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European Journal of Breast Health

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

The journal is owned by Turkish Federation of Breast Diseases Societies and it is published quarterly on January, April, July, and October. The publication language of the journal is English. The target audience of the journal includes specialists and medical professionals in general surgery and breast diseases.

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

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Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.eurjbreasthealth.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

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Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

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Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
BI-RADS: Breast imaging, report and data systems					

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

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

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While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. References published in PubMed should have a PMID: xxxxxx at the end of it, which should be stated in parenthesis. The reference styles for different types of publications are presented in the following examples.

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

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

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

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

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

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

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

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

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

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

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A Patient Advocacy Group Summit, Cancer Care in Turkey and The Society of Breast Health

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Keywords: Patient advocacy group, patient rights, health system, summit, cancer care, Turkey

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According to the World Health Organization (WHO), cancer now causes more deaths than all cardiac or all other diseases (1). The number of new cases is expected to rise by about 70% over the next 2 decades. Globally, nearly 1 in 6 deaths is due to cancer, and approximately 70% of deaths from cancer occur in low- and middle-income countries (2). There is a significant disparity in cancer care and outcome of cancer patient results between developed and developing countries. The most important aims of cancer management are prevention, screening, early detection, and effective treatment. In addition to the health care system, patients are the most important stakeholders of cancer care. Patient advocacy groups (PAG) are non-profit, non-governmental (NGO) organizations, and they may play an important role to acquire and protect patients' rights for better cancer management. PAGs can incorporate cancer scientists in a way similar to The Society of Breast Health to perform basic, reliable, and reasonable clinical projects based on the economic, socio-cultural and educational structure of a country. The number of PAGs should be increased and representatives of them should be participated in governmental organizations (such as National cancer Advisory Board, National Cancer Institute, etc.) to advocate and acquire their rights. Their participation absolutely provides integrity in health care systems.

To be a more effective and powerful part of cancer care, PAGs should come together in national and international platforms to share their problems and find solutions. Additionally, expert panelists in this field may explain more useful solutions to increase the benefit of these summits. There was an important patient advocacy group (PAG) summit in Vienna on 15-16, September, 2017. I would like to share my views and opinions about this summit as an invited speaker. Twenty-three delegates from 22 patient-groups representing 17 Central and Eastern European (CEE) countries and seven international experts came together at a first-of-its-kind oncology summit (Figure 1). The aims of the summit were to learn from each other about how to improve cancer care through advocacy in their countries, and to inform, empower and equip patient groups so that they are better able to address the challenges they face. The meeting also encouraged relationship-building and the strengthening of peer-to-peer networks between groups and countries.

The summit objectives were below:

- Bring together the cancer patient community to encourage sharing of experiences and ideas
- Facilitate dialogue and learning about capacity building, communications and effective cancer policy campaigning
- Inform the community about relevant developments in cancer and global standards
- Empower patient advocates to take on old challenges with new insight
- Equip organisation with new skills and knowledge to be more effective.

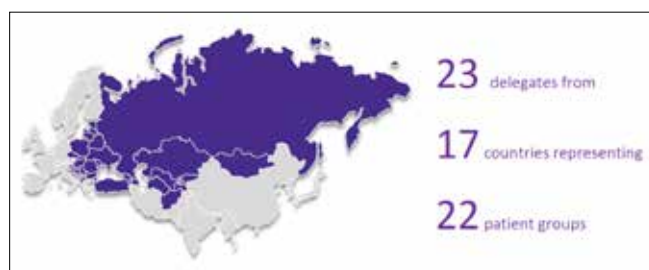


Figure 1. Oncology Collaboration Patient Group Summit brought together 22 patient advocacy groups (PAG) from 17 Central and Eastern Europe Countries in Vienna in September 2017

The summit was designed to support patient groups in the region to share best practice with one another whilst also providing an opportunity to pose questions to an array of oncology and advocacy experts. Survey responses from the attendees highlighted the broad range of skills and experiences the delegates brought to the summit. The delegates were ambitious and passionate about improving cancer outcomes across the Central and Eastern European region. The importance of collaboration became clear through the course of the summit. As did the need for collaboration across patient groups, healthcare professionals, media, government and the pharmaceutical industry to work in partnership towards a common goal.

A summit in four sessions

The agenda of the meeting was developed based on the attendee's feedback, and included four key topics:

- Storytelling and messaging
- Working with social and traditional media
- Engaging with policy influencers
- The power of patient groups

The final session brought the topics together in a workshop where attendees prepared a comprehensive creative campaign to improve cancer care.

These elements defined the four sessions of the summit. Each session featured expert speakers, a relevant case study and an interactive workshop

Small countries can make a big difference

Professor Mark Lawler shared his experience in improving cancer care in Northern Ireland through the development of an European Cancer Patient's Bill of Rights in 2014. Lawler set out the vision for Cancer Control in Europe and outlined the significant disparities between different European countries. He concluded that the European Cancer Patient's Bill of Rights was a crucial catalyst to "get things done", and cooperation and a strong common purpose were essential to have among patients and professionals, governments, non-governmental organisations (NGO) and industry. He also reminded us all that small countries like North Ireland could do big things together with NGOs.

Landscape of cancer patient advocacy

Professor Richard Sullivan presented the findings from an audit conducted among patient organisations across Central and Eastern European (CEE) countries. Notably, the audit findings from 18 countries revealed that 143 national patient groups were identified and only 54 groups were found to have clear published objectives in oncology at national level and active public profile.

Expert media panel

A panel of international experts with experience of working with the media provided insights on engaging media and other relevant channels to engage stakeholders. The panelists explained the positive role of media to increase cancer awareness and obtain better cancer care, and improve the healthcare system in a country. The media can also aid in organizing patient advocacy groups for more effective activities. The panel featured the head of a Polish patient group, a global public health professor, a cancer research professor, a professor of cancer policy and a health journalist specialising on oncology.

Oncoalliance and Uchelsda

In the four workshops, the delegates engaged with a fictional patient advocacy organisation, OncoAlliance, on its journey towards better cancer care in the imaginary country of Uchelsda. Delegates learned about the role of stakeholders such as the minister for finance and the potential importance of the President's wife! At each stage, there were new challenges to overcome as the story took on new challenges to improve cancer care and access.

The importance of national cancer policy

To demonstrate the essential role of National Cancer Control Plans (NCCP) in government policy and cancer care, Professor Tit Albrecht illustrated that cancer was a major challenge in Europe and CEE countries, touched on the changing cancer outcomes across Europe and explained how patient organisations could play a role in implementing NCCPs. He also stated that Europe had one eighth of the World population and it had one quarter of the global total deaths from cancer. Despite 87% of all countries having a National Cancer Control Plan, this falls to just 54% in CEE with many citing implementation failures. As per the available data, CEE has 32% higher mortality from cancer than Western Europe. According to Professor Albrecht, cancers in CEE countries have worse prognosis due to the lack of cancer prevention, late diagnosis, limited access to therapy, financial barriers, lack of cancer registries and national cancer control plans (NCCP).

Digital system and working with the media

Following a lively question and answer session on working with the media, Alivia Foundation CEO, Bartosz Polinski, showed delegates what could be achieved by utilising digital presentation of videos in an interactive, fundraising computer game designed by the Alivia Foundation. This campaign uniquely managed to engage young men who were a hard-to-reach audience for many charities.

Cancer Care in Turkey and The Society for Breast Health

In this specific summit, I made a presentation on cancer care and the National Cancer Control Program (NCCP) in Turkey. I also explained scientific studies and activities of The Society of Breast Health (MEMEDER) as a founder of this society. Turkey has a population of 80.000.000 and 163.500 new cancer patients in a year. Breast cancer in women (50/100.000), and lung cancer in men (60.4/100.000) are the most frequently seen cancers. The Turkish healthcare system is made up of a combination of compulsory health insurance and private medical practice. While it is possible to access free healthcare, standards and availability change considerably from region to region. Residents that are part of the social security system can get cancer care free of charge at the public and state university hospitals. The first NCCP started in 2008 (Phase I-2008-2013), and the second will be completed in 2018 (Phase II-2013-2018). The NCCP has minimally six pillars (registry, prevention, screening, treatment, advocacy and awareness, and collaboration).

Policy challenges to effective cancer care in Turkey include the increasing population (%13.5/2016), increasing number of cancer patients, aging, geographical, socioeconomic, and educational disparities that make it difficult to deliver homogenous healthcare across regions, westernization of the life style, end extensive tobacco use. Other important barriers include the lack of quality control and standardization among cancer centers, frequent bureaucratic and political changes, heterogeneity in the educational level of population, less awareness of, interest and participation in screening programs, and difficulty in the implementation of screening and treatment guidelines prepared according to national resources.

Steps taken by the healthcare system to overcome those challenges

Establishment of cancer early diagnosis, screening and treatment centers (KETEM) in Turkey (270 centers in 81 cities), participation of representatives of PAGs in National Cancer Advisory Board (NCAB), and promotion of anti-tobacco and anti-alcohol efforts (smoking is prohibited in indoors areas, and alcohol consumption and sale are also prohibited in some areas) were steps taken by the healthcare system to overcome those challenges. Mobile breast, cervix and colo-rectal cancer screening systems started screening target population, working maternity leave was extended to 10 months.

What did go well in Turkey?

According to data from the Cancer Control Department of Turkey, active cancer registry program worked well and was extended to the whole country, the number of KETEMs increased from 122 to 270. Additionally, tobacco consumption and incidence of lung cancer decreased, and early stage breast cancer increased in the last decade.

Participation of PAG delegates in NCAB, strong support and commitment from politicians, media, system managers, physicians and scientific environment were also positive steps. The government also increased resources allocated to cancer prevention, screening and treatment. Great efforts were made by the national scientific societies to educate healthcare professionals and target population with aid of postgraduates courses, certification programs, and conferences, and awareness activities.

The Society of Breast Health (MEMEDER-2007–2017)

The Society of Breast Health is a scientific and social, non-governmental, non-profit patient advocacy group (PAG). It is funded by breast experts, survivors, their relatives and volunteers. The aims of the society are to produce basic clinical trials, to promote breast cancer knowledge and awareness in population, communicate with other international and national societies, institutes, governmental organizations. The other objectives of the society are as follows: to find feasible, reliable, and cost-effective guidelines for breast cancer (BC) screening, diagnosis and treatment suitable for national infrastructure and limited resources, and to share and convince system providers to implement results of clinical trials.

Completed or ongoing projects of the society

To conduct a survey on breast cancer awareness and knowledge in Turkish women (3) and BC treatment delay in Turkey and 11 Eastern European Countries (4-5), Bahcesehir organized a population based BC Mammography Screening Project (6-8), i.e., BC Registry Project (2005-2017, 25.000 BC patients registered). Many BC awareness projects were among the most important projects conducted by the Society of Breast Health. Since half of the BC patients in the registry program and Bahcesehir Screening Project were under 50 years old, The Cancer Control Department decreased screening age from 50 to 40 years in Turkey.

Five blind men and an elephant

Kawalidip Sehmi, CEO of the International Alliance of Patient Organisations (IAPO) focused on a grassroots movement which has grown its membership globally. Sehmi reminded delegates of the tale of five blind men and an elephant and the importance of collaboration between patient organisations and stakeholders to get the full picture and improve cancer care for patients everywhere.

Developing a campaign and delegates' ideas

Throughout the workshops, delegates were tasked with developing plans for OncoAlliance given the challenges presented in the case study. The fourth and final workshop involved developing a comprehensive campaign for OncoAlliance. Whilst the exercise focused on how the fictional patient group, based in Ucheldsa, would campaign to improve cancer outcomes following the development of a National Cancer Control Programme, each of the breakout groups arrived at very different conclusions.

The structure of the summit was designed so that delegates would be introduced to several disciplines for achieving sustainable and measurable change throughout the two days. The concluding workshop worked through creative campaign development, drawing upon all three previous workshop sessions. Each breakout group presented a summary of a campaign. Notably, each took equally valid, but quite different routes.

The first one focused on the need for a registry to gather the essential evidence. The second one noted the importance of early detection with awareness and screening programs. The third one employed political pressures to drive rapid change, and then drew upon celebrity and mass media to engage the public in the priorities for a new NCCP.

Conclusions

Cancer incidence and mortality rates have been increasing in Turkey and other developing countries. Cancer patients have a relatively advanced stage at diagnosis due to the lack of national cancer control plans or difficulty in the implementation of available plans. There are many policy challenges to obtain effective cancer care in spite of steps taken to overcome them. PAGs such as The Society of Breast Health can provide both advocacy and produce clinical trials and establish guidelines according to the country's social, cultural factors and economic resources. The Board of Directors of PAGS should include active cancer experts, survivors, and volunteers and they should participate in the healthcare system to explain their problems and solutions so that they can be easily solved. Every country has a national cancer control plan (NCCP), and healthcare system partners should strictly adhere to and follow this plan without any compromise.

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Managing Male Mammary Maladies

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ABSTRACT

This review examines the symptoms, need for referral and management of the benign breast conditions which afflict males, together with the steps that are necessary to exclude or confirm male breast cancer. The most common complaint is gynaecomastia, either true or pseudo, and the majority of these cases need reassurance without over-investigation. Drugs that induce breast enlargement are described in order that, when possible, a medication switch can be made. Men receiving endocrine therapy for prostate cancer may develop painful gynaecomastia and this can be relieved with tamoxifen. All men with breast cancer need mammography as part of their work-up but this should not be used as a screening technique for symptomatic males. Because of lack of lobular development, both cysts and fibroadenomas are very rare in men; but those with nipple discharge need referral and investigation as some will have underlying malignancy.

Keywords: Male breast cancer, gynaecomastia, prostate cancer, mammography, ultrasound

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Introduction

It is important to appreciate that men presenting with breast problems are in unfamiliar territory. Unlike their female counterparts, they may have had little experience of medicine having been spared the problems of menstruation, contraception and childbirth. Whereas the majority of women with a breast problem will consult their general practitioner (GP) within a month, there may be long delays for men since the majority do not consider themselves as being at risk for serious breast problems.

For many, the embarrassment of having to attend a largely female-orientated breast clinic needs to be assuaged by a sympathetic and open consultation so that the reassurance given does not fall on deaf ears for the majority. The gender differences are important and significant and a "one size fits all" approach will at best be counterproductive and at worst give rise to serious misunderstandings with potential for acrimonious litigation.

Kipling et al. (1) administered a questionnaire to males attending a breast clinic over an 18-month-long period which was completed by 78. The age range was from 18 to 78 years and the average duration from the start of symptoms to clinic attendance was 6.65 months. Twenty two (28%) of those responding admitted to being embarrassed about consulting their GP for a breast problem and 16 (20%) were embarrassed in the Breast Clinic. When offered the chance of a male-only clinic but with a longer waiting time for an appointment, the men preferred a mixed gender clinic almost unanimously.

In terms of breast structure, before puberty, there is no gender difference so there is fibrofatty tissue containing ducts with a single lining of epithelial cells surrounded by myo-epithelium. The pubertal testosterone surge leads to involution of the ducts with the adult male breast comprising fat, stroma and a vestigial nipple-areolar complex attached to a blind-ending ductal system, without lobules and with no supporting ligaments of Astley Cooper. This paucity of anatomical structure has important consequences for the presentation of male breast diseases.

As an example of the spectrum of male breast disease, Singh et al. (2) reported cytological finding in a series of 119 men attending a breast clinic. Their results are summarised in Table 1.

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Table 1. Spectrum of male breast disease subjected to cytology (Singh 2012) (2)

Total	Benign	MBC	Gynae-comastia	Inflammation or abscess	Duct papilloma	Lipoma	Benign change
119 (100%)	105 (88%)	14 (12%)	86 (72%)	3 (2.5%)	1 (1%)	1 (1%)	14 (12%)

Table 2. Drugs and gynaeconomastia (Deepinder 2012) (3)

Definite cause	Probable association
Spironolactone	Risperidone
Cimetidine	Verapamil
Ketoconazole	Nifedipine
Human growth hormone (hGH)	Omeprazole
Estrogens	Alkylating agents
Human chorionic gonadotrophin (HCG)	Anti-HIV Efavirenz
Antiandrogens	Anabolic steroids
Gonadotrophin releasing analogues (GnRH)	Alcohol
5 alpha reductase inhibitors	Opioids

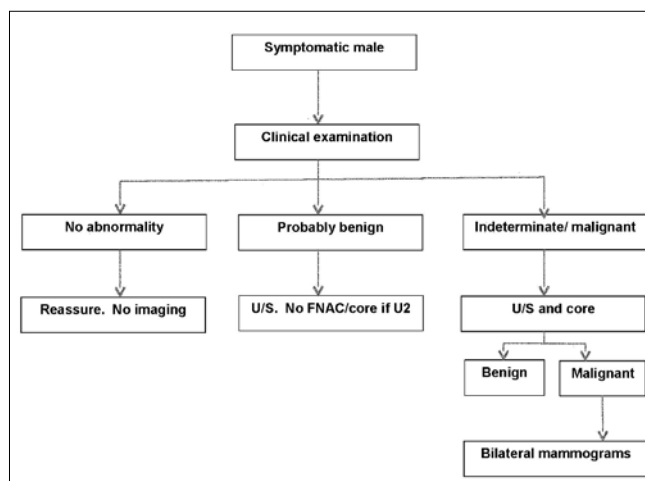


Figure 1. Breast Clinic management of symptomatic males

Assessment in Primary Care

In trying to maintain a balance between over-referral of men with breast problems and missing a rare disease, i.e., male breast cancer, the primary care physician is in a difficult position. Presenting symptoms in men may vary from breast enlargement (gynaeconomastia), mastalgia, lump and discharge to nipple distortion. The major cause of gynaeconomastia is obesity, which gives rise to pseudogynaeconomastia resulting from excess deposition of subcutaneous fat but without any enlargement of the underlying mammary glandular tissue.

Several frequently used medications may produce gynaeconomastia and those drugs that have been definitely and probably implicated in increasing risk are detailed in Table 1, Table 2 (2, 3). When possible, a switch of medication may be of benefit, but this may not be an option if the patient is receiving an essential and irreplaceable therapy.

