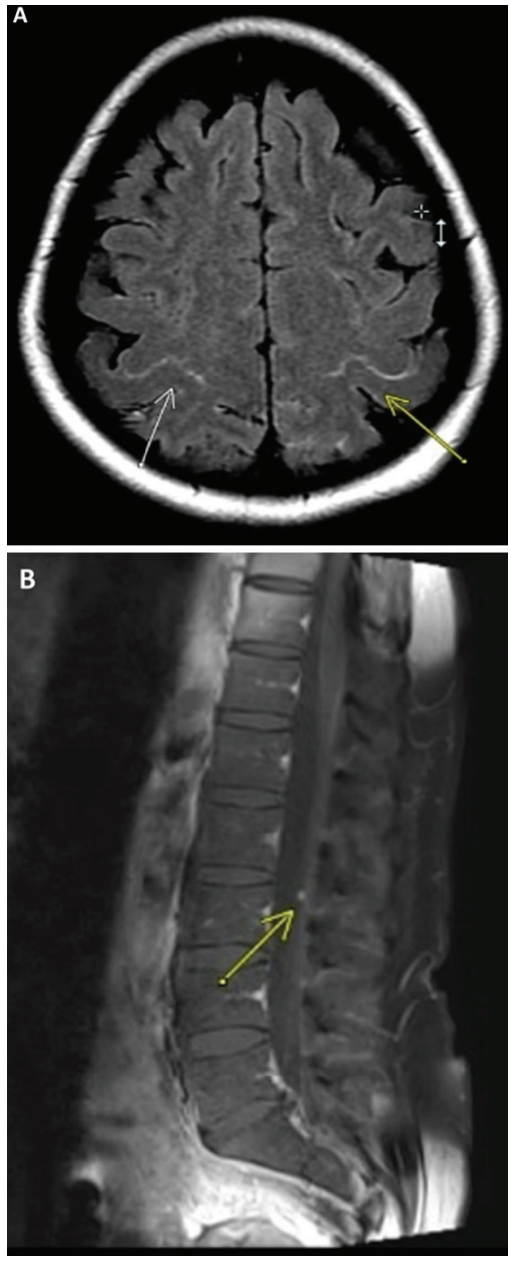

Figure 2. a) MRI brain with leptomeningal enhancement in the parietal sulci **b)** A leptomeningal enhancing focus along a nerve root in the lumbar spine.

MRI: Magnetic resonance imaging

equivocal (suspicious or atypical cells present) in 15%, and negative in 36%. Figure 3 shows an example of CSF cytology showing LMC from a patient with poorly differentiated gastric carcinoma with signet ring features. As depicted in Figure 4, the Kaplan-Meier curves revealed differences in OS by CSF cytology: median OS for CSF negative patients was 3.8 months (95% CI: 2.1, 9.8), for CSF equivocal was 2.4 months (95% CI: 0.5, 11.0), and for CSF positive patients was 0.9 months (95% CI: 0.5, 1.3) (p<0.005).

Management of therapeutic strategy

Of the 153 patients, 24 (16%) had no new treatment after LMC diagnosis and 129 (84%) had a new addition of radiation to the brain or spine, addition of intrathecal chemotherapy, or a new systemic chemotherapy agent. The most common addition was radiotherapy in 30 patients (42%). The most likely new agent was the addition of capecitabine in six patients (8%). Twenty-eight (18%) patients received intrathecal chemotherapy with 27 (96%) receiving liposomal cytarabine and one (4%) receiving thiotepa. The median OS for patients with no new treatment after LMC diagnosis was 0.7 months (95% CI: 0.6, 1.2) and for those with a change in treatment after LMC diagnosis, 2.4 months (95% CI: 1.6, 3.1) (p<0.001).

Breast cancer subset analysis

A separate analysis was performed specifically on the subset of patients with a primary breast cancer (see Table 1 for tumor

characteristics). Thirty-seven breast cancer patients received radiotherapy for LMC (56%) and 64 received chemotherapy for either the primary disease or LMC (97%), with 22 patients (36%) receiving intrathecal chemotherapy and 42 patients (64%) receiving hormonal therapy.

Of the 66 patients, there were 64 (97%) observed deaths; and the survival differed for patient based on their biomarker status. Median OS for all patients was 2.4 months (95% CI: 1.2–4.4). Median OS for ER+/PR+/HER2- patients (n = 40, 61%) was 4.1 months (CI: 1.7, 9.8), for triple negative breast cancer (TNBC) patients (n = 17, 26%) was 0.9 months (CI: 0.2, 1.9) and for HER2+ patients (n = 6, 9%) was 0.7 months (CI: 0.0, 15.8). A significant difference in OS between subtypes based on hormone receptor status was found (p-0.002, log-rank test). OS was improved with new treatment after LMC diagnosis, with median OS of 2.8 months (CI: 1.3, 5.7) in treated patients (n = 57, 86%) compared to 1.2 months (CI: 0.03, 3.6) in untreated patients (n = 9, 14%) (p-0.026). The median OS in CSF negative patients was 15.3 months (CI: 3.6, 30.1), 6.9 months in CSF equivocal patients (CI: 1.5, 76.2), and 0.9 months in CSF positive patients (CI: 0.4, 2.0) (p = 0.009, Log rank test).

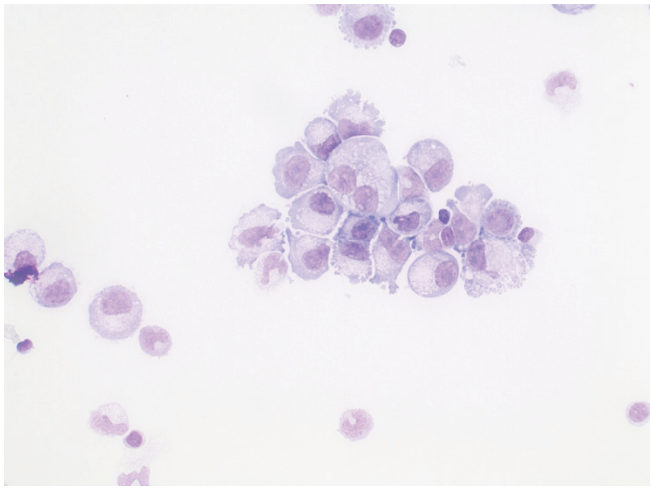

Figure 3. CSF cytology showing LMC from a patient with poorly differentiated gastric carcinoma with signet ring features