Prostate cancer-associated gynaeconomastia

For men with prostate cancer receiving palliative therapies including non-steroidal antiandrogens (bicalutamide, flutamide and nilutamide),

gynaeconomastia with or without mastalgia is a common problem, affecting up to 79% of patients (4). There is however evidence of effective therapy based on the results of three randomised trials (5-7). Perdoni et al. (5) used a 3-way randomisation with 51 patients receiving bicalutamide 150 mg daily, 50 taking bicalutamide 150 mg plus tamoxifen 10 mg for 24 weeks and 50 patients given bicalutamide 150 mg per day preceded by breast irradiation (12-Gy in one fraction) the day before starting bicalutamide. Of those taking bicalutamide alone, gynaeconomastia and/or mastalgia developed in 35 (69%) and they were subsequently randomised to tamoxifen (17 patients) or breast irradiation (18 patients). Gynaeconomastia developed in 4/50 (8%) of those given tamoxifen and 17/50 (34%) men were treated with breast irradiation. Skin rash or erythema occurred in 2 men in each of the bicalutamide and bicalutamide/tamoxifen groups compared with 22 in the irradiated group.

Among the 35 patients originally assigned to bicalutamide, who developed gynaeconomastia/mastalgia, tamoxifen significantly reduced the incidence of gynaeconomastia.

In order to determine the optimum tamoxifen dose for reducing gynaeconomastia and/or mastalgia, Fradet et al. (6) conducted a double-blind, parallel-group, multicentre trial comprising 282 men with prostate cancer who were randomised to bicalutamide 150 mg daily for 12 months plus tamoxifen at a dose of 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg or placebo. This was followed by 12 months of bicalutamide alone and results are shown in Table 3. This indicates the dose response with significant reduction in symptoms at dosages >2.5mg compared with placebo. Hot flushes occurred in 8% of the placebo group compared with 20% of those taking tamoxifen 20 mg daily.

In an Italian trial, Bedognetti et al. (7) compared two different tamoxifen schedules in 80 patients with prostate cancer who were suitable for bicalutamide monotherapy. Patients were randomised to either daily (41 patients) or weekly (39 patients) tamoxifen, the latter being given tamoxifen originally for 8 weeks. Treatment was discontinued because of side effects in 3 patients in the weekly group and 1 in the daily group. Of the men in the daily group, breast symptoms developed in 13 (32%) compared with 29 (74%) in the weekly group. Because of this lack of efficacy of the weekly tamoxifen schedule (the daily schedule is effective), the trial was halted prematurely. There was no increase in venous thromboembolism in any of the tamoxifen trials. Taken together, these studies suggest that tamoxifen at a dosage of 20 mg is an effective and reasonably well-tolerated therapy for antiandrogen-induced gynaeconomastia and mastalgia and this treatment could be started in primary care. Nevertheless, the long-term side effects and impact on prognosis are not known warranting the set-up of well-designed large randomised trials (RCTS).

In men with benign prostatic hypertrophy (BPH), 5-alpha reductase inhibitors (5ARIs) are of value, but may increase the risk of breast enlargement. Hagberg et al. (8) conducted a cohort study of men aged >40 years with BPH and determined exposure to 5ARIs (dutasteride or finasteride) or alpha blockers, ABs (Terazosin, Doxazosin, Alfuzosin, Tamsulosin and Silodosin). Compared with no exposure, there was a threefold increase in risk of gynaeconomastia risk for men taking 5ARIs

Table 3. Breast symptoms with bicalutamide in relation to tamoxifen dose (Fradet 2007) (6)

Time	Placebo	1mg	2.5mg	5mg	10mg	20mg
6 months	98%	90%	80%	54%	22%	10%
12 months	99%	95%	84%	56%	38%	19%

alone or together with ABs. There was however no increase in the risk for male breast cancer associated with 5ARIs or ABs in this study.

Body builders

Body builders may take a “stack” of non-prescription anabolic steroids, predisposing to gynaecomastia and this practice is very widespread (9). Evans surveyed 100 athletes at 4 gyms in Wales with an anonymous self-administered questionnaire (10). All were using anabolic steroids and 15% had taken them for 6-12 years at dosages of from 250 to 3200 mg per week. Side effects included acne, striae, and gynaecomastia together with withdrawal symptoms. Calzada et al. (11) administered anabolic steroids including nandrolone decanoate, Ropionate, phenilpropionate, isocaproate and testosterone decanoate to 12 bodybuilders over 6 months and compared steroid hormone levels in their blood with that of 10 healthy controls (11). In the bodybuilders, there was a >50% reduction in testosterone and LH and FSH levels were reduced by 23% and 13%, respectively compared with controls. A further risk is thrombophlebitis (Mondor's syndrome) which may simulate malignancy by causing skin retraction (12). De Vries et al. (13) reported a 29-year-old male with a painless breast lump who had been diagnosed with gynaecomastia 4 years ago following anabolic steroid abuse. This proved at excision biopsy to be an intraduct papilloma.

Mastalgia may often arise from the rib cage and this can be verified by identifying the trigger point. Treatment is reassurance with occasional recourse to NSAIDs. Gynaecomastia with associated pain can be distressful for men with prostate cancer. If the pain is prolonged and severe, referral should be considered since some may benefit from tamoxifen therapy. For individuals with a discrete lump, nipple discharge, distortion or unilateral gynaecomastia, malignancy is a possibility; therefore, urgent referral to a breast clinic is advisable.

Breast Clinic assessment of symptomatic males

Although the principles of clinical evaluation of men with breast symptoms are similar to those used in females, there are still some important differences. In terms of history-taking, a family history of female breast cancer (FBC) and occasionally male breast cancer (MBC) should be inquired after eliciting the presenting sign(s) and duration. For the reproductive history, those who are in a heterosexual partnership but without children should be asked whether this was out of choice. Prior testicular damage or undiagnosed Klinefelter's syndrome may be responsible for male infertility with an associated increase in the risk for MBC. Many of these patients will be retired, but their prior occupation should be inquired since some such as blast furnace workers may have testicular malfunction due to a prolonged high ambient temperature. As described previously, the drug history may indicate possible cause(s) for gynaecomastia.

Clinical examination

After inspection and palpation of the breasts, axillae and neck with the patient in the supine position, he is then asked to turn halfway on his side so that the palpation can be repeated both facing towards and away from the examiner. If there is nipple discharge, this should be tested for the presence of occult blood. Following the breast examination, the abdomen is palpated to determine whether hepatomegaly is present

together with any evidence of hepatic dysfunction. Finally, the testes should be examined for signs of atrophy or tumour. The clinician should then be in a position to make a working diagnosis and determine the need for further evaluation. Selection of imaging should be based on the benefits and disadvantages of mammography and ultrasound.

Mammography

Whereas mammography plays an intrinsic role in the investigation of women aged >40 who have breast symptoms, this should not be the default position for males. Although mammography may be reasonably comfortable for men with grade III/IV gynaecomastia, for others it can be very painful and of little value. As part of the work-up of men with male breast cancer, mammography is mandatory in order to determine the extent of disease and to exclude contralateral cancer. As a screening investigation, it is of dubious value.

Hanavadi et al. (14) carried out an audit of all 220 male patients referred to the breast clinic at the University Department of Surgery, Cardiff between January, 2001 and December, 2003. Mammography was carried out in 134 (61%), usually before the patient was seen by a clinician. There was a total of 4 cancers diagnosed and in every case the diagnosis was suspected on clinical examination and subsequently confirmed histologically. It was concluded that mammography was unnecessary for most males and did not have a role in routine imaging.

Hines et al. from (15) the Mayo Clinic reviewed the mammograms of 198 men who had 212 mammograms of which 9 (4%) showed suspicious signs. Eight men underwent biopsy, which yielded a breast cancer diagnosis in 2 (1%). Of the 212 mammograms, 203 (96%) showed benign findings, including gynaecomastia on 132 (62%). One patient with a benign-appearing mammogram later underwent breast biopsy, and malignant disease was diagnosed. All the men with breast cancer had a dominant mass on clinical examination and other findings suggestive of breast cancer. Of the 132 mammograms showing gynaecomastia, 110 (83%) were from men who had taken predisposing medications or who had predisposing medical conditions. The conclusion was that mammography added little information to the initial patient evaluation, being of benefit only for image-guided biopsy of a suspicious mass.

Lapid et al. (16) reported the outcomes of imaging with mammography or ultrasound of the male breast in 557 patients seen over a 10-year period. The most common reason for referral was breast enlargement present in 74% of patients: 25% complained of pain and 10% had a lump. The majority of images were reported as BI-RADS 1 or 2, with only 38 being BI-RADS 3 or higher. Cancer was diagnosed in five patients (0.89%) and all of these had suspicious symptoms and signs. The probability of finding cancer with clinically benign examination was negligible. They concluded that imaging was unnecessary unless there were suspicious clinical abnormalities present and routine imaging of gynaecomastia should be discouraged. This is important both in terms of patient comfort and conservation of resources.

Ultrasound

Chen et al. (17) determined the incremental benefit of ultrasound in males with gynaecomastia who had normal mammograms. In a retrospective study, those whose ultrasound diagnosis differed from the initial mammographic evaluation were analysed in relation to extra benign findings together with signs that warranted biopsy. Out of 353 mammograms in males aged 18–95, gynaecomastia was the sole finding in 259 (73%). Ultrasound was performed in 220 cases (85%) resulting in 6 (2.7%) having further benign findings, and 4 (2%) with suspicious findings which were biopsied but no cancers were found. All cases of the cancers manifested with visible masses on mammography. This indicates the limited value of ultrasound which may lead to more unnecessary biopsies. An outline of management of male cases, based on the available evidence, is shown in Figure 1.

Spectrum of male breast diseases

Gynaecomastia

The most frequent male complaint is gynaecomastia, either true or pseudo, and the primary need is for reassurance. When accompanied by pain, the cause is often linked to medication and relief may be obtained by modification of drug or dosage. When this is not possible, tamoxifen can be of value in both relieving pain and diminishing the size of the swelling. Because of embarrassment, some men with grade III gynaecomastia may ask for surgery. In a series of 1261 men seen over a 10-year period at the Frenchay Hospital Bristol, 938 (74%) had gynaecomastia and surgery (subcutaneous mastectomy) was performed on 224 (18). Post-operative complications were infrequent: the most common one being haematoma (12%), followed by seroma (3%), infection (1%), wound dehiscence (1%) and nipple necrosis (1%). Further surgery was necessary in only 3%.

Because standard surgery with excision through periareolar or T-shaped can produce extensive scarring, Bailey et al. (19) developed a different approach using liposuction followed by a pull-through technique to remove glandular tissue. In a series of 75 patients with gynaecomastia, the proportions of grade I–IV were 31%, 36%, 23% and 10%, respectively. There were no complications in this series. Ultrasound assisted liposuction was performed through a 2–4 mm stab wound in the lateral inframammary fold. Following this, a Kocher clamp was inserted through the same incision site and glandular tissue was grasped and pulled externally before being excised. Only one patient required re-operation and there were no complications of the procedure which achieved acceptable cosmetic results.

In a study from Rigshospitalet, Copenhagen, 786 men with gynaecomastia underwent clinical examination, testicular ultrasound of the testicles and endogenous serum hormones assays (20). Of those aged ≥18 years, underlying causes were identified in 43% whereas an abnormality was detected in only 8% of younger men. This suggests that a careful clinical examination and endocrine profile is important for identifying older individuals with potentially treatable causes for gynaecomastia.

Other male breast lumps

The most common benign breast lumps in females are cysts and fibroadenoma. However, as both are derived from lobules, which do not normally develop in males, they are rare conditions in men. Robertson et al. (21) described a 27-year old male with fibrocystic change in association with papillary hyperplasia. Parsian et al. (22) reported a benign breast cyst in a 58-year old male who was undergoing staging tests for mantle cell lymphoma.

In a study from the US Armed Forces Institute of Pathology, there were only 4 fibroadenomas in male breasts, all of which had co-existent gynaecomastia with lobular development (23). Fibroadenomatoid hyperplasia has been described in association with long-term spironolactone medication and fibroadenoma can develop as a result of leuprolide treatment for prostatic cancer (24, 25). Ashutosh et al. (26) reported a 72-year-old man who presented with a giant fibroadenoma (25 cm) having received 4 years of anti-androgen therapy for prostate carcinoma after orchidectomy.

Fat necrosis

Fat necrosis may manifest as a breast lump, sometimes with skin tethering, hence malignancy may be suspected. Predisposing factors include trauma, prior breast surgery, radiotherapy and occasionally in those on warfarin anticoagulation. The first case of a male with fat necrosis of the breast was described by Silverstone in 1949; although this was confirmed histologically, there was no past history of trauma, nor any other apparent causes (27). Akyol et al. (28) reported a 57-year-old male with a left breast lump one year following chest trauma. On examination, there were hard, fixed lumps in the upper outer quadrant with no axillary lymphadenopathy. Ultrasound showed a combination of scattered small cysts together with a complex cyst with two irregularly isoechoic solid masses which projected into the cyst. Additionally, there were scattered, well-circumscribed subcutaneous lesions with a posterior enhancement.

Fat necrosis elicits a fibrotic reaction and the appearance is mammographically affected by the extent of fat liquefaction (oil cysts) and occasionally associated microcalcification. There may be a classical oil cyst, a radiolucent lesion with a thin surrounding membrane. Intense fibrotic reactions display irregular, or poorly defined margins, sometimes replacing the cyst to form a spiculated mass mimicking malignancy.

Nipple discharge

Johnson & Kini reviewed 225 patients with nipple discharge of whom 9 were male (29). There was a significantly increased risk for cancer in males: 2/9 (22%) versus 3/216 (1.5%) in females. Detraux et al. (30) reported 7 males with unilateral nipple discharge but with no palpable abnormality. They used galactography to determine the underlying cause, which was cancer in 2 cases, both of whom had bloody discharge. Another 2 had benign papillomas (one bloody, one serous), 2 had duct ectasia (both non-bloody) and 1 had a breast abscess (serous), and two were ductal ectasia (non-bloody).

Morrogh and King reported 24 males with breast problems seen at Sloan-Kettering Memorial between 1995 and 2005 (31). Of these, 14 (58%) complained of nipple discharge whereas the other 10 (42%) had palpable lumps with no discharge. Of those with nipple discharge, 7 (50%) had a lump present on palpation. Cancer was the underlying cause of the discharge in 8/14 (57%) and this was DCIS in 2 and invasive disease in 6 patients. This does indicate the need for hospital referral to evaluate all men with nipple discharge.

Hyperprolactinaemia is a side effect of long-term phenothiazine administration and may lead to the development of papillomas in males. Sara et al. (32) described a 71-year-old white male who had received thioridazine followed by fluphenazine for several years and developed coffee-coloured left nipple discharge. The discharge stopped 6 months before he was seen and the breast enlarged with a 10 cm subareolar mass. At surgery, this proved to be a cyst containing an intraductal papilloma. In males, intraduct papillomas are more likely to present as breast lumps rather than with a nipple discharge (33).

Reid-Nicholson et al. (34) reported a series of 11 males with papillary breast lesions, all of whom had breast lumps. The age range was from 23-78 years of age with masses measuring 0.5-3 cm. Cytology showed smears of varying cellularity but there were consistently papillary clusters of epithelial cells with and without fibrovascular cores. Only 2 males had a bloody nipple discharge and both had benign papillomas.

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A Systematic Review and Pooled Analysis of Studies of Oral Etoposide in Metastatic Breast Cancer

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ABSTRACT

Objective: Oral etoposide has been used as a later line therapy for metastatic breast cancer for more than twenty years. Its efficacy and clinical usefulness has been suggested in small phase II studies in the metastatic breast cancer population and the drug has also the added advantage of convenient oral administration. Despite these advantages, the place of oral etoposide in treatment of metastatic breast cancer has been challenged in the last decade due to introduction of several other chemotherapeutics, including options available orally, as well as novel targeted therapies. This report pools the data on response rates and survival from all available oral etoposide studies in order to reach a more precise estimate of the clinical benefit of the drug.

Materials and methods: A review of the literature was performed for studies of oral etoposide in metastatic breast cancer. Data were extracted from eligible studies and summary statistics derived. Calculations of pooled response rates and survival estimates were performed according to a random or fixed effect model as appropriate.

Results: The pooled estimate of Response Rate derived from twelve studies found in the English literature was 18.5% (95% CI 11.5-25.5%). The pooled estimate of Clinical Benefit Rate (CBR) was 45.8% (95% CI 38.6-53.0%) and median Overall Survival (OS) approached 1 year. Summarized adverse effects profile data show an overall manageable toxicity.

Conclusion: This pooled analysis provides evidence of a moderate clinical effectiveness of oral etoposide in metastatic breast cancer that could be useful in situations that options are limited but active treatment still appropriate.

Keywords: Breast cancer, metastatic, chemotherapy, oral etoposide; metronomic

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Introduction

Several chemotherapy options exist for the treatment of patients with metastatic breast cancer. Newer drugs such as capecitabine (Xeloda, Roche, Basel, Switzerland), vinorelbine and eribulin (Halaven, Eisai, Tokyo, Japan) have been introduced in recent years to supplement anthracyclines and taxanes and help control disease and prolong the life of these patients (1). Before the introduction of these newer options, as well as several targeted treatments such as Cyclin-Dependent Kinase 4/6 inhibitors and mechanistic Target of Rapamycin (mTOR) inhibitors, oral etoposide had been one of the few available systemic treatments in the oncology armamentarium for advanced breast cancer. This drug can be given in daily low doses with a brief interruption of a few days at every three-weekly or monthly cycle. It has the advantage of oral administration that makes it a preferred option in the palliative setting and is still used, although less commonly, when other options are not available or had already failed but a treatment is appropriate. Nevertheless the efficacy of oral continuous dose etoposide in metastatic breast cancer has only been studied in small phase II trials with a few patients in each of them. These studies have been one arm, non-randomized and non-blinded with all possible biases associated with this design. The current paper reports a pooled analysis of all available trials of oral low dose daily etoposide in advanced breast cancer in order to obtain a more accurate efficacy evaluation of the drug. This estimation, although not negating the above limitations associated with the source studies, will inform better the

clinician on the benefits that could be expected with the use of the drug in the palliative setting. In addition an overview of the toxicity profile of oral etoposide derived from the whole body of data in these studies will be discussed.

Materials and Methods

The two essential databases of medical literature, Medline/PubMed and Embase were searched for articles related to oral etoposide in advanced breast cancer. Search terms used were “oral etoposide” and “metastatic breast cancer” or “advanced breast cancer”. Studies were retained for further data extraction and data analysis if they were published in English, were describing the use of low dose daily etoposide as monotherapy in metastatic breast cancer patients and included more than twenty patients. Articles in other languages, case reports or case series of less than 20 patients and studies describing pre-clinical, pharmacokinetic or pharmacodynamics data were excluded. Also excluded were studies using etoposide in other cancers, in the adjuvant setting, in combination with other chemotherapy drugs, in high dose intermittent schedules or with an intravenous administration. In addition to the electronic search, a scanning of references of retained articles manually for additional publications fulfilling the inclusion criteria was performed.

Data obtained from the retrieved studies pertaining to patients' population characteristics and treatment efficacy and adverse effects were tabularized and stored in a database. Patients' data extracted for this pooled analysis included age of the patients, Eastern Cooperative Oncology Group (ECOG) performance status, number and type of previous lines of treatment for metastatic disease, number and site (visceral versus non-visceral) of organs involved, and biologic type of the breast cancer [Estrogen Receptor (ER) and Human Epithelial Growth Factor Receptor family member 2 (Her2) receptors expression], when available. Efficacy outcomes of interest included Response Rate (RR), Clinical Benefit Rate (CBR), median Overall Survival (OS), median Progression-Free Survival (PFS) or Time to Progression (TTP). Data on all grades and grade 3 and 4 toxicity rates were also obtained from the included studies for this pooled analysis.

There have been no conflicts of interest regarding this work. As this study involves only analysis of previously published data and no new data with human participants, no informed consent was required and no approval by the institution Ethics Committee.

Statistical analysis

Summary statistics were calculated for outcomes of interest measurements. Only part of the characteristics and outcomes of interest were available from each study included in the analysis. Thus, presented data in each occasion as well as efficacy and toxicity outcomes and their means and confidence intervals were calculated with the total number of patients in the studies with the given characteristic or outcome of interest as the denominator. The number of studies from which each outcome of interest was derived is also presented in the results tables. Pooled outcomes rates calculations were weighted according to the number of patients in each study. As several studies provided TTP instead of PFS as the survival measure of treatment efficacy, for the purpose of the current analysis, a pooled estimate of both PFS and TTP was calculated. In cases where TTP was provided instead of PFS, estimated 95% confidence intervals were calculated from the range according to the formula: $\text{variance} = \text{range}/4$ (2). Heterogeneity among the studies was evaluated with the Cochran's Q and I^2 tests. The fixed

or random effect model was employed as appropriate according to the degree of heterogeneity (3). Calculations were performed in Excel (Microsoft Corp., Redmond, WA) with some modifications of a previously described method (4).

Results

Review of the literature led to the retrieval of sixty two articles (Figure 1). After exclusion of preclinical, pharmacokinetics, pharmacodynamics reports and reviews or case reports and publications not in English, thirty eight clinical reports remained. Twenty six of them were further excluded because they were not referring to breast cancer (nine publications), were studying etoposide in combination with other drugs or in the adjuvant setting (fifteen publications), were probably partially overlapping with one of the included studies (one publication) (5) or used higher dose intermittent schedule (one study) (6). Twelve publications were retained for the current analysis (Table 1). Included studies were published between 1993 and 2015 and reported on a total of 483 patients (Table 2). All studies except one that was retrospective (7), had a prospective phase II, non-randomized, one arm design (8-18). Besides two studies that were from China (17, 18), all other reports originated from Europe and the United States (Table 1). The median age of patients in most included studies was between 50 and 60 year-old with a wide range. Most patients for whom data were available had a performance status of 0 (33%) or 1 (44%) (Table 2). The median number of previous lines of chemotherapy ranged from 1 to 8 in the different studies with older studies published before 2001 including mostly first and second line patients while the few studies published more recently including later line patients, mostly third line and beyond. Information on previous treatments was reported in only six studies for anthracyclines and four studies for taxanes. In these studies most patients had previously received the two drugs (Table 2). In two studies from the era after the introduction of capecitabine, previous exposure to this drug was observed in 54% of the patients. ER status of patients was reported in five studies and was positive in 63.6%. Only three studies dated from the era after the introduction of routine use of HER2 evaluation and reported a HER2 positivity of about 27%. The dose and schedule of oral etoposide used most commonly was 50 mg/m² for 21 days of a 28-day cycle in seven studies, while the two Chinese studies used a dose of 60 mg/m² for 10 days of a 21-day cycle and two others used a fixed dose of 100 mg for 10 days of a 21-day cycle and of 50 mg for 20 days in a 28-day cycle, respectively.

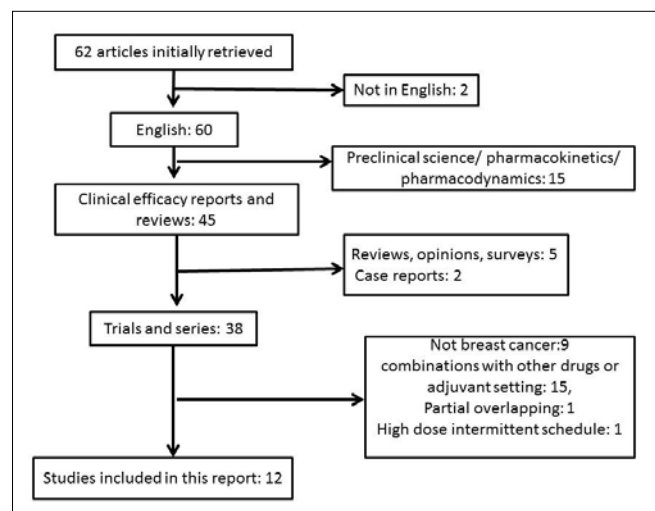


Figure 1. Schematic diagram of studies initially evaluated for the current pooled analysis and reasons for exclusion

Table 1. The twelve studies included in this pooled analysis of oral daily etoposide in metastatic breast cancer patients. Question mark denotes that CBR is not reported in the study

Study [Reference]	Year of publication	Country	Number of patients	RR (%)	CBR (%)
Saphner et al. [8]	2000	U.S.A., S. Africa	30	30.0	?
Pusztai et al. [9]	1998	U.S.A.	30	4.2	33.3
Atienza et al. [10]	1995	U.S.A.	30 (26 evaluable for response)	19.2	42.3
Palombo et al. [11]	1994	Spain	18	22.2	55.6
Martin et al. [12]	1994	Spain	43	34.9	?
Bontenbal et al. [13]	1995	The Netherlands	25	9.5	42.9
Calvert et al. [14]	1993	U.K.	38	21.1	36.8
Neskovic et al. [15]	1996	Serbia	21 (18 evaluable for response)	33.3	88.9
Jagodich et al. [16]	2001	Slovenia	75	37.3	50.7
Yuan et al. [17]	2012	China	32	25.0	68.8
Valabrega et al. [7]	2015	Italy	66	4.5	37.9
Yuan et al. [18]	2015	China	75	9.3	48.0

CBR: Clinical Benefit Rate; RR: response rate

Table 2. The twelve studies included in this pooled analysis of oral daily etoposide in metastatic breast cancer patients. Question mark denotes that CBR is not reported in the study

	Pooled studies (%)	Total patients with data	Number of series with data		Pooled studies (%)	Total patients with data	Number of series with data
Age (median, range)	50-62 (26-83)	483	12	2	49 (32.7%)	150	3
ECOG PERFORMANCE STATUS				3	33 (22.0%)	150	3
0	77 (32.9%)	234	6	≥4	24 (16.0%)	150	3
1	71 (44.1%)	161	5	SITES INVOLVED			
2	20 (10.5%)	191	6	Visceral	87 (56.5%)	154	4
3	9 (2.8%)	321	9	Non-visceral only	67 (43.5%)	154	4
# PRIOR LINES OF CHEMO				ER STATUS			
0	64 (16.5%)	387	10	Positive	138 (63.6%)	217	5
1	119 (33.3%)	357	9	Negative	71 (32.8%)	217	5
2	111 (31.1%)	357	9	Unknown	8 (3.7%)	217	5
≥3	97 (25.1%)	387	10	HER2 STATUS			
Median #	0-8	483	12	Positive	47 (27.2%)	173	3
Range #	0-13	423	10	Negative	118 (68.2%)	173	3
TYPES OF PRIOR CHEMOTHERAPY				Unknown	8 (13.7%)	173	3
Anthracyclines	215 (80.2%)	268	6	Triple negative	18 (12.8%)	141	2
Taxanes	116 (74.8%)	155	4	EFFICACY			
Capecitabine	27 (54%)	50	2	Median OS (months) (95% CI)	11.7 (9.6-13.8)	228	5
Hormonal	136 (59.1%)	230	6	Median PFS or TTP (months) (95% CI)	3.6 (2.6-4.6)	303	6
# ORGANS INVOLVED				RR% (95% CI)	18.5 (11.5-25.5)	483	12
1	54 (31.6%)	171	4	CBR% (95% CI)	45.8 (38.6-53.0)	410	10

PFS: Progression-Free Survival; ER: Estrogen Receptor; RR: Response Rate; CBR: Clinical Benefit Rate

A Response Rate (RR) pooled analysis has included all twelve studies that provided RR data and referred to a total of 466 evaluable patients. Pooled RR was 18.5% (95% CI 11.5-25.5%) (Figure 2). Evaluation for heterogeneity between studies disclosed a high I^2 value of 74 (Cochran's $Q=42.44$, $\chi^2 p=0.0001$). Thus, calculations were made under a random effect model.

Information on Clinical Benefit Rate (CBR) was provided in ten studies with 393 patients, which formed the basis for a pooled analysis presented in Figure 3. This analysis disclosed a CBR of 45.8% (95% Confidence Interval (CI) 38.6-53.0%). Heterogeneity between studies was low ($I^2=10.8$, Cochran's $Q=10.09$, $\chi^2 p=0.34$) and both fixed and random models produced similar results. Results presented in Figure 3 depict the analysis with the random effect model.

Progression-Free Survival (PFS) data were available in three studies (13, 17, 18) and three additional studies provided Time to Progression (TTP) data instead (7, 10, 16). The total number of patients in these six studies was 295. For the pooled analysis PFS and TTP were analyzed together as, although they are not identical, they are of similar

clinical value. Heterogeneity between studies was intermediate ($I^2=49$, Cochran's $Q=9.9$, $\chi^2 p=0.07$) and a random effect model was used. The pooled PFS derived was 3.6 months (95% CI 2.6-4.6 months) (Figure 4).

Overall Survival (OS) data were available in five of the studies that included a total number of 224 patients (7, 8, 13, 16, 17). Heterogeneity between studies was low and both random and fixed models gave similar results ($I^2=0$, Cochran's $Q=2.35$, $\chi^2 p=0.67$). Results presented in Figure 5 show the analysis with the random effect model. The pooled OS was 11.7 months (95% CI 9.6-13.8 months). One of the studies (8) had a clearly higher median OS of 24 months, although with a wide range than the other four. About half of the patients in this trial were treated in the first line metastatic setting, while the others mostly contained patients in second or later line setting.

Three studies presented RR according to number of previous chemotherapies (8, 10, 15). In the first of these, RR was 57.1% (eight of 14 patients) in patient treated with first line oral etoposide and 6.25% (one of 16 patients) in patients receiving the drug as a second or later

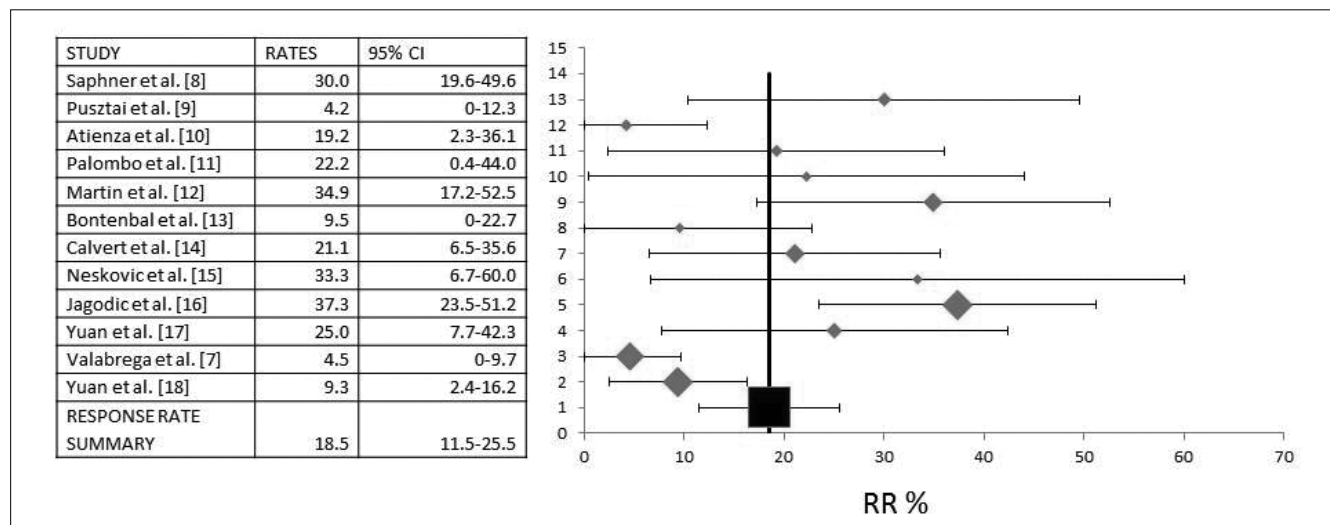


Figure 2. Diagram of pooled analysis of Response Rates (RR) and 95% Confidence Intervals (CI) of studies of oral etoposide in metastatic breast cancer. Twelve studies that included a total of 466 patients that provided information on the RR were analyzed. Overall, RR was 18.5% (95% CI 11.5-25.5%)

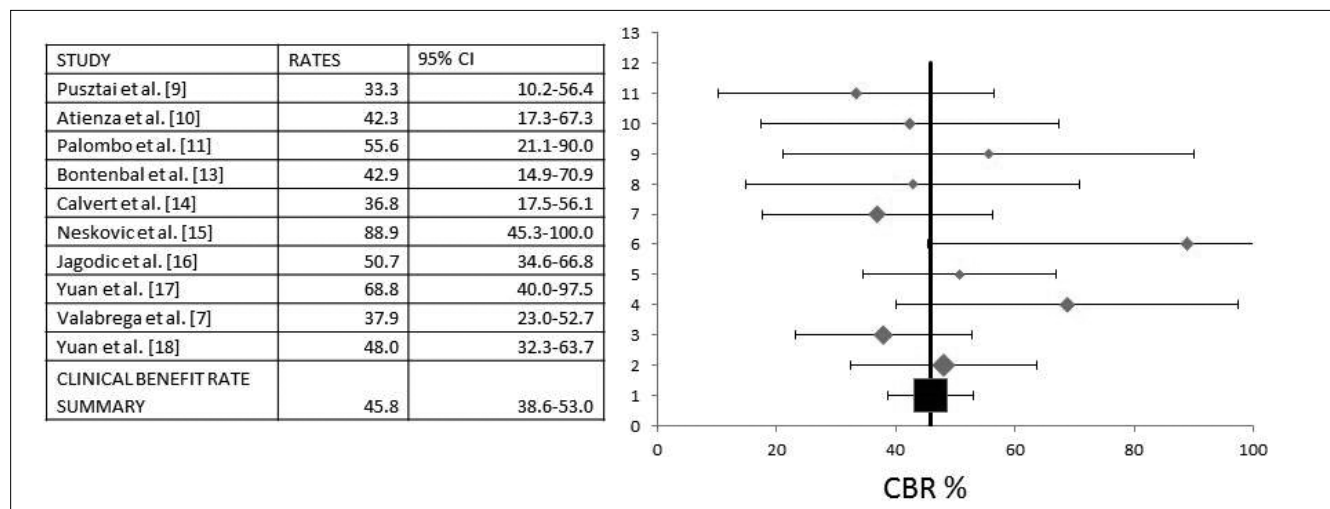


Figure 3. Pooled analysis of Clinical Benefit Rates (CBR) and 95% Confidence Intervals (CI). Ten studies with a total of 393 patients that provided information for CBR were included in this analysis. The overall CBR was 45.8% (95% CI 38.6-53.0%)

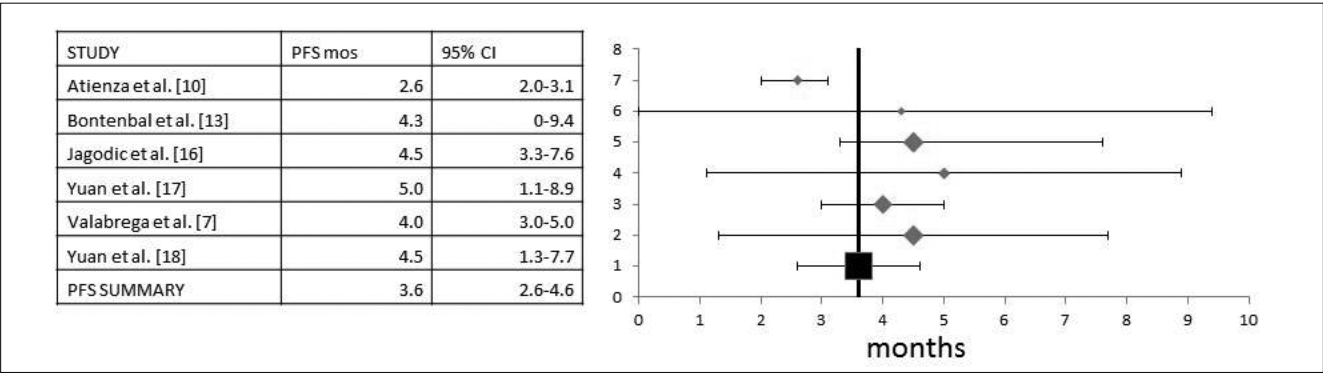


Figure 4. A pooled analysis of Progression-Free Survival (PFS) (three studies with TTP instead) and 95% Confidence Intervals (CI) includes six studies with a total of 295 patients. Overall PFS was 3.6 months (95% CI 2.6-4.6 months)

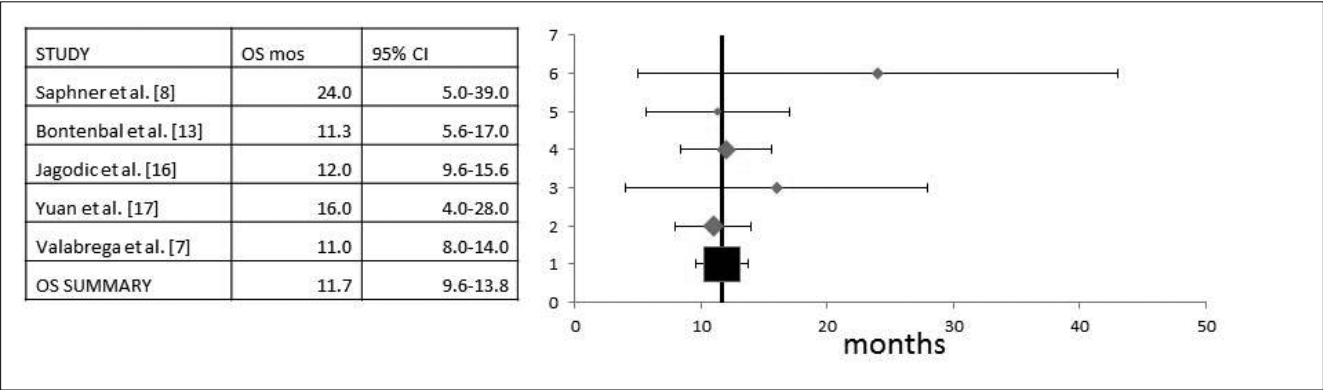


Figure 5. Pooled analysis of Overall Survival (OS) and 95% Confidence Intervals (CI). Five studies with a total of 224 patients that provided information for the OS were included. Pooled OS was 11.7 months (95% CI 9.6-13.8 months)

line treatment (8). In another study the respective RR in first and later lines were 20% and 18.75% (10). In the third study that included only patients receiving etoposide as a second or later line treatment, RR were 28.6% (four of 14 patients) in the second line, 35.8% (19 of 53 patients) in the third line, and 54.2% in the fourth or later line (15). Three studies reported on responses in different metastatic sites (11, 12, 15) and noticed that a variety of metastatic sites were among the responding sites. Another study performed a PFS analysis according to metastatic site and reported that patients with visceral metastases had a worse PFS than the rest of the populations in the study (18). No study provided any information on responses of brain metastases to oral etoposide.