CSF: Cerebrospinal fluid, LMC: Leptomeningeal carcinomatosis

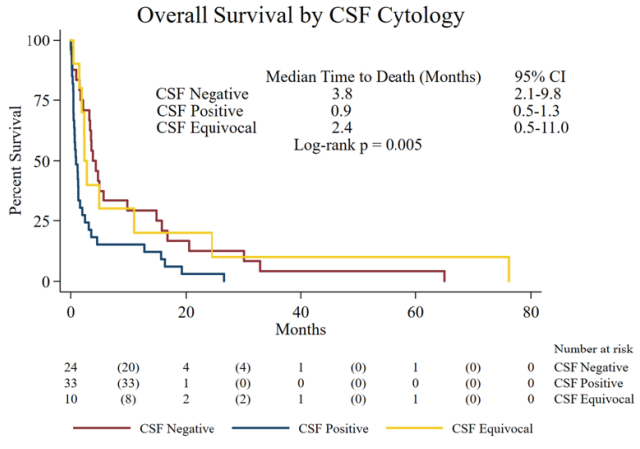

Figure 4. Kaplan-Meier survival curves showing the overall survival based on the CSF cytology

CSF: Cerebrospinal fluid

Discussion:

In patients with solid tumor malignancies, LMC is considered one of the most serious complications. We present a comprehensive overview of diagnostic methods and treatments of patients with LMC associated with solid tumors over a 10-year period at our institution. LMC is commonly associated with breast cancer, lung cancer, skin melanoma along with various other cancers (5, 30). In our cohort, all patients underwent MRI of the brain and/or spine and 97% demonstrated radiographic evidence of LMC. This high rate demonstrates that at our institution MRI is the preferred initial diagnostic modality prior to attempting high volume LP.

The presence of malignant cells in the CSF versus equivocal or negative cytology was associated with a significantly lower overall survival in our cohort (0.9 months vs 3.8 months). This highlights the importance of repeating LP if CSF is initially negative as accurate CSF cytology is essential to further delineate an individual patient's prognosis.

Patients with LMC at our institution most commonly presented with stage IV breast cancer, lung cancer, or melanoma with metastases to the brain or bone. In the literature, the survival from the time of diagnosis of LMC is 4 to 6 weeks without treatment and 2 to 6 months with therapy (5, 6, 22-25, 31). Our cohort included 153 patients with a mixed population including patients who received treatment and some who proceeded with comfort care or hospice alone following diagnosis of LMC. The median OS of our cohort was 1.9 months (CI: 1.3, 2.5).

In our study, treatment of LMC either by intrathecal chemotherapy, radiation to the brain or spine, or systemic therapy was associated with an improvement in survival versus no treatment (Figure 4). The higher CSF protein level present in patients with LMC demonstrates that there is likely a blood-brain barrier disruption and resultant increased levels of systemic chemotherapy delivered to the subarachnoid space (32). Systemic chemotherapy is primarily based on the histology of the primary tumor as in other forms of metastatic disease. Use of systemic cytotoxic agents such as high-dose methotrexate can induce a response in LMC from various solid tumors and improve survival outcomes, however its use is limited due to systemic side effects, the potential for significant hematologic toxicity and the need for inpatient administration (32). A significant limitation to the efficacy of systemic chemotherapy in the treatment of LMC is resistance to therapy as most patients developed disease progression despite multiple lines of systemic chemo and/or hormonal therapy prior to development of LMC.

Intrathecal methotrexate is a commonly utilized and relatively well-tolerated agent associated with leukoencephalopathy (33). The efficacy of intrathecal trastuzumab is currently unclear and is being investigated for LMC from HER2-positive breast cancer given that systemic trastuzumab appears to have poor penetration into the CSF (26, 27). Liposomal cytarabine administered intrathecally has been associated with complete cytological remission likely due to its unique formulation which allows for persistence for up to 28 days in the CSF (19). However, this agent is no longer available for clinical use due to the manufacturer discontinuing production of this preparation; the shorter acting version can still be utilized. The decision to use intrathecal chemotherapy in the setting of LMC must be carefully considered taking into account the extent and status of systemic disease, the patient's functional status, and impact of the treatment and frequency of administration on the quality of life.

Breast cancer appears to be particularly responsive to therapy with overall survival of 7.5 months with therapy in the literature (34). However, as evidenced in our cohort of breast cancer patients, TNBC and HER2+ patients have a significantly worse prognosis as compared to ER+/PR+/HER2- patients. Patients with a primary lung cancer or melanoma appear to be less responsive. In these patients, targeted therapy in the setting of certain actionable mutations (e.g osimertinib in EGFR mutant NSCLC or BRAF inhibitor or checkpoint inhibitors in melanoma) have shown preliminary evidence of activity against LMC in these tumors (35). In this mixed cohort of patients with and without treatment, the median OS for primary breast cancer was 2.4 months which was significantly longer than primary lung cancer (OS: 1.3 months) and primary melanoma (OS: 1.7 months). Despite treatment, prognosis remains poor and confirmation of diagnosis is challenging.

Strengths and limitations

A strength of the study was the relatively large cohort size of 153 patients given the relative rarity of LMC. We used not only the ICD9 and ICD10 codes for carcinomatous meningitis or unspecified meningeal disease, but we also included patients who were diagnosed with a malignant solid tumor, who had undergone a procedure indicative of leptomeningeal carcinomatosis according to CPT codes. There are several limitations to our study including its retrospective nature, somewhat limited sample size for specific treatment modalities, and the 5-year period of review during which time imaging techniques and treatment options changed significantly for many solid tumors. The range of treatments and histologic diagnoses was too heterogeneous, and sample sizes were too small to statistically assess the impact of specific drugs or treatment modalities on specific cancer diagnoses. Future multi-institution studies may reveal more information specific to LMC of difference histologies.

In conclusion, the risks and benefits of treatment in patients with LMC must be considered in detail on an individual basis. This study may provide additional information for physicians to communicate prognostic information to patients based on an individual's cancer type, stage, grade, molecular status, and CSF cytology results.

Ethics Committee Approval: This study was an IRB-approved (registration #: OSU2016C0053) retrospective chart review of clinical and histopathologic data from patients treated at The Ohio State University Comprehensive Cancer Center, (OSUCCC)-James that was initially approved on 05/04/2016 between January 1st, 2010 and December 31st, 2015.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions

Conception: H.R., M.K., E.M., A.S., A.G.; Design: H.R., M.K., E.M., A.S., A.G.; Data Collection and/or Processing: H.R., M.K., E.M., M.D.P.G.P.E., A.M., I.A.; Analysis and/or Interpretation: M.P., J.A.S., M.L., R.W., S.S., D.S., J.V., M.C., P.G., V.K.P., N.W., B.R., A.M.N.; Writing: H.R., M.K.; Critical Review: M.L., R.W., S.S., D.S., J.V., M.C., P.G., V.K.P., N.W., B.R., A.M.N.

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Case Report

Eur J Breast Health 2021; 17(4): 378-382
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Stewart-Treves Syndrome: A Rare But Aggressive Complication of Breast Cancer-Related Lymphedema

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ABSTRACT

Stewart-Treves syndrome (STS) is an angiosarcoma that usually develop in an extremity with longstanding lymphedema. Most affected patients have a history of breast cancer treated with radical mastectomy. Here, we report a case of STS with breast cancer-related lymphedema (BCRL) for a period of seven years. A 56-year-old woman presented with chronic lymphedema of the left arm. Nine years previously she had modified radical mastectomy for grade 2, invasive, ductal breast cancer. Upon physical examination, a tender, purplish lesion on the medial half of the affected arm was observed. The lesion spread rapidly with different-sized, scattered, purple-colored lesions in the affected area. A prompt skin biopsy was reported as STS. An immediate arm amputation was performed. However, a few months later she presented with new lesions on the anterior thorax and subsequent local recurrence around the scar. She received radiation-therapy. However, six months later the angiosarcoma had spread to the pelvic and upper limb area with scattered skin lesions. She had several problems during the chemotherapy and radiation-therapy, although she survived beyond 20 months.

In conclusion, STS is a rare but aggressive and important complication of BCRL. Awareness of rapidly progressing skin lesions and detailed investigation, as well as prompt surgery is necessary for patients with BCRL in order to relatively increase the survival time.

Keywords: Breast cancer, lymphedema, lymphangiosarcoma, Stewart-Treves syndrome

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Key Points

- STS is a rare but important complication of BCRL. Awareness of STS, early diagnosis, use of prompt and aggressive therapies, and close monitoring will relatively extend the survival time. Diagnostic ultrasonography may be a clinically useful imaging modality to detect possible malign transformation earlier for patients with BCRL and having suspicious skin lesions.

Introduction

Stewart-Treves syndrome (STS) is a rare and aggressive angiosarcoma developing in an extremity with longstanding lymphedema. Stewart and Treves (1) reported the first lymphangiosarcoma of the upper limb in six patients who underwent post-mastectomy in 1948. STS originates from the endothelial cells of the lymphatic and blood vessels, but the precise pathomechanism of this phenomenon remains unknown (1, 2). Diagnosis is made based on skin biopsy and imaging studies, and the prognosis is poor when radical surgery is not performed (3-5).

We report the case of a 56-year-old woman with STS who underwent modified radical mastectomy for breast carcinoma nine years previously and subsequent breast cancer-related lymphedema (BCRL) for seven years.

Case Presentation

In October 2016, a 56-year-old woman presented with chronic lymphedema of the left arm. She had undergone modified radical mastectomy for grade 2, invasive, ductal breast cancer and received chemotherapy, irradiation, and hormonotherapy in 2007, and had right arm edema for the seven years prior to presentation. Physical examination revealed stage 2 lymphedema with Stemmer-sign positivity. Inspection indicated a tender, purplish lesion (1.5 cm × 4 cm) on the medial half of the affected arm (Figure 1a). She denied any trauma or infection history

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and no history of comorbidities except hypertension. Her routine biochemical test and anticoagulation status were normal. A diagnostic ultrasonography (US) revealed areas of altered echotexture containing multiple subcutaneous, hypoechoic masses in the right inner arm with solid and cystic components (Figure 2a and b). Due to the suspicion of metastasis, magnetic resonance imaging (MRI) was requested. The MRI showed hematoma-like, yellow-colored alterations at the edges of the patient's lesion. The lesion spread rapidly with different-sized, scattered, pink- and purple-colored lesions in the affected area (Figure 1b). A prompt skin biopsy was performed, which demonstrated large, hyperchromatic, and atypical neoplastic cells, some of which showed luminal projections. Low-power view showed extensive infiltration of the dermis by the vascular tumor. Pathology also revealed irregular, anastomosing vascular channels lined by endothelial cells exhibiting different degrees of atypia and mitotic activity, filling the dermis with cells forming luminal structures, interspersed with slit-like spaces, or small nests. Immunohistochemical staining for cluster of differentiation (CD) 31 and CD34 was positive, and pancytokeratin showed no immunoreactivity, indicating angiosarcoma and eliminating cutaneous metastases (Figures 3a, b and c). MRI indicated dermal diffuse thickening with subcutaneous enhanced-contrast nodular components, similar to the US findings (Figures 4a and b). Based on these results, STS was diagnosed.

Total abdominal US and chest X-ray were normal. Consultation with oncologist and orthopedic surgeon resulted in a planned, immediate, forequarter amputation. Surgical margins were found to be clear of tumor with a more than 3 cm-cuff of tumor-free tissue. The clavicular bone biopsy appeared normal without any obvious evidence of local infiltration or metastatic seeding. During the follow-up visit of the patient, two months after the operation, the amputation scar had healed clearly (Figure 5) but she had phantom limb pain. Thus pregabalin, 150 mg twice daily, was prescribed for phantom pain.

At the six week control visit, a new lesion on the anterior thorax was detected (Figure 6). The performed biopsy again revealed angiosarcoma. A wide surgical excision of the tumor was performed on the anterior thorax (Figure 7). Two months later, new lesions around the scar of the thoracic mass surgery and the left axilla were detected (Figures 8a and b). Punch biopsy revealed further recurrence of angiosarcoma. Therefore, radiation-therapy was performed on the metastatic areas. Three months later she reported pain and similar lesions over her right hip and upper leg and attended the oncology and dermatology units (Figures 9). Pelvic bone metastasis was found on positron emission tomography scan. The management decision was palliative chemotherapy. However, during the third cycle of chemotherapy, she visited the emergency department with fever, dyspnea, cough, and breathlessness. She had severe pneumonia, resistant to multiple therapies, and was hospitalized in the intensive care unit for three weeks. After resolution of symptoms and findings,