Common adverse effects of all grades reported with oral etoposide included alopecia (59%), nausea and other GI toxicities (58.8%), anemia (42.4%), neutropenia (52%), mucositis (31.8%), asthenia/fatigue (28.2%), and anorexia (25%) (Table 3). Neutropenia was the most common grade 3 or 4 toxicity (19.7%) and it was febrile in 7.5% of patients and fatal in 1.7% of patients. No other type of grade 3 or 4 toxicity was observed in more than 10% of patients (Table 3).

Discussion and Conclusion

Despite increasing options for the systemic treatment of patients with metastatic breast cancer, low dose etoposide remains a valid option for later line treatment of these patients, preferred by some clinicians for its ease of administration by the oral route that may favor quality of life and avoids clinic visits and drug infusions. The low, protracted mode of dosing of chemotherapeutic drugs, mostly with daily oral administration, often referred to as metronomic, is proposed to have an

indirect effect on tumor progression through interference with neo-vascularization (19). This dosing produces different pharmacokinetic levels and clinical effects than the intravenous administration of etoposide used in other settings such as in regimens with cisplatin for the treatment of Small Cell Lung Cancer or Germ Cell Tumors (20, 21).

Etoposide is a podophyllotoxin derivative antineoplastic drug that works as an inhibitor of topoisomerase II (topo II). Inhibition of the alpha isoform of the enzyme by the drug results in stabilization of double stranded DNA cleavage sites induced by topo II and delays transition of cells through the S phase of the cell cycle and leads to cycle arrest in the G2 phase (22). Oral low dose protracted administration of etoposide was introduced in the 1990s based on data from few small phase II studies with a number of patients ranging up to few dozens in each (8-15). These have predated the introduction of more modern options such as capecitabine, vinorelbine and eribulin and included, in general, patients with few lines of previous chemotherapies in the metastatic setting (mostly 0 to 2). They confirmed the ease of administration and acceptable toxicity profile; although a low percentage of high grade toxicities and even rare fatalities from sepsis were also observed (14). More recently, a revival of the interest in oral etoposide has been seen in the literature with a few additional phase II studies and a retrospective series including now later line patients, given that other options are available (7, 17, 18).

This report pools all available studies on oral etoposide in metastatic breast cancer that used a metronomic mode of administration with daily doses in general ranging from 50 mg/m² to a fixed daily dose of 100 mg in order to reach a more accurate estimation of these regimens

Table 3. Toxicity of oral etoposide in patients in the pooled studies. The third and fifth columns contain information on the total number of patients and number of series the percentage depicted in the second and fourth columns is based on

	% all grades	Total patients with data/ series with data	% Grade 3 and 4	Total patients with data/ series with data
TOXICITY				
Asthenia/ fatigue	28.2	39/2	NA	0
Neutropenia	52.0	375/8	19.7	385/9
Febrile neutropenia			7.5% (1.7 gr 5)	173/4
Anemia	42.4	375/8	5.5	398/9
Thrombocytopenia	9.9	375/8	3.7	428/10
Peripheral Neuropathy	10.3	107/2	0	107/2
Nausea/ GI toxicity	58.8	308/8	6.2	289/7
Mucositis	31.8	267/6	2.2	184/3
Alopecia	59.0	273/8	NA	
Anorexia	25.0	54/2	2.9	171/3
Transaminitis	7.5%	173/3	0	141/2

efficacy and toxicity. This analysis confirms a modest PFS/ TTP with oral etoposide of 3.6 months and OS of just below one year. A pooled RR rate estimation of about 18% and CBR of about 45% confirm the clinical impression that some patients derive a benefit from the drug. Nevertheless, it should be noted that since several of the studies have been performed in patients with fewer lines of treatment than current patient populations, who have mostly several lines of metastatic treatment before etoposide, a lower RR and CBR may be expected. Older studies performed in the 1990s used the 50 mg/m² for 21 days of a 28-day cycle dosing, while the four studies done after 2000 used either a fixed dose of 50 or 100 mg or a dosing of 60 mg/m² for 10 days of a 21-day cycle. Although comparisons between studies are difficult and there is variability of RR even in studies that used the same dose and schedule, it appears that no significant effect of dose exists. This may be due to the fact that the various dosing and schedules result in small overall difference in dose density received (e.g. total dose 600 mg/m² in 21-days with the 60 mg/m² for 10 days of a 21-day cycle and total dose 760 mg/m² in 21-days with the 50 mg/m² for 21 days of a 28-day cycle).

In the last decade several new chemotherapy options have been added to the later line metastatic breast cancer armamentarium including capecitabine, vinorelbine, gemcitabine and eribulin. With the caveats that inter-trials comparisons always entail, the current data suggest that oral etoposide remain a valid option with similar efficacy in metastatic breast cancer. For example a recent analysis of retrospective series of eribulin in pretreated metastatic breast cancer has disclosed a RR of 20%, a CBR of 46%, a pooled PFS OF 3.8 months and OS of 9.7 months, all very similar with the respective results for oral etoposide (23). In our series of metastatic breast cancer patients treated with vinorelbine in the first or later line setting, RR was 37% overall but only 12% as a second or later line treatment (24). The median TTP was six months for the whole series independently of line of treatment. A meta-analysis of twenty two studies of chemotherapy labeled metronomic in metastatic breast cancer patients was recently published (25). Treatments in the summarized studies were heteroge-

neous and included cyclophosphamide, methotrexate, vinorelbine and capecitabine among others alone or in combinations. No studies with oral etoposide were included. Pooled RR was 34.1% and the OS at 6 months 70% (25). Although these results appear to be somewhat better than the rates obtained with oral etoposide, patients were probably less heavily pre-treated, at least in some studies, and received combination with non-metronomic schedules in several of the included studies in this meta-analysis.

Oral etoposide in the doses and schedules used in the twelve pooled studies showed a manageable toxicity profile (Table 3). Although most patients experienced some toxicity of any grade, rates of grade 3 and 4 toxicities were low. Most common grade 3 and 4 toxicity was febrile neutropenia that was observed in almost 20% of patients for whom information was available and febrile neutropenia was present in 7.5% of patients. This is similar, for example, with the grade 3 and 4 neutropenia and febrile neutropenia rates observed with eribulin in heavily pretreated metastatic breast cancer patients (28.1% and 5.4% of patients respectively) in a similar pooled analysis (23).

There are limitations of the current analysis as already alluded to. First several of the included studies date from the nineties, they are small in size without comparison arms and their patient population is different from the patient population that would most probably be treated with oral etoposide today, as there are additional options, including oral targeted therapies. Nevertheless, the current analysis suggests that the overall efficacy of oral etoposide is probably not very different from other chemotherapy options available for later line metastatic breast cancer and given that it is cheaper than other alternatives, it represents a high benefit to cost option in the current financially conscious health systems environment. Additionally, oral etoposide could be a valid option for health systems with sparse resources.

The current analysis confirms that the older regimen of low dose oral etoposide given in a protracted manner has a modest benefit for patients with metastatic breast cancer, in general similar to other more recently introduced options and an acceptable adverse effect profile.

Thus, it may still be considered in this clinical scenario if active palliative treatment is warranted.

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Informed Consent: Informed consent was not requested for this study.

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Characteristics of Special Type Breast Tumors in Our Center

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ABSTRACT

Objective: Breast cancer is a heterogeneous disease with different histological types. Ductal breast cancer constitutes the vast majority of the breast cancers. However limited data are present in the rest of breast cancers called special or rare type breast cancers. Here in this study, we tried to describe the clinical features of special type breast cancers in our center.

Materials and Methods: Retrospective descriptive study was performed in Kocaeli University School of Medicine, Department of General Surgery between January 2000 and January 2016. Women diagnosed with primary breast cancer other than ductal carcinoma were included to the study. In total, 101 patients were evaluated according to histologic types, molecular types, Tumor Node Metastasis (TNM) stages, and grades. Survival of the patients was also evaluated.

Results: Medullary and metaplastic types showed basal type; tubular, mucinous, micropapillary carcinoma, cribriform, lobular and apocrine tumors showed luminal type molecular pattern. Neither the existence of ductal carcinoma nor any histologic types had any effects on survival. Apocrine tumors were presented in younger ages.

Conclusion: Histologic types of breast cancer are closely related with the molecular types of the breast cancer. Tumor size, grade, stage of the disease can show differences among histological types which might be due to the genetic background, late onset or limited number of patients. In order to achieve more significant results, multicenter national studies are needed.

Keywords: Breast carcinoma, histological tumor type, molecular classification, rare tumors

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Introduction

Breast cancer, which is the most diagnosed cancer among women, is a heterogeneous disease, consisting of numerous, distinct clinical and biological features. Breast cancer is a collection of different diseases with different risk factors, clinical presentations, pathological features, and treatment responses and outcomes. In order to classify different breast cancers, several parameters have been used. Tumor grade, Tumor Node Metastasis (TNM) staging, histological classification, existence of axillary lymph node metastasis, immunohistochemical biomarker characterization, and molecular profiling are the parameters used for classification of breast tumors (1).

Histological type is derived from the growth pattern of the breast tumors. Specific morphological and cytological patterns are associated with distinctive clinical presentations and/or outcomes (2). The most common type of breast cancer is an invasive ductal carcinoma (IDC). In the last version of the World Health Organization classification, at least 17 distinct histological special types have been recognised and specialized types account for up to 25% of all breast cancers (3). Special or rare breast tumor terminology was first described in the study of Weigelt B. et al. (2). Although new treatment protocols depend on molecular findings, histological groups still carry important clinical implications (3). As the prevalence of special type breast cancer is low, not as many studies are concerned with the clinical and molecular characteristics of special type breast cancer (4). In this study, we aimed to describe the clinical features of special type breast cancer in our center.

Material and Method

This retrospective descriptive study was performed at Kocaeli University School of Medicine, Department of General Surgery between January 2000 and January 2016. The study was approved by local the ethics committee (KOU KAEK 2015/261). Patient information was collected from the hospital database and pathology reports. Pathology slides in which the pathology reports lacked the desired information were re-evaluated. Women diagnosed with primary breast cancer were collected from our data. As being a retrospective study, inform consent was not received from the patients. Patients with IDC, malign phyllodes, and sarcomas were excluded from the study. The remaining 101 patients were diagnosed with medullary, tubular, mucinous, metaplastic, micropapillary carcinoma, cribriform, lobular, and apocrine tumors. Patients' ages were obtained. Information about sides, sizes, axillary lymph node statuses, molecular types, stages, and cancer grades were collected. The presence of ductal carcinoma in situ (DCIS) in the breast tissue samples with the primary tumor was examined. Identified special type

tumors were subgrouped into molecular subtypes according to the St. Gallen Consensus (5). According to the St Gallen Consensus, immunohistochemical analyses were performed in order to define the status of estrogen and progesterone receptors (ER and PR, respectively), human epidermal growth factor receptor 2 (HER-2), and the proliferation marker, Ki-67. Staining >10% for ER and PR are regarded as positive. Membranous uninterrupted staining of tumor cells with HER-2 >10% is regarded as positive. The set point for Ki-67 is accepted at >20%. The follow-up times and patient survival were recorded. Data were recorded in SPSS 15.00 (SPSS Inc. Chicago, IL, USA). The results were given by mean $\pm$ standard deviation. Comparison of molecular type and stages between histological types were performed by the chi-square Monte Carlo method. Comparisons of mean tumor size between groups were performed by analysis of variance (ANOVA). Comparisons of lymph node status between subgroups were performed by Chi-squared test. These comparisons, however, were formed between groups which had >5 patients. Patient survival was measured with the Kaplan-Meier test. p values <0.05 was accepted as significant.

Table 1. Characteristics of rare breast tumor types

	Medullary (n=12)	Tubular (n=5)	Mucinous (n=18)	Metaplastic (n=5)	Lobular (n=56)
Mean Age (Year)	56.5	59.8	58.9	56.8	53.9
Right/Left	8/4	2/3	5/13	1/4	33/23
Mean Tumor size*	3.7	1.5	3.8	3.9	4.3
Tumor size (cm)					
<2.0	1	4	3	1	8
2.0-4.9	6	1	12	3	28
≥ 5.0	5	0	3	1	20
Lymph node status					
Negative	5	4	12	4	21
Positive	7	1	6	1	35
Molecular type					
Luminal A	1	4	10	0	40
Luminal B	0	1	8	0	11
HER2/ER	2	0	0	0	1
Basal	9	0	0	5	4
Grade					
I	0	5	12	0	31
II	0	0	3	2	23
III	12	0	3	3	2
Stage					
I	1	4	5	1	8
II	10	1	9	3	19
III	1	0	4	1	29
IV	0	0	0	0	0
Existence of DCIS	0	4	2	2	120
*p=0.2 (ANOVA) DCIS: ductal carcinoma in situ					

Results

Of the eight histological types assessed, the characteristics of breast tumors were given in Table 1. There were no significant differences between the mean tumor size of histological types ($p=0.2$). When the tumor sizes were grouped according to T staging, there was a significant difference between T stages in different groups ($p=0.019$). It can, however, be seen that micropapillary carcinoma was more likely to be diagnosed with the tumors that were ≥ 5.0 cm while tubular carcinoma cases were more likely to be diagnosed when they were <2.0 cm. There were no significant differences between the groups according to the lymph node positivity ($p=0.25$). However medullary and micropapillary carcinoma cases also were more likely to be diagnosed with lymph node-positive disease. The number of patients with stage II medullary, mucinous carcinoma were significantly higher than the other stages ($p=0.02$). Rare breast tumors generally presented at stages I and II (20.7% and 54.5%, respectively). None of the patients presented at stage IV. There were no differences between right or left side tumors in rare breast tumors ($p=0.54$).

Table 1. (Continued)

	Micropapillary (n=3)	Cribriform (n=1)	Apocrine (n=1)	Total (n=101)
Mean Age (Year)	55.1	68.0	41.0	59.4
Right/Left	1/2	1/0	0/1	23/30
Mean Tumor size*	5.5	4.0	5.0	3.8
Tumor size (cm)				
<2.0	0	0	0	9 (17%)
2.0-4.9	0	1	0	28 (53%)
≥ 5.0	3	0	1	16 (30%)
Lymph node status				
Negative	0	1	0	20 (37.7%)
Positive	3	0	1	33 (62.3%)
Molecular type				
Luminal A	3	1	1	31 (58.4%)
Luminal B	0	0	0	
HER2/ER	0	0	0	5 (9.4%)
Basal	0	0	0	17 (32.2%)
Grade				
I	0	1	0	30 (56.6%)
II	1	0	0	6 (11.3%)
III	2	0	1	17 (32.1%)
Stage				
I	0	0	0	11 (20.7%)
II	0	1	0	29 (54.7%)
III	3	0	1	13 (24.6%)
IV	0	0	0	0
Existence of DCIS	3	1	1	15 (28.3%)

* $p=0.2$ (ANOVA) DCIS: ductal carcinoma in situ

When the special type of breast tumors were evaluated according to the molecular types, all types except medullary showed unique molecular patterns. Medullary type breast cancer showed 75% basal type tumors. Lobular breast tumors were mostly classified as luminal type (91.4%). Luminal type breast cancers included tubular, mucinous, micropapillary, lobular, cribriform, and apocrine tumors. Basal type breast tumors were medullary, lobular, and metaplastic. HER2 tumors were composed of medullary and lobular type breast tumors. This indicated that special type breast tumors have specific molecular patterns.

Existence of DCIS was significant in apocrine (100%), cribriform (100%), and tubular (80%) type breast tumors. However DCIS was not seen in medullary type tumors. Only 28% of the patients with rare breast tumors had DCIS (Table I). Although the numbers of patients were low, survival of the patients did not showed significant differences according to the tumor types or existence of DCIS (Figure 1) ($p>0.05$).