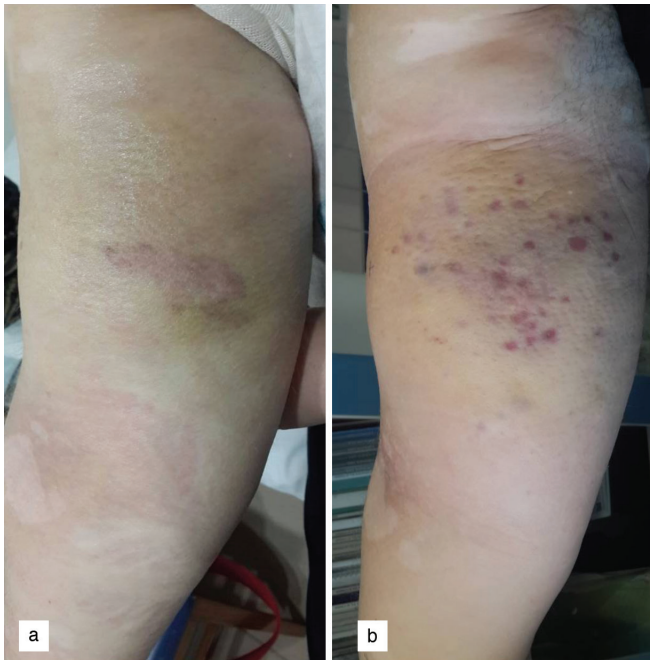

Figure 1. a, b. Purplish lesion that spread rapidly with different-sized, scattered, pink and purple-colored lesions on the right upper extremity

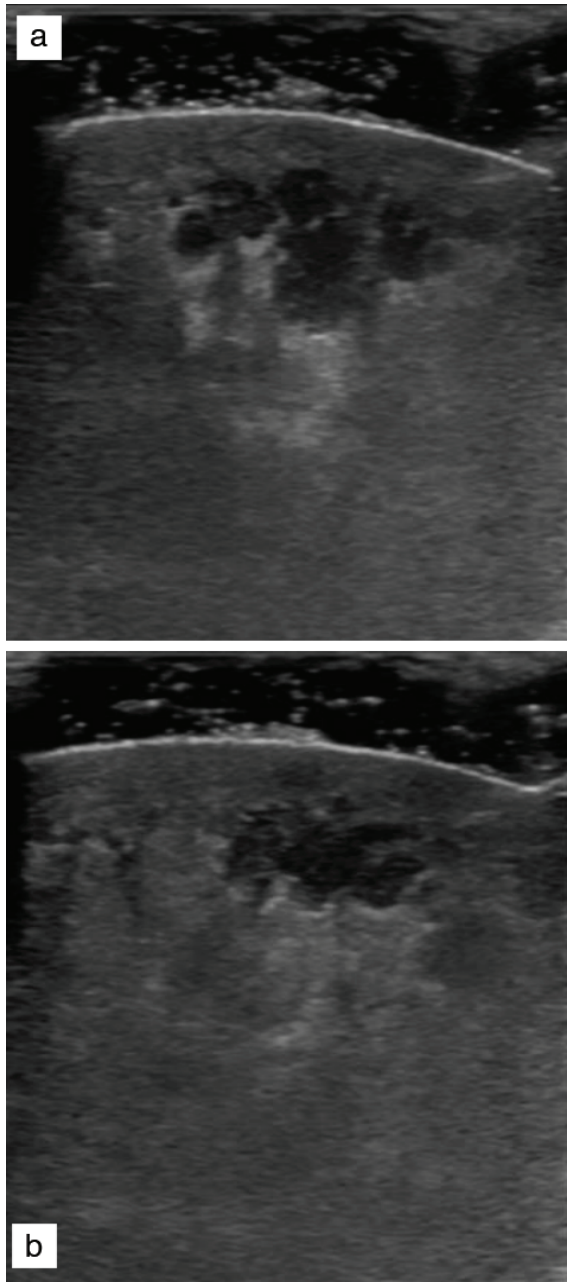

Figure 2. a, b. US revealed multiple masses in the right inner arm with solid and cystic components appearing as subcutaneous irregular hypoechoeic lesions

US: Ultrasonography

she was discharged with palliative suggestions. A few weeks later, she received radiation-therapy for the pelvic metastatic area and chemotherapy was initiated again. On her final visit, three months after chemotherapy completeion, she had severe pain in the lower back and legs. She was placed on palliative pain control but subsequently developed urinary tract infection and was lost due to sepsis.

Discussion and Conclusion

STS is a rare but deadly angiosarcoma that develops due to chronic lymphatic obstruction; STS may be either primary or secondary (1-10), and affects an estimated 0.07%–0.45% of patients who survive longer than five years after radical mastectomy (7, 10-12). Causative factors including radiation-therapy, immunodeficiency, and an association between STS and cardiovascular conditions have previously been reported (11), but the underlying pathophysiology is still uncertain (2, 13). The period between the onset of lymphedema and the appearance of STS lesions varies between 5–11 years. The tumor is characterized by multiple purplish, painless, macular lesions, which may be dismissed, and then develops into a plaque or nodule (3, 7, 13-15). The diagnosis depends on histopathological findings but imaging-modalities can also be helpful (3, 4, 15). Histopathological findings may vary among cases but are commonly reported as irregular and anastomosed endothelial tissue in the most-differentiated areas, as well as atypical epitheloid and spindle masses in less-differentiated areas. Immunopathological studies indicate positive staining for endothelial cell markers comprising laminin and antibodies against CD31 and CD34 are positive. Absence of epithelial differentiation markers, such as cytokeratin, helps in the elimination of cutaneous metastases of breast cancer (2, 4, 11, 13, 15).

Our patient had right, modified, radical mastectomy with resection of 26 axillary-nodes and postoperative radiation nine years previously, and lymphedema had been evident for more than seven years. However, our patient was relatively young, and the survival period was relatively longer to identify the aggressive nature of the tumor and high-risk recurrence affecting different areas and responsiveness to radical therapies. In our case US was performed and revealed similar lesions to