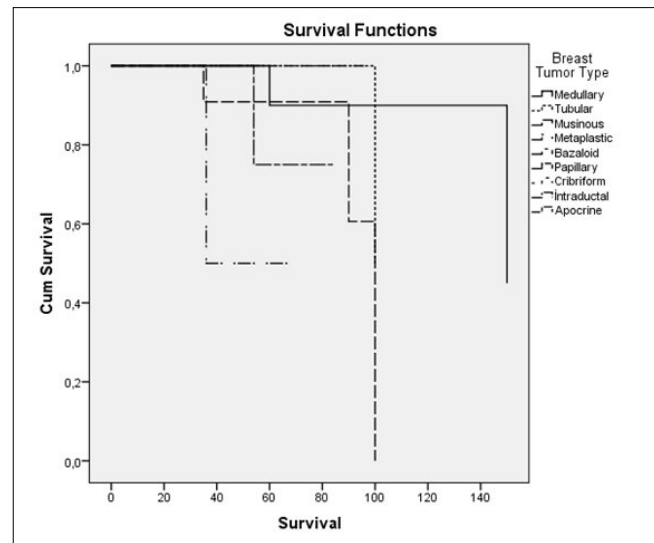


Figure 1. Survival of rare breast tumors

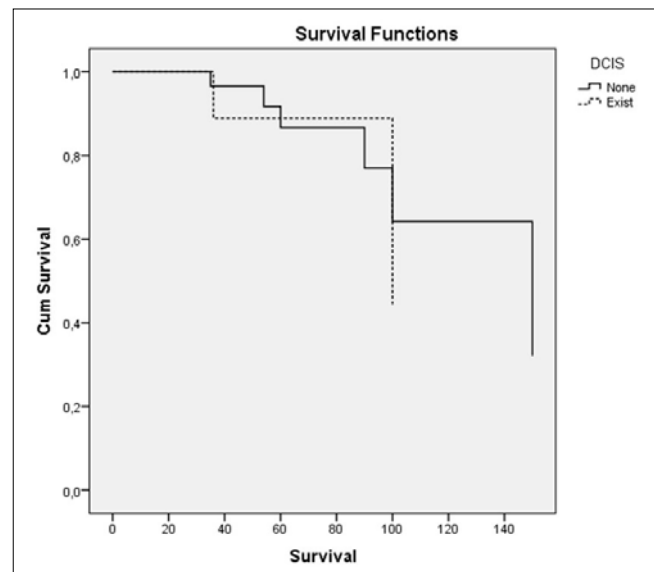


Figure 2. Survival of rare breast tumors according to existence of ductal carcinoma in situ

Low grade tumors were seen more frequently in tubular, mucinous, and cribriform cancers. On the other hand, high grade tumors were seen much more frequently in apocrine and metaplastic type tumors. Among the histological types, cribriform cases had the oldest age at diagnosis (68 years) and apocrine cases had the youngest age at diagnosis (41 years). The number of deaths during the follow-up of the patients was as follows: two for medullary, one for tubular, three for mucinous, and one for metaplastic. Survival rates are shown in Figure 2. Of note, net survival rate for lobular carcinoma was not achieved.

Discussion and Conclusion

This study determined the characteristic of special type breast tumors and showed that histological breast cancers have unique molecular types. Rare breast tumors are generally detected in early stages. Before interpreting the study results, it's important to acknowledge the study's limitations. Firstly, the number of cases was limited and statistical analysis could not be performed as desired in some comparisons. Pathological evaluations were not performed by one pathologist as the time period for this retrospective study covered 16 years. Finally, information about treatment and surgery were not given. However the results were sufficient enough to reach an outcome.

Previous studies that have explored age distribution of different histological types of breast cancer have shown that micropapillary and mucinous carcinomas tend to increase with age, whereas medullary carcinomas tend to decrease (6, 7). In our study, the mean age of patients with histological types of breast cancer were >55 years except in cases of apocrine carcinomas. The genetic background and low number of cases in our study might be the reason for the difference among those different types of carcinomas.

Medullary carcinoma includes breast tumors with medullary features and is less likely to present at an advanced age. Although one fourth of the medullary cancers are diagnosed in patients before 35 years, only 13% of them have Brest Cancer Susceptibility Gene 1 (BRCA1) germline mutations (8). Gene expression analysis of medullary breast cancer has revealed upregulation of genes involved in Th1 immune cytokines and genes related to apoptosis. Conversely, genes associated with skeletal cell architecture are downregulated (9). These specific mutations, rather than Brest Cancer Susceptibility Gene (BRCA), have also led triple negative molecular features and expression of basal markers (1). Showing a high level of genomic instability and basal features, the presence of lymphocytic infiltrate and cell invasion-associated downregulated genes has led to high grade, but favorable, outcomes (10). Occurrence of host reactions is thought to be the mechanism for these favorable outcomes. As in the literature, our medullary carcinomas showed basal markers of high grade with early stages of the disease. Basal molecular types are mostly seen in medullary type breast cancers as mentioned in the literature. In the study of Chu Z. et al. (11), 44.4% of medullary type breast cancer patients were in the basal-like molecular group. However, our luminal type medullary cancer cases were more prevalent than those described in the literature. In the literature, the two year disease-free survival was reported at 79% for basal type medullary breast cancer (12). In our study, two cases which were basal-like died during the follow-up period. Molecular subtype is the most important factor affecting medullary prognosis has yet to be determined. Although the lymph Node (LN) metastasis in medullary cancer was found to be <30%, in our study LN metastasis was >50% (11).

Tubular carcinoma is more often seen in older patients and is generally detected in screening mammography as calcifications and small masses (1). Nearly one fifth of the patients with tubular breast carcinoma are mul-

tifocal. Only 10% of cases present with axillary metastasis. For this reason most of the patients present with early stages. In our study, the mean age of tubular carcinoma was 59.8 years, and 80% of cases had tumors <2 cm with a mean diameter of 1.5 cm, and 20% of cases had lymph node involvement. As in previous studies, tubular carcinomas present luminal type markers (9). DCIS involvement has been shown at 52% in previous studies, which was less than in our study (80%) (13). Tubular carcinoma was the breast tumor with the highest DCIS existence rate in our study.

Mucinous breast cancer are generally seen in patients >55 years. These tumors can present with different sizes ranging from 1 to 20 cm. Mucinous carcinomas are luminal type and usually present at an early stage and are often low histologic grade (14). Besides pure mucinous breast cancer, some types of mucinous carcinomas can contain neuroendocrine differentiation which shows invasive carcinoma features (9). In a detailed search, we found that three of our cases showed invasive forms. These three patients were in stage III with high grade tumors. For this reason, mucinous tumors should be carefully investigated as to whether there is neuroendocrine differentiation. Our results were similar with the previous studies (1, 4).

Metaplastic carcinomas have features of neoplastic cell differentiation into squamous cells and mesenchymal elements. Metaplastic carcinomas are generally large and display a basal-like phenotype (14, 15). These findings were similar to those in our study. Axillary lymph node metastases are less commonly seen but distant metastasis without lymph node metastasis can be seen. The reason for worsening prognosis of metaplastic carcinoma depends on the mutation of genes related to myoepithelial differentiation, Wnt signaling pathway genetic activation, BRCA1 DNA response pathway, and the phosphatase and tensin homolog and DNA topoisomerase 2-alpha genes (16, 17). These features cause the tumor to be more resistant to chemotherapy. The vast majority of metaplastic breast tumors are basal-like and have a worse patient prognosis than the triple negative infiltrating ductal carcinoma (18). Although worse prognosis were indicated in especially basal-like types, survival of histological groups did not showed any differences in our study. This may be related to the early stage of the metaplastic carcinomas or the genetic background of our cases.

Invasive micropapillary carcinoma is a special type of breast tumor composed of tumor cells arranged in morula-like cell clusters with lack of a fibrovascular core in the stromal spaces. This pattern can be seen in all areas or can be partially seen as a component of invasive ductal carcinoma. Existence of micropapillary patterns of at least 75% of the tumor is accepted as pure invasive micropapillary carcinoma (19). Micropapillary carcinomas are generally seen in postmenopausal women, and the mean age of the patients reported in the literature was given between 50 and 55 (20). Micropapillary carcinomas are often medium-high grade tumors. When compared to nonmicropapillary carcinoma, micropapillary carcinomas had more lymphovascular invasion, lymph node metastases, and invasion to perinodal fatty tissue infiltration (21). Most of the micropapillary carcinomas stained positive with ER and PR, but HER-2 positivity was seen in 4%–15% of the cases in the literature (22–24). The cases of the worst micropapillary carcinoma prognoses rather than ductal carcinomas depended on the genetic instability.

Apocrine carcinomas are special types of breast tumors which are composed of dark eosinophilic, granular, and vacuolated cytoplasm and significant nuclei. Apocrine features can be seen in many breast tumors, but apocrine carcinoma is applicable when the morphology is seen in every part or nearly every part of the tumor. Apocrine carcinoma constitutes 1%–4% of all breast tumors. It can be seen at all ages but is more prevalent in the postmenopausal period. Apocrine tumors are high grade tumors.

Lymphovascular invasion in apocrine tumors occurs much more than in infiltrating ductal carcinoma. Apocrine tumors are generally ER positive, and only half of them showed HER2 positivity (25). Only one case in our study showed HER2 and ER positivity. Apocrine tumors were reported in the study of Zhang et al. (26) in which apocrine breast tumors were associated with older age, lower ER and PR proportions, larger tumor size, higher grade, more positive LN, an aggressive stage, and higher HER2 amplification than seen in infiltrating ductal carcinomas.

Cribriform carcinomas are considered to belong to a low-grade breast neoplasia family with small size and less frequent axillary LN metastases, higher ER and PR receptor positivity, and lower proliferation indices (27). The important feature of invasive cribriform breast cancer is the cribriform growth pattern that is used for differentiation from tubular carcinoma. Cases with a component of another carcinoma type accompanying cribriform pattern are regarded as mixed type invasive cribriform cancer and have less favourable outcome than pure cribriform cancers (28). Cribriform breast cancers consist of the luminal type and have better survival rates (27).

Pathological features of invasive lobular carcinomas are small, uniform, epithelial cells with intracytoplasmic lumina that are arranged in a single file, and concentric arrays around ducts forming a targetoid appearance (29). The characteristic discohesive growth pattern of lobular carcinomas is the result of dysregulation of cell-cell adhesion properties, primarily driven by the adhesion molecule, E-cadherin. Several types of lobular carcinoma can be recognised according to their morphologic features. In our study, we did not classify cases of lobular carcinomas into subgroups. Lobular breast cancer is associated with a higher age at diagnosis, higher pT stage, higher percentage of multifocal, multicentric, and bilateral cases, lower histological grade, and higher rate of hormone receptor positivity (<95% of cases in recent series) (30). Although the features of our cases are similar to those in the literature, there are some cases that were basal and HER2 types with high grades. This was probably due to the subgroups of lobular carcinoma-like pleomorphism, which has more cellular atypia and increased mitotic rate. Lobular tumors have more favourable outcomes than ductal carcinomas during short-term follow-up periods but worse prognoses than ductal carcinomas in the long-term because of the risk of distant metastases after a long period of time.

In our study, it was seen that the patients presented with later stages. Patients in stage III constituted 24.6% of all study patients, which is worrisome. On the other hand, patients in stage II constituted 54.7% of all study patients. The stage distribution of patients with special type breast cancers in our study was similar to the results of our breast cancer stage distribution (31). The delay in the treatment in all kinds of breast cancer in our country presents a great problem and can only be reduced by increased breast cancer awareness, implementation of organized population-based screening programmes, and funding cancer centres (32). Late presentation is not specific to special type tumors but is a national health problem. Our results were in accordance with the data in the literature.

Molecular classification of breast tumors is gaining more importance because chemotherapy, hormone therapy, and surgical treatments are decided according to molecular patterns of the tumors. Generally luminal-type tumors are composed of mucinous, tubular, lobular, and micropapillary tumors. The HER2 type is generally composed of lobular, micropapillary, and apocrine tumors. Basal-like tumor type is generally composed of medullary and metaplastic breast tumors (2). Our results are compatible with those reported in the literature.

All of the cases with micropapillary, cribriform, apocrine, and tubular breast tumors, which are the luminal type, had DCIS lesions in our study. However, only a minority of mucinous and lobular breast tumors were accompanied by DCIS. Several genetic changes were present in DCIS progression. Microenvironmental changes are another factor for DCIS progression (33). There is, however, no clear relationship between DCIS and special type breast tumors. The ratio of existence of DCIS in our study was 28%. This ratio was similar with ratios (20%-25%) of DCIS existence in newly diagnosed breast cancer (33).

This study showed the importance of molecular characteristics of different histological breast cancer types. Understanding the underlying molecular features of special types of breast cancer will provide new approaches and new study areas for the treatment modalities. There are several genetic alterations that might help target the treatment (34). With the increase in the understanding of genetic background of the breast cancer in different geographic regions, we can target the new treatment approaches. The molecular types, grades, and stages of special type tumors can change in different regions depending on race, cancer prevention programs, and geographic regions (25). We thought that this study would be the helpful and informative for future studies about special type breast tumors and molecular patterns in this geographic region. Although the distribution of special type breast tumors among molecular types are similar with those reported in the literature, there were exceptions in our cases. These exceptions might have been related to race, late diagnosis, and environmental factors. Lack of data about personal history, treatment modalities, BRCA gene mutations, and risk factors are the limitation of our study. As the number of cases is limited, multicenter national studies are needed.

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Breast Cancer Screening Behaviors of First Degree Relatives of Women Receiving Breast Cancer Treatment and the Affecting Factors

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ABSTRACT

Objective: First-degree relatives of women with breast cancer are under higher risk when compared with the general population. The aim of this study is to evaluate breast cancer screening behaviors of women who are first-degree relatives of women with breast cancer and factors affecting these behaviors.

Materials and Methods: This descriptive study included 240 patient relatives, who agreed to participate in the study through contact with first-degree relatives of 133 patients who were receiving breast cancer treatment at the Oncology and Chemotherapy unit of an university hospital in Turkey. Data were collected using the "Descriptive Characteristics Form," which consisted of socio-demographic characteristics, health history, breast cancer risk level and health beliefs as well as the "Breast Cancer Screening Behavior Evaluation Form".

Results: Out of the subjects, 17% reported doing breast self examination (BSE), 18% reported getting clinic breast examination (CBE) and 17% reported getting mammography.

Logistic regression analysis showed that perceived susceptibility increased BSE by 0.57 times and increased mammography by 0.77 times. Physical exercise increased CBE by 0.21 times and increased mammography by 0.13 times.

Conclusions: It was found that women with familial breast cancer history (FBCH) had lower participation in screening behaviors. Higher susceptibility perception and regular physical exercise are the determinant variables. Women with a higher susceptibility can be led towards the screening and their participation can be increased. In women with family history, the development of healthy lifestyle behaviors like physical exercise should be supported.

Keywords: Breast cancer screenings, family history, health beliefs, susceptibility

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Introduction

Breast cancer is the most common cancer among females in Turkey. Incidence rate in the year 2008 was 40.7 in 100,000 and this rate increased to 43 in 2014 (1). Breast cancer incidence in Turkey is similar to the other developing countries but mortality is higher when compared with these countries (2). The best way to fight cancer is to prevent its development by controlling the known risk factors. The most important risk factors for breast cancer are female gender, advancing age and family history. First-degree relatives (mother, sister and daughters) of women with breast cancer are at higher risk when compared with the general population and it has been reported that family history has a role in 5-10% of cases (3). Studies from Turkey have reported the genetic risk ranging from 5.4% to 25.9% (4-7). One study found that in all age groups, the breast cancer rate was higher in sisters of women with breast cancer when compared to women without familial breast cancer (8). Early diagnosis and treatment are crucial in preventing and reducing cancer-related deaths in high risk groups (9-10). Family history is an unchangeable risk factor and when it is present, early diagnosis can be possible by opportunistic screening programs and medical counseling (11). American Cancer Society (ACS) recommends annual magnetic resonance imaging for high risk women in addition to national screening programs (12). According to the protocol of breast cancer screening program in Turkey, it is required for women aged between 20 and 40 years to perform breast self examination (BSE) and routine clinic breast examination (CBE)

should also be done by a physician yearly for women that have FBCH in their first-degree relatives and once every 2 years for women that do not have family history. All women aged between 40-69 years should have routine CBE yearly and mammography done every 2 years by a physician (13).

Breast cancer screening rates are very low in Turkey. According to the Ministry of Health, the monthly BSE rate was 22.9% and the routine rate for mammography every 2 years was 13.6%. Every year, many women die because of breast cancer, which illustrates the importance of screening in reduction of breast cancer-related deaths (1). Schwab et al. (14) reported that better results were achieved regarding tumor size, disease phase and histological examination through screening programs in women with breast cancer. In a study conducted in Turkey (15), groups having higher risk for breast cancer had mammography rates 11 times higher than the others and in another study, it was determined that the CBE rate was 48.1% in women with a family history (16).

The fact that women do not participate in breast cancer screening programs which are free of charge and for the individual's benefit can be explained by behavioral change models. In studies evaluating participation in cancer screening, the Health Belief Model (HBM) is the most commonly used. This model draws attention to individual perception, which affects individual's health behavior. Components of the model are as follows: perceived susceptibility, perceived seriousness, benefits, perceived barriers, self-efficacy and health motivation. Perceived susceptibility includes a person's belief about getting a disease. According to HBM, an increase in perceived susceptibility will result in an increase of attitude and behavior towards early diagnosis in breast cancer. Perceived seriousness is one's opinion of how serious a condition and its consequences are. Health motivation is one's motivation to realize that a behavior sustains and develops health. In some studies, it has been reported that early screening behavior for breast cancer changes positively with increased perceived susceptibility, perceived seriousness, and health motivation (17-19).

Evaluation of screening participation among women with FBCH may help in the planning of future interventional studies. The aim of this study was to evaluate breast cancer screening behaviors of women who were relatives of women with breast cancer and also factors affecting these behaviors.

Materials and Methods

Design and samples

This descriptive study included relatives of 133 patients receiving breast cancer treatment at the Oncology and Chemotherapy unit of the biggest university hospital in the southwestern Turkey between March and May, 2014 and those who agreed to participate were included. Phone numbers of these patients' biological mothers, daughters older than the age of 20 or sisters were recorded. Two hundred forty relatives were invited via phone and all of them agreed to participate in the study. All the data were collected via face-to-face interview from the participants at a designated address. The study sample power was calculated after the data were collected. When the mammography percentage (91%) given in the previous study for sample power was taken as the primary variable (20), the power was calculated as 100% with a sided, $\alpha = 0.05$ and 95% confidence interval (21).

Data collection tools

The data were collected using the "Descriptive Characteristics Form," which consisted of sociodemographic characteristics, health history

and health beliefs as well as the "Breast Cancer Screening Behavior Evaluation Form".

The descriptive characteristics form had four parts: Socio-demographic characteristics, health history, breast cancer risk level and health beliefs of the participants. Questions about the socio-demographic characteristics and health history were prepared by the researchers by reviewing the literature (3, 11, 20-22).

Sociodemographic characteristics: In this part, education, marital status, having a child, residence, working status and perceived income, family structure and health insurance were evaluated using closed-ended questions while age was evaluated via open-ended questions.

Women's health history: In this part, at least 6 months of breast feeding, receiving hormone replacement therapy for more than 5 years, use of oral contraceptives for 5 years, physical exercise for at least 30 minutes for 3 times a week, chronic diseases, alcohol consumption more than 2 units or more a day, breast cancer history and cognizant of breast cancer signs (nipple retraction, nipple discharge, redness, pitting that resembled the skin of an orange) were evaluated using yes/no choices.

Breast cancer screening behavior evaluation form: breast cancer screening behaviors were evaluated by a structured questionnaire prepared by the researchers based on a literature review (14, 20). This form consisted of questions regarding regular BSE in the last 6 months, getting CBE in the last year and undergoing mammography in the last year as evaluated using yes/no answers. **Breast cancer health beliefs:** The Turkish version of the Breast Cancer and Screening HBM was used to evaluate health beliefs about breast cancer (23). This model was developed by Champion in 1984 (24) and adapted to Turkish by Gözümler and Aydın in 2004 (23). This scale has 3 items for the "susceptibility" subscale, 6 items for "severity" and 5 items for "health motivation." A 5-point Likert-type scale was used where 1 meant 'strongly disagree' and 5 'strongly agree'. For every dimension, higher scores indicated more positive health beliefs for that dimension. Internal consistency of the Turkish version of the scale was found to be 0.69, 0.75 and 0.83, respectively (23).

Ethical approach

Official permission was obtained from Akdeniz University; IRB approval was obtained from the Medical Faculty with the board decision dated 01.04.2014 and number 70904504/138. Written and signed informed consent was taken from participants with FBCH.

Statistical analyses

Statistical analyses of the data were conducted using the Statistical Package for the Social Sciences SPSS for Windows, version 20.0 (SPSS Inc.; Chicago, IL, USA). The effects of independent variables (socio-demographic characteristics, health history, breast cancer risk level, health beliefs) on the dependent variables (breast cancer screening behavior) were analyzed using basic statistical tests (Pearson's Chi-square test, Fisher's exact test and t-test) depending on whether data was categorical or continuous. These basic analyses were conducted separately for BSE, CBE and mammography. After basic analyses, for every statistically significant variable, each screening method was evaluated using a logistic regression model. In logistic regression, $p > 0.05$ in Hosmer-Lemeshow test was the criteria. The statistical power of each test was calculated by using G*Power program and it was more than 90%. The level of statistical significance was set at $p < 0.05$, and a confidence interval of 95% was determined.

Results

Socio-demographic characteristics of the participants

The mean age of the 240 participants was 43.1±12.9 years ranging from 21 to 72 years, with 52.5% of women being older than 40 years. Most participants were married (89.6%), had completed high school and higher (50.0%), and/or were employed (57.5%). Seventy one point seven percent of the participants were residing in the Antalya city center, 76.3% had less income than their expenses and all had social security (Table 1).

Participants' screening behaviors and related factors

Seventeen percent of participants were performing BSE, 18% were receiving CBE and 17% had mammography, %48 haven't had screening (Table 2).

When socio-demographic factors related to BSE were evaluated with basic statistical analysis (Chi-square), the BSE rate was found to be higher in participants with higher education and with an income equal to or higher than the expenses ($p<0.05$); the other factors (age, marital status, residence and working status) were not significant ($p>0.05$).

When the health history factors that can affect the BSE were analyzed using basis statistical tests (Chi-square and t-test); the BSE rate was higher in participants who had a child, were regularly exercising and

cognizant of breast cancer signs (nipple retraction, discharge, redness, pitting that resembles the skin of an orange) ($p<0.05$). Health beliefs and breast cancer risk points had no effects on BSE behavior ($p>0.05$). However, the time of diagnosis of the first-degree relative, perceived susceptibility and health motivation were significantly effective factors ($p<0.05$). When these significant factors were further analyzed using logistic regression, only increased perceived susceptibility was found to be correlated with increased BSE (OR: 0.57, $p<0.05$) (Table 3).

When factors that can affect getting a CBE were analyzed using basis statistical tests, CBE rate was found to be higher in participants with higher education, income equal to or higher than expenses, used oral contraceptive for less than 5 years, did regular physical exercise, were cognizant of breast cancer signs (nipple retraction, discharge, redness,

Table 2. Screening attendance status (n=240)

Screening	Attending	
	n	%
BSE	41	17
CBE	42	18
Mammography	40	17
Non-screening	117	48

BSE: breast self examination; CBE: clinic breast examination

Table 1. Sociodemographic characteristics (n=240)

Variables	n	%
Age		
40<	114	47.5
40≥	126	52.5
Mean (SD)	43.1±12.9	
Marital status		
Married	215	89.6
Single	25	10.4
Education status		
Illiterate	34	14.2
Primary school and Secondary school (1-8)	86	35.8
High school and higher (9+y)	120	50.0
Employment status		
Yes	138	57.5
No	102	42.5
Place of residence		
Antalya city center	172	71.7
Other	68	28.3
Economic status		
Income<expenditure	183	76.3
Income=expenditure	54	22.5
Income>expenditure	3	1.2
Social security		
Yes	240	100.0

Table 3. Logistic regression: prediction of the likelihood of BSE (n=41)

Variables	Odds Ratio	95% CI	p
Education	4.46	0.05-39.29	0.511
≤5y (1)			
>5y			
Economic status	0.20	0.01-2.76	0.227
Income <expenditure (1)			
Income ≥expenditure			
Having a child	1.64	0.08-35.34	0.753
Using oral contraceptive for more than 5 years	0.06	0.00-8.78	0.264
Doing regular physical exercise	1.16	0.02-73.21	0.945
Nipple retraction	0.10	0.00-57.78	0.683
Nipple discharge	0.02	0.00-1.85	0.088
Redness of the breast skin	43.40	0.01-62.94	0.318
Pitting resembling the skin of an orange	0.15	0.00-56.51	0.650
The time of diagnosis of the first-degree relative	2.14	0.17-27.50	0.561
Susceptibility	0.57	0.33-0.99	0.048*
Health motivation	1.06	0.66-1.71	0.810

BSE: breast self examination

NOTE: Hosmer- Lemeshow test: $p=0.743$

*Significant $p<0.05$

pitting resembling the skin of an orange) and had higher health motivation ($p<0.05$). In logistic regression analysis, only regular physical exercise was correlated with higher CBE rates (OR: 0.21, $p<0.05$) (Table 4).

When health history factors were analyzed using basis statistical tests (Chi-square and t-test), education level equal to high school or higher, regular physical exercise, being cognizant of breast cancer signs

Table 4. Logistic regression: prediction of the likelihood of CBE (n=42)

Variables	Odds Ratio	95% CI	p
Education	1.04	0.42-2.60	0.92
≤5y (1)			
>5y			
Economic status	0.57	0.25-1.31	0.18
Income<expenditure (1)			
Income≥expenditure			
Using oral contraceptive more than	0.49	0.22-1.11	0.09
5 years			
Doing regular physical exercise	0.21	0.07-0.63	0.01*
Nipple retraction	1.25	0.37-4.24	0.72
Nipple discharge	0.39	0.12-1.20	0.10
Redness of the breast skin	0.69	0.14-3.31	0.64
Pitting resembling the skin of an orange	0.54	0.14-2.17	0.39
Health motivation	0.90	0.76-1.07	0.23

CBE: clinic breast examination
NOTE: Hosmer- Lemeshow test : $p=0.47$
*Significant $p<0.05$

Table 5. Logistic regression: prediction of the likelihood of mammography (n=40)

Variables	Odds Ratio	95% CI	p
Education	1.09	0.43-2.75	0.85
≤5y (1)			
>5y			
Doing regular physical exercise	0.13	0.04-0.43	0.01*
Nipple retraction	1.24	0.36-4.28	0.73
Nipple discharge	0.34	0.11-1.07	0.07
Redness of the breast skin	0.62	0.13-3.12	0.57
Pitting resembling the skin of an orange	1.25	0.26-6.10	0.78
Susceptibility	0.77	0.66-0.90	0.00*
Health motivation	0.92	0.78-1.09	0.34

NOTE: Hosmer-Lemeshow test: $p=0.25$.
*Significant $p<0.05$.

(nipple retraction, discharge, redness, pitting resembling the skin of an orange) and having higher perceived susceptibility were related to higher mammography rates ($p<0.05$). Only two variables were found to be significant in the logistic regression: regular physical exercise (OR: 0.13, $p<0.05$) and perceived susceptibility (OR: 0.77, $p<0.05$) (Table 5).

Discussion and Conclusion

In this study, the BSE rate was almost two times higher than the Turkish Ministry of Health¹ data but only approximately 1 in 5 of them was performing BSE. Mammography rates were low, which was similar to the Turkish population. In other studies from Turkey, regular mammography and BSE rates were higher in women with family history when compared with women without family history (16, 25). In studies from different parts of the world, screening behavior of women with BCFH in the last year ranged from 56.8% to 91% (20, 22, 26-27). In our study, the BSE rate was higher than CBE and mammography rates; however, participation rates for all three methods were very low. Low participation for CBE and mammography screening reveals that these women's breast cancer screening awareness was limited to BSE. Fair et al. (28) reported that high breast cancer risk was not enough to provide courage to face breast cancer and it might cause fear, thus preventing women from getting mammography. Another explanation for low participation in screening programs could be that screening programs in Turkey are new (since 2015) and there are no special screening programs for women with family history. Another explanation for the low rate of participation in screenings in this study is that screening program specific to those having family history in Turkey started only recently (in 2015).

In this study, basic statistics revealed that higher education and income, having a child, regular physical exercise, being cognizant of breast cancer signs (nipple retraction, nipple discharge, redness, pitting resembling the skin of an orange) and perceived health motivation positively affected BSE behavior. However, a logistic regression model with these variables showed that only perceived susceptibility was slightly correlated with BSE. Similarly, women who felt that their family history of breast cancer was a risk had increased susceptibility towards cancer and they cared about the cancer screening behavior (29). In the study by Fouladi et al. (30), perceived susceptibility was higher in women with family history when compared with others. This was explained by higher apprehension among the women with BCFH. However, other studies have shown that perceived susceptibility does not have any effects on BSE behavior (16, 31).

In this study, regular exercise was an effective factor in getting CBE and mammography. This was a significant finding. Moderate physical activity among Turkish women is very low: only 20.2% (32). This can indicate that regular physical exercise is a sign of an individual's sensitivity towards developing and protecting health behavior. An individual diagnosed with cancer in a family can increase susceptibility of the other family members who have similar genetic and environmental characteristics. This may lead other family members to participate in healthy lifestyle behaviors like exercise (33). However, in two different studies (20, 34), healthy lifestyle behaviors like physical exercise were not effective when it came to screening behaviors.

In this study, perceived susceptibility was another factor which increased mammography participation. Because perceived susceptibility is also effective in BSE behavior, this group seems ready to participate

in screening. Ersin et al. (35) and Aker et al. (36) have reported that perceived susceptibility is an important factor for getting mammography. However, Baysal and Gözümlü (37) have found in their study women with lower perceived susceptibility had no intentions to undergo mammography. Since the perceived susceptibility is an important factor in having mammography in this study, the importance of considering the perceived susceptibility in the interventions to be made to encourage women to have mammography has been suggested.

Women with BCFH participate in breast cancer screening even less often than the general population in Turkey. Perceived susceptibility and regular physical exercise are determining variables for breast cancer screening behavior. Healthy lifestyle changes like physical exercise should be supported in women with family history. Because perceived susceptibility is an important determinant of participation in screening, health professionals should be supportive in directing women with family history towards screening. Also, it is important to prioritize the screening and direct them to screening.

The limitations of the study

While evaluating the results of this study, it should be taken into consideration that probability sampling method was not used in selection of the participants and the study was conducted with patient relatives coming to only one hospital. The sample size could be considered as small; however, the statistical power of the study was found to be enough to interpret the data obtained in the study.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Akdeniz University (Decision Date: 01.04.2014, Decision Number: 70904504/138).

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

Peer-review: Externally peer-reviewed.

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Efficiency of Imaging Modalities in Male Breast Disease: Can Ultrasound Give Additional Information for Assessment of Gynecomastia Evolution?

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ABSTRACT

Objective: The purpose of this study is to present mammography and ultrasound findings of male breast lesions and to investigate the ability of diagnostic modalities in estimating the evolution of gynecomastia.

Materials and Methods: Sixty-nine male patients who admitted to Taksim and Bakırköy Education and Research Hospitals and underwent mammography (MG) and ultrasonography (US) imaging were retrospectively evaluated. Duration of symptoms and mammographic types of gynecomastia according to Appelbaum's classifications were evaluated, besides the sonographic findings in mammographic types of gynecomastia.

Results: The distribution of 69 cases were as follows: gynecomastia 47 (68.11%), pseudogynecomastia 6 (8.69%) primary breast carcinoma 7 (10.14%), metastatic carcinoma 1 (1.4%), epidermal inclusion cyst 2 (2.8%), abscess 2 (2.8%), lipoma 2 (2.8%), pyogenic granuloma 1 (1.4%), and granulomatous lobular mastitis 1 (1.4%). Gynecomastia patients who had symptoms less than 1 year had nodular gynecomastia (34.6%) as opposed to dendritic gynecomastia (61.5%) ($p<0.01$) based on mammography results according to Appelbaum's classifications. In patients having symptoms for 1 to 2 years, diffuse gynecomastia (70%) had a higher rate than the dendritic type (20%). Patients having the symptoms more than 2 years had diffuse gynecomastia (57.1%) while 42.9% had dendritic gynecomastia ($p<0.001$). With sonographic examination patients who had symptoms less than 1 year had higher rates of dendritic gynecomastia (92.3%) than nodular type (1.9 %). Patients having symptoms for 1 to 2 years had more dendritic gynecomastia (70%) than diffuse type (30%). Patients having symptoms more than 2 years had diffuse gynecomastia (57.1%) comparable to dendritic gynecomastia (42.9 %).

Conclusion: Diagnostic imaging modalities are efficient tools for estimation of gynecomastia evolution as well as the diagnosis of other male breast diseases. There seems to be an incongruity between duration of clinical complaints and diagnostic imaging classification of gynecomastia. The use of these high resolution US findings may demonstrate an early phase fibrosis especially in patients visualized by mammography as with nodular phase.

Keywords: Male breast, gynecomastia, breast cancer, ultrasound, mammography, imaging

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Introduction

Most male patients who have breast complaints admit with similar symptoms and physical examination findings. Overwhelming majority of male breast problem is benign and includes gynecomastia (1). Male breast cancer forms 0.17% of all male cancers and 0.5-1% of all breast cancers (2). The key point to distinguish gynecomastia from a malignant mass is the presence of a palpable lump without a mass located beneath the nipple or skin thickening neither nipple retraction. Despite these indicators, it is not easy to distinguish gynecomastia from malignant masses with physical examination. Previously, imaging was not performed in men with a palpable breast mass (3). A high positive predictive value, sensitivity and specificity have been reported for both mammography (MG) and breast ultrasound (US) for diagnosing male breast cancer (4-6). Therefore, it is critically important to differentiate benign and malignant masses with imaging modalities.

Radiological findings of gynecomastia vary according to the developmental stage. Appelbaum (7) has classified MG patterns of gynecomastia in regard with the pathological development phases. However, the success to demonstrate gynecomastia and its developmental phases by US is less discussed in the literature.

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There are no standardized algorithms for the evaluation of the male breast disease. Currently, the recommended protocol for palpable mass in male patients is to perform x-ray MG (to distinguish gynecomastia from pseudogynecomastia and to identify suspicious lesions) followed by high-frequency breast US (8). Some studies suggest that US is widely accessible and furthermore, MG is not preferable in young adults. Therefore US imaging can be used as first-line imaging modality (4).

Considering the current conflict in the literature, the purpose of this study is to present mammography and ultrasound findings of male breast lesions and to search the ability of diagnostic imaging modalities in estimating the evolution of gynecomastia.

Materials and Methods

Patients: Sixty-nine male patients who underwent MG and US in two different radiology departments between January 2008 and December 2010 were retrospectively evaluated.

The clinical presentations of these patients were categorized into four groups: Unilateral or bilateral breast enlargement, palpable mass, tenderness or pain, more than one of these symptoms.

The cases which were not evaluated by both MG and US were excluded. Lumpectomy, mastectomy, or core biopsy samples (if present) were evaluated at our pathology department. According to our monitoring protocol, radiologic follow-up is performed for at least 2 years in patients without histopathological evaluation. All the US and mammographic images accessed via picture archiving and communication system (PACS) were retrospectively analyzed by two radiologists who have an experience of evaluating more than 1500 diagnostic mammograms per year. Both radiologists were blind about the histopathological reports. The MG and US findings were recorded for each lesion. In cases of discrepancy between the two observers, consensus is achieved by discussion between them.

Mammography scans were performed by Lorad M3 with standard film screen techniques integrated with Computerized Radiography (CR) at the Taksim Hospital whereas mammography scans were performed by using (Siemens MAMMOMAT Novation Digital Radiography DR) at the other hospital. US examinations were done by two different radiology units with same high-resolution US equipment (model LOGIQ 9 with a high-frequency linear transducer with multiple focal zones GE Healthcare). CR system is an image digitization system designed to acquire and digitize X-ray images from image storage phosphor plates.

Diagnostic assessments; Breast Imaging Reporting and Data System (BI-RADS) category assessments were used to categorize MG and US examination of patients with mass lesions (9).