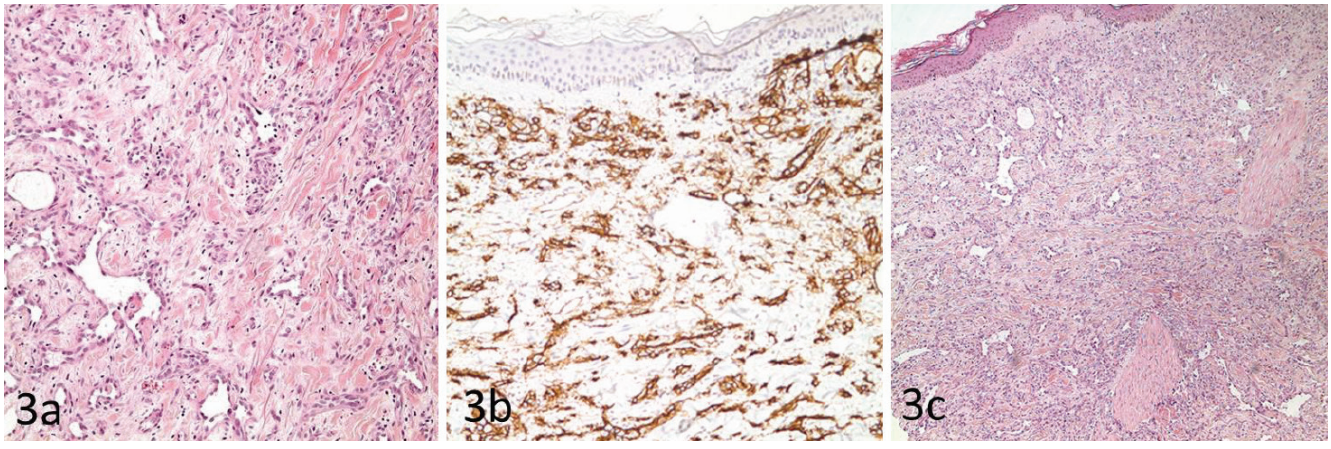

Figure 3. a, b, c. Histological examination revealed irregular anastomosing vascular channels lined with endothelial cells exhibiting different degrees of atypia and mitotic activity, filling the dermis with cells forming luminal structures, slit-like spaces, or small nests. Immunohistochemical staining for CD31 and CD34 was positive

CD: Cluster of differentiation

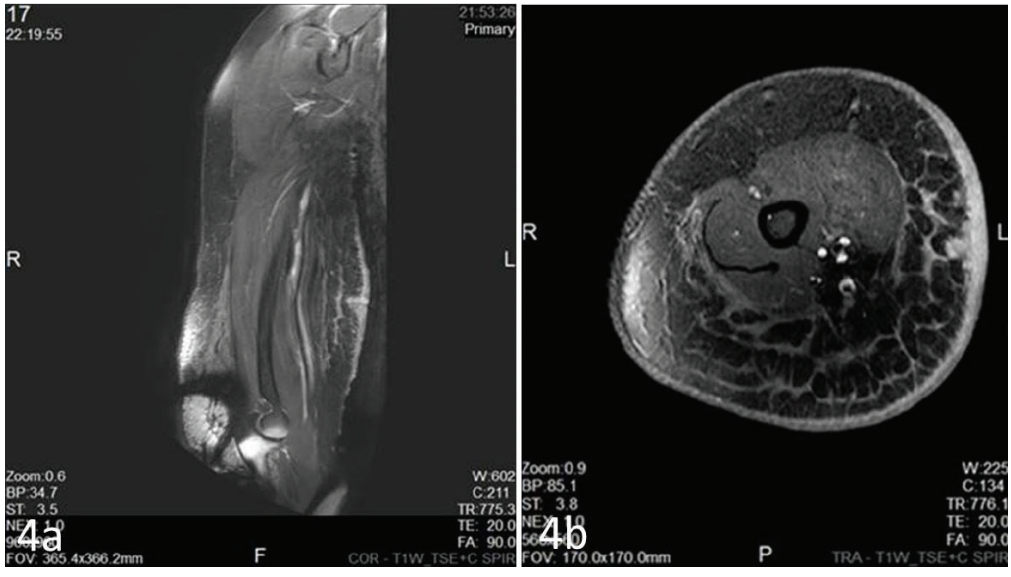

Figure 4. a, b. MRI indicated dermal diffuse thickness with subcutaneous enhanced-contrasting nodular components

MRI: Magnetic resonance imaging

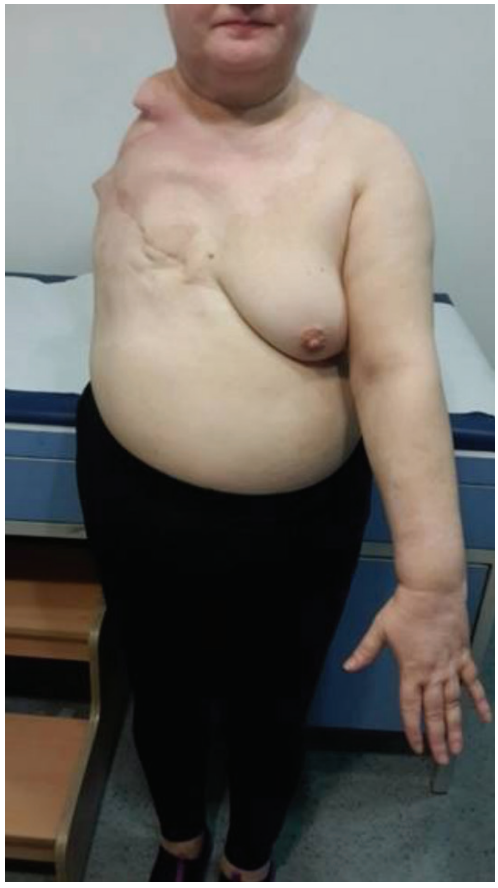

Figure 5. Amputation scar after 2 months

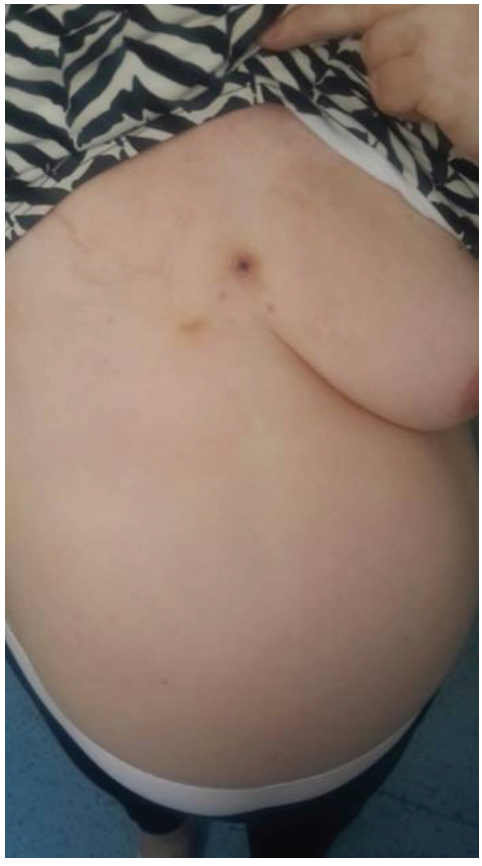

Figure 6. New lesion on the anterior thorax

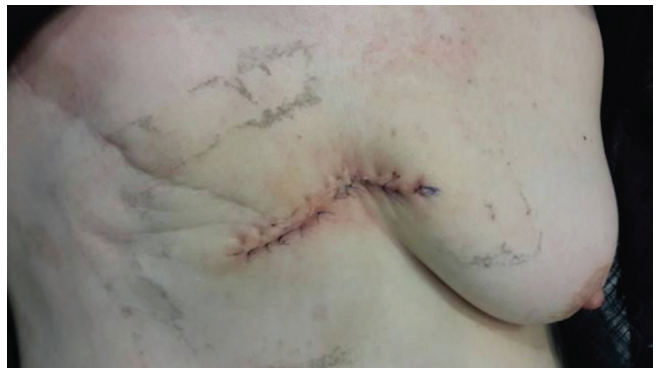

Figure 7. Wide surgical excision of the tumor on the anterior thorax

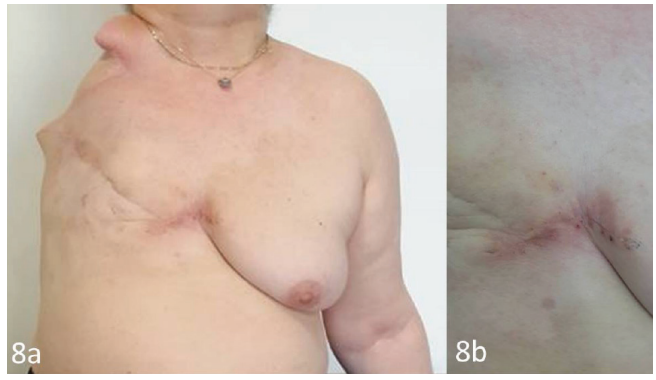

Figure 8. a, b. New lesions around the scar of the thoracic mass surgery and on the left axilla, three months after the second surgery

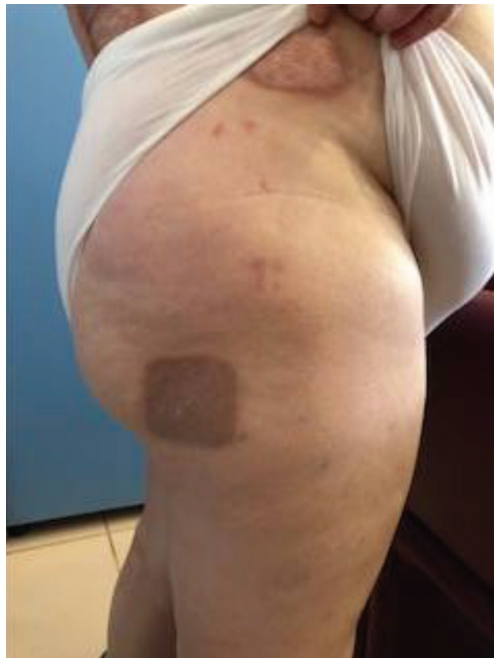

Figure 9. New skin lesions in gluteal area and right upper leg in which punch biopsies were taken

those reported on MRI findings. In recent years, US has been widely used in patients with lymphedema for differential diagnosis to monitor effects of treatments (16). Angiosarcomas have variable features on US examination, such as well-circumscribed or poorly marginated hypoechoic or hyperechoic masses, and US was previously used to

visualize these lesions (17). We suggest diagnostic US for evaluation of STS skin lesions and early diagnosis, as a practical, easy, and affordable method. However, further studies are needed to confirm the diagnostic value and advantages of US over MRI or computed tomography in such lesions.

STS has poor prognosis, and due to its rarity and high rate of local recurrence and metastatic disease, no standardized therapy is recommended (2, 3, 7, 5, 15). As the presentation of the tumor may be confused with traumatic ecchymosis or benign vascular lesions, awareness of this condition is crucial. Our patient had a relatively short duration between the development of lymphedema and presentation of angiosarcoma. After prompt STS diagnosis, early radical amputation was performed because of the local extent of the tumor and the likelihood of it being very aggressive. Unfortunatly, the tumor was so aggressive that it spread to the anterior thorax just a few months later, and local recurrences and bone metastasis were observed within a few months. Our case also demonstrates that even prompt amputation does not guarantee prevention of local recurrence, and recurrences may be common after wide surgical resections. With multi-modal and aggressive management, she managed to survive beyond 20 months.

In conclusion, STS is a rare but important complication of BCRL. Awareness, early diagnosis, prompt and aggressive therapies, and close monitoring will relatively improve the duration of survival time, as seen in our patient. US may be a clinically useful imaging modality for earlier detection of possible malign transformation in patients with BCRL having suspicious skin lesions.

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions

Conception: P.B.; Design: A.Y.; Supervision: P.B.; Materials: A.Y.; Data Collection and/or Processing: A.Y.; Analysis and/or Interpretation: Ö.G.; Literature Search: P.B.; Writing: P.B.

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

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Case Report

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Chest Wall Silicone Granuloma Following Ruptured Silicone Breast Implant Causes Giant Chest Wall Abscess and Osteomyelitis: The First Report

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ABSTRACT

Silicone breast implant ruptures have been widely reported in the literature. Granuloma formation is a known complication of such ruptures with reported sites including the axillae, limbs, chest wall muscles, and internal organs, such as the lungs and the liver. To the best of our knowledge, there are no reported cases of a silicone granuloma causing osteomyelitis of the sternum and multiple ribs in the absence of infection. We therefore report on the case of an 81-year-old patient who presented with an anterior chest wall discharging sinus tract on the background of a ruptured silicone breast implant. We raise awareness about the potentially devastating complications resulting from a ruptured silicone implant with relevance to cardiothoracic practice.

Keywords: Silicone breast implant, rupture, granuloma, chest wall, cardiothoracic

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Key Points

- Recognition of this rare but serious complication.
- Early intervention is vital to avoid significant chest wall destruction.
- Ensure meticulous surgical debridement of all involved tissue to a healthy, bleeding margin.
- Reconstruct with a well-vascularized, preferably pedicled, graft to protect against any infection of the composite prosthesis.

Introduction

Silicone breast implants have been used extensively in cosmetic and reconstructive surgery for over 50 years (1). Implant ruptures are a known complication and likely have an underestimated incidence due to their asymptomatic nature (2). In most cases, the leak of silicone gel remains confined within the intact fibrous capsule. However, in 12% to 26% of cases, silicone may spread beyond the capsule and reach the breast parenchyma, termed an extracapsular rupture (3), potentially causing foreign body inflammation leading to a silicone granuloma (4). Rare cases of silicone granuloma involving the axillae, limbs, chest wall muscles, liver, lung, abdominal wall, and inguinal area have been described (5-11). However, to the best of our knowledge, this is the first report of an advanced silicone granuloma causing osteomyelitis of the ribs and sternum.