Pseudogynecomastia-adipomastia refers to breast enlargement in men. The breast enlargement is generally caused by adipose tissue excess, rather than by the growth of the glandular tissue. Clinically it may seem similar to gynecomastia. These two entities can be easily differentiated by mammography which enables determination of fatty tissue. Subareolar densities, which are not apparent in pseudogynecomastia, are also easily recognized in gynecomastia.

The presence and type of gynecomastia were evaluated with mammograms. The mammographic patterns of gynecomastia were grouped according to the criteria defined by Appelbaum et al. (7). We correlated mammographic patterns of gynecomastia with US findings according to Appelbaum classification. US findings are classified as nodular (well

circumscribed-oval shaped), dendritic (spider leg-shaped, angulated) and diffuse (a similar appearance with adult female breast).

Three mammographic patterns of gynecomastia may be represented by degrees and stages of ductal and stromal proliferation (10). These patterns are the nodular, dendritic, and diffuse glandular patterns. Nodular pattern; At MG, there is nodular subareolar density. The density usually blends gradually into the surrounding fat, but it may be more spherical. By using US a well circumscribed ovoid shaped hypoechoic area enclosed by fat tissue also can be detected (Figure 1)

Dendritic pattern (10, 11); Mammograms show star-shaped irregular retroareolar radiodensity which merges with the enclosing fat tissue. The US study presents a heterogeneous hypoechoic area placing the nipple at the center with an irregular posterior border which is surrounded by echogenic fibrous tissue (Figure 2).

At MG Diffuse pattern reveals a widespread radiodensity caused by proliferated fibro glandular tissue as in female breast. US exhibits hyperechoic glandular tissue is found, with increased subcutaneous adipose tissue anteriorly and without the hypoechoic central nodule (12) (Figure 3).

Gynecomastia cases were defined as three groups according to the duration of symptoms. In the first group, symptom duration was less than one year. In the second group symptom duration was between one and two years, whereas in the third group it was more than two years. Duration of symptoms and its relation with gynecomastia subtypes determined in MG were compared statistically.

Statistical analyses; NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for all statistical analysis. In addition to descriptive statistics (frequency, ratio), Chi-square test was used for qualitative data. Values for $p < 0.05$ were accepted as significant.

Informed consent was obtained from patients who participated in this study. No institutional review board approval was required for this retrospective study.

Results

The most common symptom was diffuse bilateral or unilateral breast enlargement without a palpable mass in 45 patients (66%), other symptoms were palpable mass in 21 patients (30%), tenderness or pain in 34 patients (49%), nipple discharge in three patients (7%) and 33 patients have more than one of these symptoms (48%). Two of three patients with hemorrhagic nipple discharge had breast cancer and the other serous one had gynecomastia. One of the 2 patients with a visible lesion at the nipple-areolar complex had papillary breast carcinoma and the other had pyogenic granuloma (Table 1).

In our study, 35 symptomatic patients were younger than 50 years of age. Four of these (11%) had breast carcinoma.

The diagnosis was established in 48 patients (70%) by radiological imaging and in 21 patients (30%; 17 excisional and 4 tru-cut biopsies) by pathological evaluation. Malignant pathological diagnoses among our cases were invasive ductal carcinoma (n=5), papillary carcinoma (n=2) and metastatic carcinoma (n=1). Their ages varied between 38 and 82 years (mean $\pm$ SD, 57.43 $\pm$ 15.78). The mean size ($\pm$ SD) of the mass was 26.57 $\pm$ 12.19 mm (range 6-45 mm) Focal benign lesions were including epidermal inclusion cyst (n=2), abscess (n=2), lipoma (n=2), pyogenic granuloma (n=1), and granulomatous lobular mastitis (n=1). In some cases, gynecomastia and benign or malignant focal lesions were observed together (Figure 4) (Table 2).

Table 1. Radiopathological findings of patients in different age groups

	Gynecomastia	Pseudogynecomastia	Other benign types	Cancer	Total
< 35	19	1	0	0	20 (28.98%)
36-50	4	2	5	4	15 (21.74%)
>51	24	3	3	4	34 (49.28%)
Total	47 (68.11%)	6 (8.69%)	8 (11.60%)	8 (11.60%)	69 (100%)

Our three cases have gynecomastia and also another benign pathology in table 1

Table 2: Mammosonographic findings of malignant primary breast masses

	MG FINDINGS	US FINDINGS
Mass with irregular, ill-defined or lobulated contour	4 /7 (57%)	5/7 (72%)
Mass with well-circumscribed contour	2/7 (28%)	1/7 (14%)
Nipple retraction and skin thickening	1/7 (14%)	1/7 (14%)
Microcalcifications	2/7 (28%)	2/7 (28%)
Number of metastatic lymph node detected *	0/7	3/7 (43%)
<= BI-RADS 3	2/7 (28%)	0/7
BI-RADS 4-5	5 /7 (72%)	6/7 (86%)

*One of three pathologically detected axillary metastatic lymph node has micrometastasis.
MG: mammography; US: ultrasound; BI-RADS: Breast Imaging Reporting and Data System

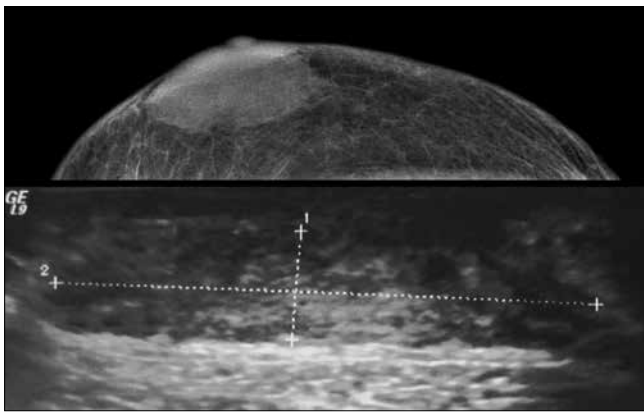


Figure 1. Pathologically proven nodular gynecomastia. Ultrasound demonstrates well-defined discoid area

Five of seven primary malignant masses were visible on mammography (72%) whereas six of them were visible by US (86%). The only case diagnosed as intraductal papillary carcinoma located in the nipple (<5mm) was invisible with US. All the masses were hypoechoic and completely solid (86%) except one which includes cystic areas (14%).

In our study, microcalcified masses were demonstrated on mammograms in two of cases. The first patient had uniform, dense, widely scattered and punctate microcalcification, while the other had partially

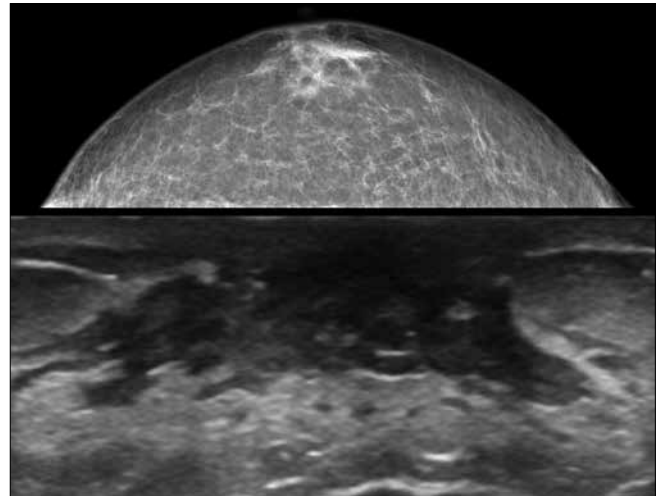


Figure 2. Typical appearances of dendritic gynecomastia (two different patients)

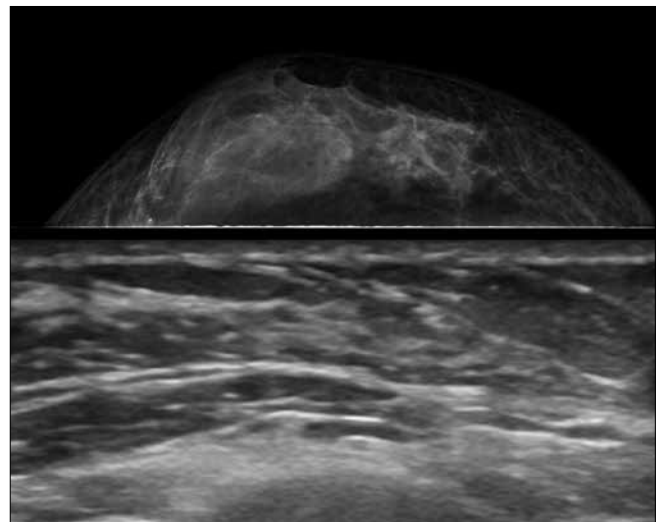


Figure 3. Typical appearances of diffuse gynecomastia

linear, punctate and clustered calcifications. Two of seven carcinoma patients (28%) had coexistent gynecomastia.

Change of posterior acoustic features has been demonstrated only in 2 benign cases (abscess and lobular capillary hemangioma). Two patients had breast abscess; on mammograms, both of them had high-density masses. Ultrasonography revealed well-circumscribed heterogeneous hypoechoic masses in these patients. Pathologically proven epidermal inclusion cysts that are present in two patients, appeared as round, well-circumscribed

Table 3. Duration of symptoms and its relation with mammosonographic gynecomastia subtypes

	<1 year (group 1)		1-2 year (group 2)		>2 year (group 3)		total	
	n=52(62.7%)		n=10(12%)		n=21(25.3%)		n=83(100%)	
	MG	US	MG	US	MG	US	MG (%)	US (%)
Nodular	18 (%34.6)+	1 (1.9%)	1 (%10.0)	0 (0%)	0 (0%)	0 (0%)	n=19 (22.9%)	n=1 (1.2%)
Dendritic	32 (%61.5)+	48 (92.3%)	2 (%20)*	7 (70%)	9 (%42.9)*	9 (42.9%)	n=43 (51.8%)	n=64 (77.1%)
Diffuse	2 (%3.8)	3(5.7%)	7 (%70.0)*	3 (30%)	12 (%57.1)*	12 (57.1%)	n=21 (25.3%)	n=18 (21.6%)
Total	52		10		21		83	
MG: mammography; US: ultrasound								
+p<0.01, *p<0.001								

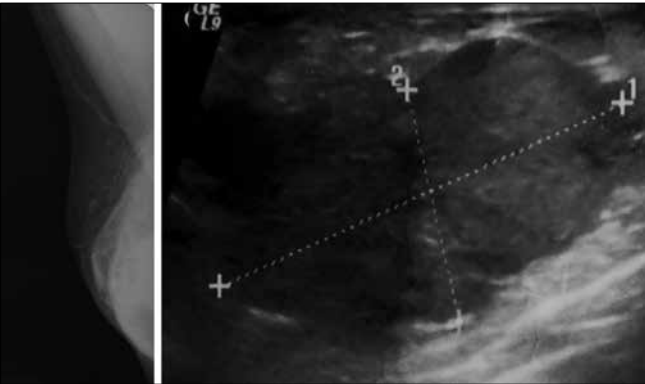


Figure 4. Huge breast mass mimicking diffuse gynecomastia on mammography scan

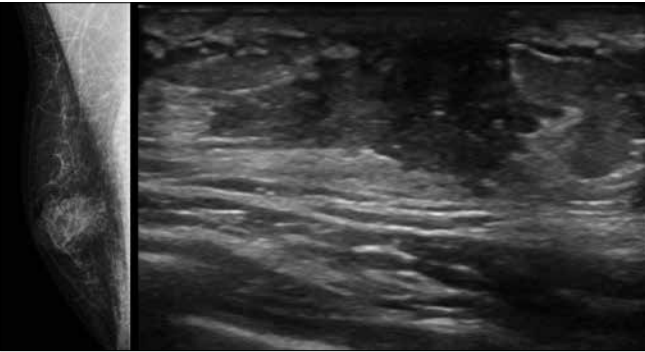


Figure 5. Patient having nodular gynecomastia on mammography had dendritic gynecomastia at ultrasonography

nodules both on mammography and US. Ultrasound demonstrated the gland neck coursing through the skin. A case diagnosed by lobular capillary hemangioma had well circumscribed hypoechoic mass while only focal skin thickening was observed by mammography. Another patient with palpable mass had retroareolar ill-defined hypoecogenic lesion trucut biopsy reveals granulomatous lobular mastitis.

In 10 of 56 patients were diagnosed with gynecomastia had clinical suspicion of real mass lesion. Only two of those patients had mammosonographically detected a benign mass. Of the remaining eight cases, (14%) which were assumed to be a real mass by clinical breast examination (CBE), were proven to be gynecomastia by both US and mammographic examinations. Six patients (11%) had pseudogynecomastia (adipomastia) as diagnosed by MG. A total of 83 breasts of 50 patients with true gynecomastia were examined. According to MG

findings, gynecomastia was unilateral in 17 cases (34%), and bilateral in 33 cases (66%) (Table 3).

There were 3 patients (5%) who have two phases of gynecomastia simultaneously.

When we statistically compared symptom durations with mammosonographic gynecomastia patterns in group 3 patients, diffuse gynecomastia has been detected significantly more than dendritic gynecomastia ($p<0.001$). In group 1 patients, dendritic gynecomastia has been detected significantly more than nodular gynecomastia ($p<0.01$). In group 1 patients mammographic nodular gynecomastia diagnosis was confirmed by sonography in only one patient. He had a well-defined discoid area regarding nodular gynecomastia at sonography. In our study, most of the early phase gynecomastia cases (92%) with the appearance of nodular gynecomastia at MG had dendritic gynecomastia when evaluated by sonography (Figure 5).

Discussion and Conclusion

A proven appropriate algorithm for the evaluation of male breast problems has not been defined. In the past, surgical intervention and percutaneous biopsy in men with a palpable breast mass had been performed without breast imaging (3). However, it has been reported that percutaneous biopsies can lead to misdiagnosis (13). As stated Munn et al. (14) combined use of mammosonography could substantially reduce the need for biopsy. Fourteen percent of our biopsy planned cases, which were interpreted as a mass with clinical examination, were diagnosed as gynecomastia after mammographic examination. Thus, these cases were diagnosed without biopsy.

One percent (1) % of male breast cancers occur under the age of 30 and 6% under 40 years (15) Cooper et al. (16) have reported that men under 50 years with breast enlargement or a palpable, non-indurated central subareolar mass is not required to undergo MG unless there are other clinical indications. In our study, 11% of our symptomatic cases below 50 years of age were cancer. Although imaging was not recommended for such young patients (5, 16) , we believe that diagnostic imaging modalities are necessary for the evaluation of male breast with enlargement or a palpable mass. Hence, avoiding mammographic evaluation will probably increase the need for sonography.

In our study, 62% of the patients had the symptoms less than one year and probably in the reversible state. Gynecomastia is reversible if the causal factors are removed in the early proliferative stages (11, 12). The nodular pattern correlates with the pathologic classification of florid

gynecomastia, which is thought to be the early proliferative phase of gynecomastia (4, 10, 11). At histologic analysis, florid gynecomastia is characterized by hyperplasia of the intraductal epithelium with loose, cellular stroma and surrounding edema. The literature reports that florid phase which corresponds to nodular gynecomastia at MG is more common but we have observed dendritic gynecomastia is more frequent in patients who had the symptoms less than 1 year. There was a statistically significant difference between dendritic and nodular forms of gynecomastia in group 1 patients ($p < 0.01$). One of the possible reasons may be the subjective nature of perceiving the symptoms among the patients. Another possible explanation may be the duration of one year is not enough to document the fibrous state of the disease. On previous reports, mammographic dendritic phase was believed to indicate fibrosis. We think this argument needs further studies evaluating correlation with mammographical and histopathological findings.

Determination of the irreversible fibrous state of gynecomastia may facilitate treatment. Gynecomastia patients with symptoms more than one year presents chronic dendritic phase. The histologic characteristics of fibrous gynecomastia are ductal proliferation with dense, fibrotic stroma (10, 11). Our data showed that diffuse gynecomastia was unexpectedly higher than the dendritic type for the group 2 cases which had the symptoms for 1 to 2 years ($p < 0.001$). We observed that the duration of symptoms of our patients who had dendritic or diffuse gynecomastia visualized by MG was shorter than that recorded in the literature.

It has been reported that dendritic phase, observed in mammography, indicates fibrosis (7, 8, 17, 18). Contrary to literature dendritic gynecomastia is more frequent in patients who had symptom less than one year ($p < 0.01$). A major part of our cases was in progression into dendritic phase within less than one year. Interestingly most of the patients evaluated as in early nodular phase by MG were seen in dendritic phase with US (92%). Our findings may reveal two results. The first one is that the use of imaging methods may be more efficient in stating the reversible phase than deciding upon the duration of symptoms. Secondly, we believe that US could expose the fibrosis earlier than MG.

Although Appelbaum classification is a simple method and it is easy to understand. The role of US in gynecomastia has still been debated. We believe that high-resolution probes can contribute to the evaluation of the developmental stages of gynecomastia through its ability to resolve micro lobulations and spiculations. Ramadan et al. (19) reported that the sonographic characteristics of gynecomastia in men are similar to the early breast development in female adolescents depending on the duration of development. Therefore, Tanner staging may be used in male patients alternatively for the sonographic evaluation of gynecomastia. It is well documented that retroareolar ovoid hyperechoic tissue was identified similar with nodular gynecomastia only in Tanner stage 1. Simple branched duct development is observed in Tanner stage 2, while central hypoechoic star-shaped areas encircled by hyperechoic peripheral rim, reflecting fibro glandular tissue development, are characteristic for Tanner stage 3-4 (20). A retroareolar hypoechoic star shaped area "encircled by hyperechoic peripheral rim" is visualized by high-resolution US in most of our cases. The use of these high-resolution US findings may demonstrate an early phase fibrosis especially in patients visualized by MG as with nodular phase. For this reason, the combination of MG-US, which is not preferred in adolescents, may be effectively used for detecting early stages of fibrosis in adult males.