Case Presentation

An 81-year-old female with a history of bilateral breast cancer was referred to our tertiary centre with a recalcitrant, right-sided, chest wall granuloma and chronic sternal osteomyelitis unresponsive to antibiotic therapy. This visit followed the removal of a ruptured right silicone implant. On inspection, the patient had extensive chest wall scarring from previous surgeries and radiation injuries to her neck and precordial area. She had skin loss around the right sternal edge, medial to her breast scar, with underlying bone exposure and a discharging sinus area, as illustrated in Figure 1. On examination, she was tender over the right sternal edge but was otherwise asymptomatic. Her observations were unremarkable, and laboratory investigations were significant for C-reactive protein of 182 mg/L. Swabs from the wound site revealed no growth of microorganisms. Her biopsy showed no signs of cancer but concurred with imaging studies showing osteomyelitis of the surrounding bone.

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Surgical management

The patient's surgical management involved both the cardiothoracic and plastics and reconstructive teams. She was admitted for an elective anterior chest wall resection involving the sternal body and ribs 2–6, including the overlying skin and subcutaneous fat, as illustrated in Figure 2. Intra-operative findings included abnormal soft tissue extending down to the ribs with adhesions to the lung and mediastinal fat, illustrated in Figure 3. The reconstruction was performed using a Marlex mesh sandwich reinforced with gentamicin cement to repair the bony defect. This was covered with a pedicled latissimus dorsi myocutaneous flap to replace the soft tissue loss. The result is shown in Figure 4.

Histopathological evaluation revealed tissue with abundant inflammatory cells, hemosiderin-laden macrophages, and foreign-body giant cells. Sections from decalcified ribs showed areas of necrosis surrounding fibrocollagenous tissue and dead bony trabeculae, confirming the chronic sinus tract clinical diagnosis. There was no evidence of malignancy.

The operation and postoperative course were uneventful, and the patient was discharged home with long-term antibiotics. She was seen in the clinic three months after inpatient discharge, showing good wound healing without evidence of cellulitis or local tenderness.

Discussion and Conclusion

The design and materials science of silicone implants have evolved considerably over the past four decades (12). The implant's shape and filler, and shell characteristics have changed drastically to minimize implant compromise (12). Despite improvements in implant stability, ruptured silicone breast implant cases are still reported in the literature. Rupture incidences have been shown to increase with implant age, particularly after the 6-year mark (13). The cumulative overall rupture incidence at six years for patients undergoing primary reconstruction after a mastectomy is 1.5% or 3.8%, although this figure varies depending on the implant manufacturer (1). Some proposed rupture mechanisms include trauma to the chest, damage caused by surgical instruments, and implant shell swelling (1). Upon rupture, the patient's body creates a fibrous capsule around the foreign silicone material (1). A rupture still contained within this capsule is termed an intracapsular rupture (1). A breach of this capsule results in an extracapsular rupture and allows the silicone to migrate to distant tissues (1). If the silicone is not removed, a chronic inflammatory state ensues, often resulting in local tissue destruction, as seen in our patient.

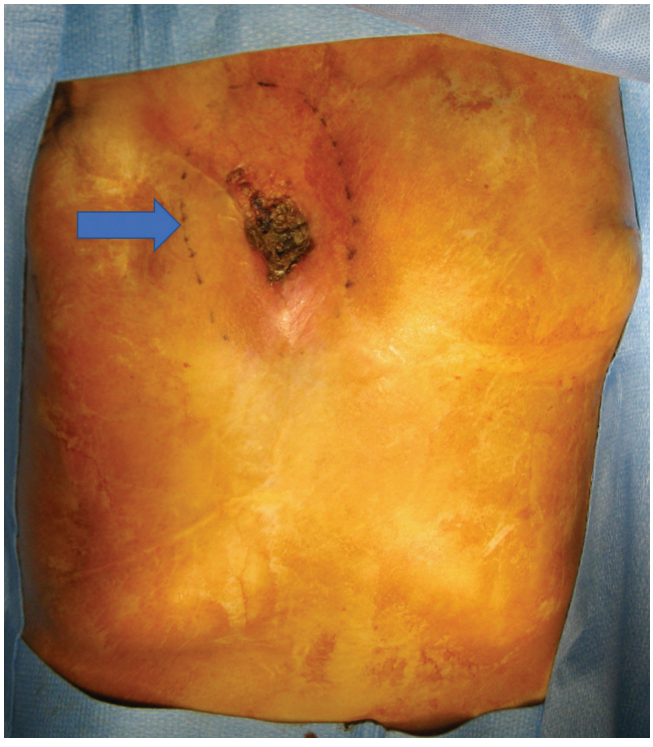

Figure 1. Image illustrating the discharging sinus area over the right sternal margin

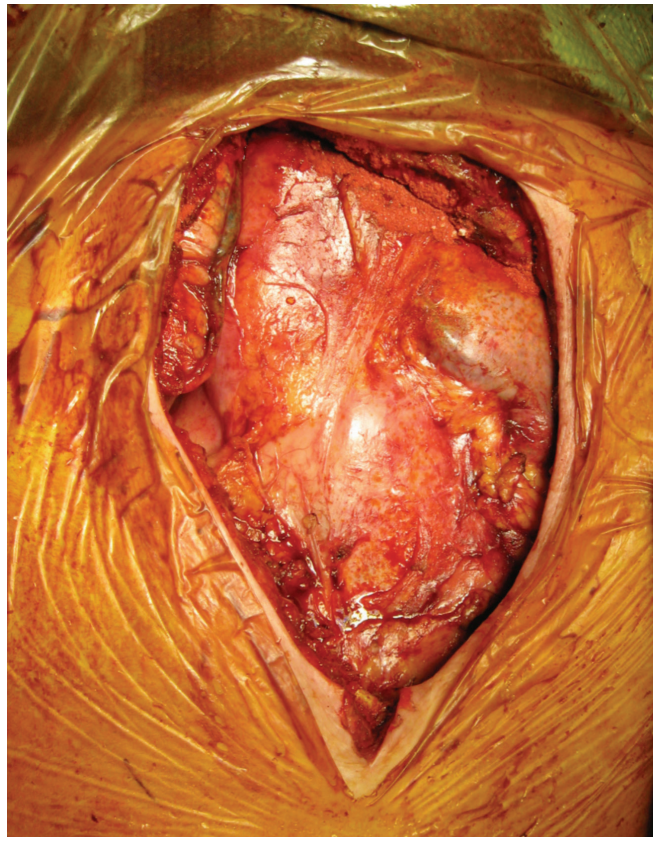

Figure 2. Site of anterior chest wall resection

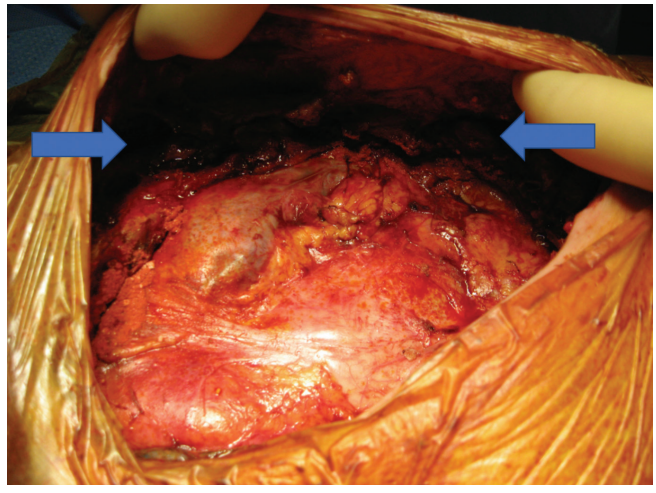

Figure 3. Extension of abnormal soft tissue into the chest wall

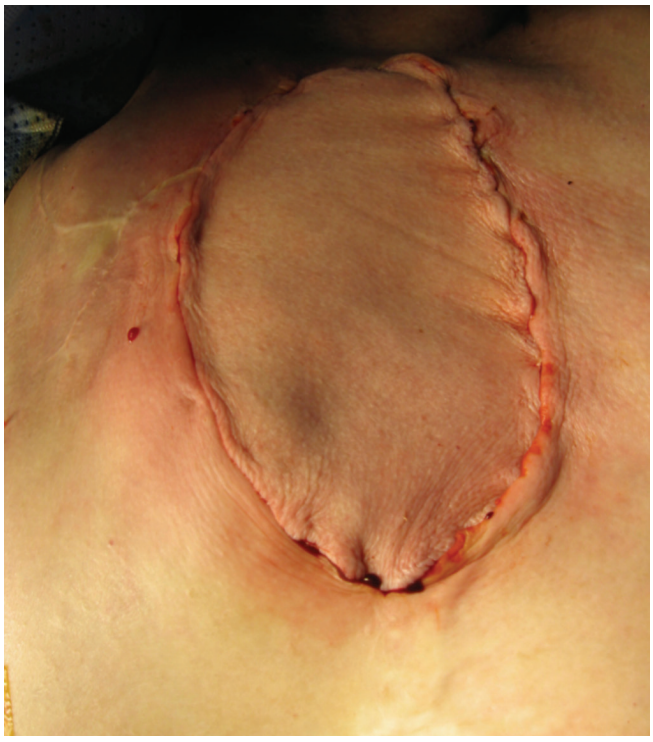

Figure 4. Post-reconstruction with latissimus dorsi myocutaneous flap

Although extremely rare, osteomyelitis of the ribs and sternum, secondary to a breast implant, has previously been reported in the context of implant infection directly spreading to bone (14). However, in our patient, wound cultures were negative for microorganisms, limiting the tissue destruction's aetiology to granulomatous inflammation due to the silicone particles inflammation.

In conclusion, although our patient recovered well, this case highlights the potential complications resulting from extracapsular silicone implant ruptures and their relevance to cardiothoracic surgery. Early diagnosis and management are vital in preventing granuloma formation and potential tissue destruction. The low incidence of these complications, patients' asymptomatic nature, and the low sensitivity of physical examinations make it challenging to detect silent ruptures. Therefore, clinicians should be aware of the potential complications of ruptured silicone implants and exercise a low threshold for imaging studies to ensure early intervention as appropriate for each patient.

Informed Consent: Consent for research and pictures were obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions

Conception: H.A., A.T., M.K., A.A.; Design: H.A., A.T., M.K., A.A.; Supervision: A.T., A.A.; Data Collection and/or Processing: H.A.; Literature Search: H.A.; Writing: H.A.; Critical Review: H.A., A.T., M.K., A.A.

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

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Letter to the Editor

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Controversy When Choosing the Anatomical Plane for Post Mastectomy Breast Reconstruction

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Dear Editor,

We congratulate the authors for the study entitled "Acute Postoperative Complications in Prepectoral versus Subpectoral Reconstruction following Nipple-Sparing Mastectomy" by Avila et al. (1).

The use of implants, tissue expanders, dermal matrix, and fat grafts to improve physical appearance and reduce symptoms in post-mastectomy breast reconstruction has taken great importance. Usually, there is a controversy about which plane the breast implant should be located, either pre-pectoral or subpectoral. Subpectoral positioning reduces the presence of animation deformity, contractures, pain, mobilization of the implant, or the presence of subsequent complications such as reconstructive failure (1, 2).

It should be noted that both techniques have similarities, such as approach, the preference of the surgical plane, the use of tissue expanders before the intervention, and the addition of dermal matrix to the reconstructive process. The role of external factors, namely comorbidities (Obesity, diabetes), procedures (radiotherapy, chemotherapy), smoking, and the prosthetic material, must also be considered key factors for surgical outcomes (1, 3).

Avila et al. (1) reported that although the subpectoral plane is the most common, the use of the pre-pectoral plane has achieved great popularity as this technique improves the dissection of the flap, causing less perfusion damage. It also synergies with the acellular dermal matrix for the posterior coverage of the prosthesis, which has achieved advantages such as reducing capsular contracture, animation deformity, pain reduction, and improved appearance of the upper pole of the breast. The most important aspects of achieving positive outcomes include maintaining a plane of dissection anterior to the mammary capsule, avoiding subjecting the dissection flaps to high temperatures, and limiting retraction. They also concluded that subpectoral planes presented a higher flap necrosis rate than the pre-pectoral reconstruction (1).

Caputo et al. (2) carried out a retrospective study with 94 patients submitted randomly to mastectomies with different surgical approaches with subsequent reconstruction with insertion of breast implants in the various planes. Complications and postoperative symptoms were evaluated, as well as the impact on quality of life. It was observed that the pre-pectoral approach had a beneficial effect on the patient's quality of life, sexual well-being, and aesthetic satisfaction (2).

In conclusion, the use of the subpectoral plane for implant positioning in postmastectomy reconstruction is still widely accepted. The pre-pectoral plane has brought new challenges as well as more questions about the best technique. Studies have shown that the pre-pectoral technique decreases the rate of less desired outcomes. There is an aesthetic improvement, a good impact on quality of life, and the rate of postoperative comorbidities decreases.

Keywords: Anatomical plane, breast reconstruction, mastectomy, reconstruction, surgery

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