The relationship between breast cancer and gynecomastia is controversial, with reported coexistence ranging from 2% to 40% (11, 21,

22). The association may be due to elevated levels of estrogens, which may be observed in both conditions. However, no histological transition from gynecomastia to breast cancer has been demonstrated (23). In our study, 28% of our carcinoma patients had coexistent gynecomastia. In one of our carcinoma case, accompanying gynecomastia obscured the visualization of the tumor mass. In the other, the tumor mass was such huge to mimic diffuse gynecomastia (see Figure 4). On the other hand, these two tumors were detected by US. As mentioned in previous papers, US may be useful to differentiate gynecomastia and mass or to detect a mass located within gynecomastia. Our experience reveals that sonography is a complementary tool for the differential diagnoses of mammographically detected abnormalities in men.

Because lobule formation is extremely rare in male breast, some common lesions of the female breast, (e.g. adenosis-fibroadenoma, fibrocystic change and lobular carcinoma) are also rare (1, 21, 24). Thus, it is very important that well-circumscribed masses should be considered as candidates for malignancy. We did not detect well circumscribed lesions corresponding to fibrocystic changes or fibroadenoma in our study. Complex cystic breast masses in men are suggestive of malignancy, and papillary DCIS should be considered in the differential diagnosis (25). Only one carcinoma case (14%) contains anechoic cystic areas in this study.

Common central and subareolar location of breast cancer in men is due to the absence of peripheral terminal ductal lobular units. The locations of the masses were retroareolar in four cases (57%), and eccentric to the nipple in one case (14%) and within the nipple in the other (14%). In the remaining one case, the mass covered the whole breast. These findings are consistent with the previous reports (1, 24). The location of the mass in respect of the nipple could be a determining factor.

Microcalcification appears mainly in carcinoma in situ (DCIS), which is infrequently seen in male cancer (26). Calcifications were found in 7%-31% of male breast cancer patients in different studies (1, 24). Calcifications that are generally considered as benign in women may be an indicator of malignancy in men (21). In accordance with the literature, microcalcification detection rate in our carcinoma cases was found to be 28%.

Eighty-five percent (85%) of male breast cancer has been reported as invasive ductal cancer (23). This study confirms the presence of high percentage value. All our tumors are ductal in origin. In our cases, six of seven cases were invasive carcinoma (86%) five of them were invasive ductal carcinoma. And the remaining case was invasive papillary carcinoma. Pure DCIS without an associated infiltrating ductal cancer is less common (2.3-17%) (23, 25). The single case of DCIS (14%) in our study was of the papillary subtype, which has been described in more than 75% of DCIS cases in men (27). All of our invasive ductal cancers are moderately or poorly differentiated. Giardino et al. (28) reported a markedly higher (90.6%) proportion of estrogen receptor (ER)-positive tumors in men. In our study, all of the four patients (with known hormone receptor status) were ER-positive.

The limitation of our study is the relatively low number of cases and lack of radiopathologic correlation in gynecomastia cases. We could not evaluate the correlation because most of the cases were not operated or did not have biopsy samples.

When we evaluate our cases in the light of literature findings, a hard-fixed and painless mass suggests malignancy, whereas a soft painful mass without skin thickening and nipple retraction may imply gynecomastia. A mass with spiculated or lobulated contour eccentric to the nipple and microcalcifications in the mammogram are findings

that support malignancy. Contrary to these findings subareolar flame-disk shaped nodular radiodensity or non-mass like subareolar density with posterior linear projections radiating into the surrounding fatty tissue indicate gynecomastia. In both of our diagnostic imaging clinics, ultrasonography is considered as the first line imaging method in patients younger than 35 years who have indeterminate or suspicious physical examination findings. Mammography was performed only in cases where suspicious findings were detected by ultrasonographic evaluation. In patients over 35 years of age we think that using both imaging modalities together will be more effective.

In conclusion, Appropriate joint use of diagnostic imaging methods in male breast problems could decrease unnecessary biopsy rates to perform a successful differential diagnosis. Furthermore, mammosonographic examination could efficiently differentiate gynecomastia from malignancy as it could determine the reversible phase of gynecomastia as well. Therefore the combination of MG and US in adult gynecomastia cases might determine the time of surgical treatment. Sonographic Tanner staging might be an alternative in order to evaluate gynecomastia evolution in adolescent cases.

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Oncoplastic Breast Conserving Surgery: Aesthetic Satisfaction and Oncological Outcomes

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ABSTRACT

Objective: Oncoplastic breast conserving surgery (BCS) involves radical excision of tumors while maintaining the natural breast contours. In this study, we present the results of the oncoplastic BCS surgeries performed in our clinic.

Material and Methods: 13 breast cancer patients who had undergone oncoplastic BCS were included in this retrospective study. Postoperative photographs and retrospective chart reviews were used to evaluate the results. Aesthetic satisfaction level was verbally obtained from the patients.

Results: Oncoplastic BCS was performed using superomedial, superolateral, superior and inferior pedicles. All the patients were highly satisfied with the final aesthetic results and tumor free at the postoperative 12 months.

Conclusion: Oncoplastic BCS can achieve favorable results regarding the final aesthetic appearance and tumor control.

Keywords: Breast conserving surgery, breast cancer, oncoplastic surgery

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Introduction

Oncoplastic breast conserving surgery (BCS) involves maintaining aesthetically natural breast contour while performing the radical resection of the tumor in patients with breast cancer (1-3). This principle could be adapted to all breast cancer patients except the ones requiring total mastectomy.

Breast-conserving surgery together with radiotherapy has been accepted as standard treatment for early stages of breast cancer (4-6). Despite successful adaptation of conventional BCS in the treatment of early-stage breast cancer in the last few decades, it has been the case that many cases ended up in aesthetical non-pleasing results (7, 8). The incidence of these cases has been reported up to 30% in some of the series. Poor aesthetic results have been associated with central-medial tumor location, large tumor size, and radiotherapy (9-11).

Oncoplastic BCS can be defined as the combination of reduction mammoplasty and mastopexy techniques with breast conserving surgery. This combination can effectively reduce the number of aesthetically displeasing results of BCS in patients with macromastia while maintaining adequate margin for the tumor excision (12, 13). In recent studies, oncological safety of this approach has been found comparable to conventional BCS (14-16). In this paper, we introduce our results with therapeutic mammoplasty.

Materials and Methods

13 patients operated between 2014 and 2015 were included in the study. Informed consents were obtained from all the patients. Ethical committee approval was not required. Mean age of the patients was 49 (36-65). All the patients had macromastia and were exclusively chosen for oncoplastic BCS. 53% of the patient was obese, and 30% of the patients had diabetes. Tumors were located in upper medial

Table 1: Descriptive analysis of the results

Clinical Parameters	
Patient characteristics	
Mean age	49 (36-65)
Obesity	53.8% (n=7)
Diabetes Mellitus	30.7% (n=4)
Tumor location	
Upper medial	15.3% (n=2)
Inferior	46.1% (n=6)
Lateral	30.7% (n=4)
Central	7.6% (n=1)
Tumor size	
T1	23% (n=3)
T2	76.9% (n=10)
Lymph node involvement	
N0	92% (n=12)
N1	7.6% (n=1)
Distant metastasis	
M1	0% (n=0)
Surgical Procedure	
Bilateral oncoplastic breast reduction	92% (n=12)
One sided oncoplastic breast reduction	8% (n=1)
Complications	
Nipple necrosis	0% (n=0)
Wound dehiscence	8% (n=1)
Postoperative debridement	8% (n=1)
Postoperative follow-up 12 months after the surgery	
Patient aesthetic satisfaction-high	100% (n=13)
Tumor relapse	0% (n=0)

(n=2), inferior (n=6), lateral (n=4) and central (n=1) sections of the breast. Postoperative photographs and chart reviews were used to evaluate the results. Aesthetic satisfaction level survey was verbally obtained from the patients (0: Not satisfied, 1: Low, 2: Moderate, 3: High rate of satisfaction). All clinical parameters are presented in Table 1.

Statistical analysis

Descriptive analysis was performed using GraphPad Prism software (GraphPad Software, Inc. La Jolla, CA 92037 USA).

Results

Bilateral oncoplastic breast reduction was performed on all patients except in one patient in whom one-sided reduction was conducted to preserve lactation (lateral pedicle). Nipple-areola complex was re-located to its new location on a chosen pedicle. The pedicle was selected according to the tumor location. In inferior location tumors superior pedicle, in lateral locations superomedial pedicle, in upper-

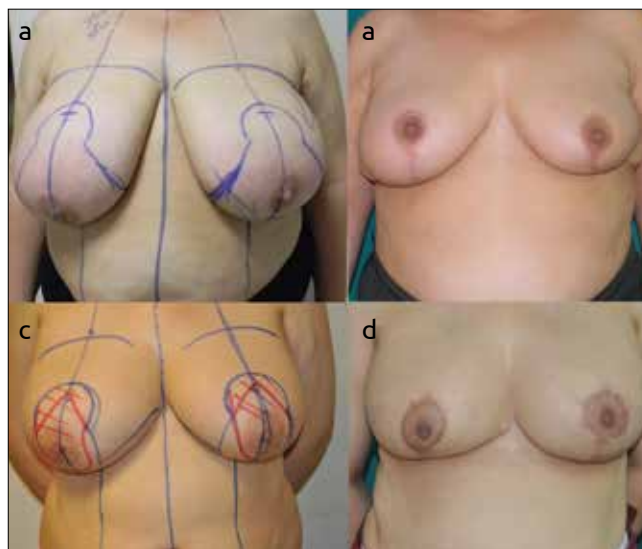


Figure 1. a-d. Two cases with superior pedicle oncoplastic breast reduction. Preoperative photograph (a-c). Postoperative photograph (b-d)

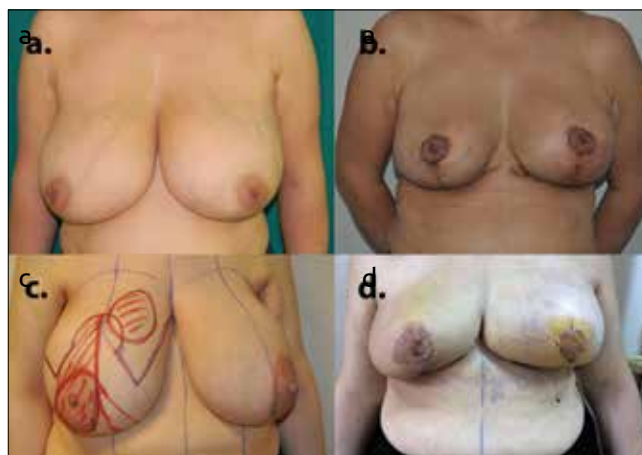


Figure 2. a-d. Preoperative (a) and postoperative (b) photographs of a superomedial pedicle oncoplastic breast reduction patient. Preoperative (c) and postoperative (d) photographs of a superolateral pedicle oncoplastic breast reduction patient

medial locations superolateral pedicle was used. In one patient with a central localization, tumor nipple areola was not preserved. Especially tumors with the upper medial location were more challenging. Pedicle design was modified to obtain longer and a wider pedicle. Pedicle was anchored to the pectoral fascia to achieve fullness in the excised area (Figure 1-2).

In the postoperative follow-ups, one patient encountered wound healing problems after radiotherapy. After debridement, the wound closure was delayed for secondary healing. The complete closure of the wound was observed three weeks after the debridement. No other complications were seen in the other patients. 12 months after the surgery all the patients were tumor free and were aesthetically satisfied.

Discussion and Conclusions

We believe that this approach to BCS in patients with macromastia has many advantages. It improves the final aesthetic results by maintaining

natural breast contours. This has been a problem with conventional BCS in recent decades (13). Especially in large tumors maintaining the breast contour after resection has proven to be challenging. It has been reported in earlier studies that more than 15-20% reduction in the breast volume, depending on the tumor location, can decrease the aesthetic outcome of the surgery significantly (5, 17). This volume was reported to be low as 5% for medial tumor locations (18).

In our series all the patients were aesthetically satisfied. These patients were also relieved from their symptoms related to macromastia such as back and neck pains, which increased their overall satisfaction. Higher rate of patient satisfaction undergoing oncoplastic BCS was reported in earlier studies when compared to conventional BCS (11, 13, 19). It was more challenging to achieve aesthetically pleasing results in tumors with central and upper medial locations as reported previously (3, 20).

Another advantage of this approach to BCS is the increase in the surgical exposure during the tumor resection. We believe that the exposure and the resection of the tumor was much easier and wider excision was possible when compared to conventional BCS with the implementation of oncoplastic breast reduction. There is a risk of 4% contralateral second primary among the survivors of breast cancer (21). Although not currently supported by the literature, we believe that risk of secondary primary might decrease with the oncoplastic BCS since the contralateral breast volume is reduced. We also believe that the efficiency of radiotherapy might increase after oncoplastic BCS since the total breast volume is decreased, but there are no studies up to date to support this idea.

In conclusion, we believe that oncoplastic BCS can achieve satisfactory results regarding the final aesthetic appearance and tumor control. Further randomized controlled studies to compare oncoplastic BCS with conventional BCS are required to prove these findings.

Ethics Committee Approval: Ethics committee approval was not requested for this study.

Informed Consent: Written informed consents were obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.K.Y., M.S.; Design - S.K.Y., M.S.; Supervision - M.Y.; Resources - S.K.Y., D.A.; Materials - Ş.A.; Data Collection and/or Processing - D.A.; Analysis and/or Interpretation - D.A.; Literature Search - S.K.Y., M.S.; Writing Manuscript - S.K.Y., M.S.; Critical Review - M.Y.

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MR Imaging Features of Tubular Carcinoma: Preliminary Experience in Twelve Masses

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ABSTRACT

Objective: We retrospectively analyzed the magnetic resonance (MR) imaging features and diffusion-weighted imaging findings of the 12 masses of 10 patients with tubular carcinoma (TC), including mammography and sonography findings.

Materials and Methods: Mammographic, sonographic and magnetic resonance imaging features in 12 histopathologically confirmed masses diagnosed as TC of the breast within 10 patients were evaluated. Morphologic characteristics, enhancement features, apparent diffusion coefficient (ADC) values were reviewed.

Results: On mammography (n=5), TC appeared as high density masses with indistinct, spiculated or obscured margins. Sonographically, TC appeared as a hypoechoic appearance (n=12) with posterior acoustic shadowing in nine. On MR imaging, the margins of ten of twelve masses were irregular. Internal enhancement patterns were heterogeneous in 10 patients. Dynamic enhancement patterns illustrated plateau kinetics (n=8). On the T2-weighted images 4 masses were hypointense, and 8 were hyperintense; hypointense internal septation was found in seven of these. Tubular carcinoma appeared as hyperintense on diffusion-weighted imaging with ADC values of $0.85 \pm 0.16 \times 10^{-3} \text{ mm}^2/\text{s}$ that was lower than the normal parenchyma of $1.25 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$.

Conclusion: According to our study with a limited number of cases, tubular carcinomas can be described as hyperintense breast carcinomas with or without dark internal septation like appearance on T2-weighted images. Low ADC values from DW imaging can be used to differentiate TC from hyperintense benign breast lesions.

Keywords: Tubular cancer, ultrasonography, magnetic resonance imaging, diffusion weighted imaging, hyperintense breast cancer

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Introduction

Tubular carcinoma (TC), a rare histologic type of invasive malignancy, forms almost 1% to 5% of the breast carcinomas (1-3). Histologically, TCs are composed of ductal epithelial tubules that spontaneously burst into the stroma and are covered by a single ductal epithelium cell and are directly associated with myoepithelial cells adjacent to the stroma (4). The absence of myoepithelial cells was detected with p53 immunostaining in tubular carcinomas. It has a more convenient prognosis than less well-differentiated invasive breast carcinomas, with fewer metastases to axillary lymph nodes and better survival rates (5-7). Despite these tumors may be discovered as large palpable masses, they are usually detected when they are less than 1 cm in diameter (8). Ultrasonography (US) or mammography (MG) features of TC have been described a few times (9-12), however, little has been published about its magnetic resonance (MR) imaging appearance (13, 14). The most frequent mammographic finding of tubular carcinoma has been described as an irregular shaped mass with spiculated margins. On sonography, tubular carcinomas are usually seen as hypoechoic masses with ill-defined margins and posterior acoustic shadowing. Ghai et al. (14) reported MR imaging findings of pure TCs but their series included only three cases with nonspecific findings. Linda et al. (13) reported that TC had low-intermediate signal on T2-weighted images and heterogeneous enhancement with Type 2 curve (persistent enhancement) on dynamic analysis, but without mentioning the number of patients or a study. The purpose of this work was

to assess the MR imaging features of TC of the breast. This study is the first MR imaging study of tubular carcinoma in the available literature.

Materials and Methods

A retrospective evaluation for 4050 breast carcinomas diagnosed at a single institution between February 2001 and February 2016, revealed 39 histopathologically proven masses of pure TC of the breast. Imaging findings were retrospectively analyzed. Twenty-one of TC were identified in mammographic screening with the addition of ultrasonography. In 18 cases, patients had clinical complaints so the masses were detected during diagnostic evaluation with MG and US. Ten of the 39 patients who underwent MR imaging in our institution were included in our study. This study was approved by local ethics committee.

All study examinations were performed on a 1.5T system (Achieva, Philips Medical Systems, Best, The Netherlands) by using a dedicated four-channel breast coil. T2-weighted (T2-W) fat-saturated turbo spin echo (TR/TE: 4130/120ms; matrix, 270x234; FOV, 340x400mm; slice thickness, 2mm; NEX, 3) and T1-weighted (T1-W) turbo spin echo (TR/TE: 498/10ms; matrix, 270x265; FOV, 340x400mm; slice thickness, 2mm NEX, 2) were performed in axial planes. For this purpose a 2D spin-echo echo-planar imaging (EPI) sequence (TR, 15180 ms, fractional TE, 86 ms; FOV, 340x340 mm; matrix, 228x226; slice thickness, 3 mm; NEX, 2 mm) was used. Sensitizing diffusion gradients in three orthogonal directions with b values of 50, 400, and 800 s/mm² were obtained. Dynamic fat-saturated 3D T1-W turbo field echo sequence (THRIVE) (TR/TE, 7/4.6ms; matrix, 340x342; NEX, 2; FOV, 336x340mm) images in the axial plane were taken once before and seven times following the administration contrast agent. Contrast materials based on gadolinium at a dose of 0.2 mmol/kg of body weight was administered with a power injector followed saline flush. Subtracted images were evaluated and the time-signal intensity curves of the masses were drawn and interpreted. The turbo field echo in sagittal plan (TR/TE, 8.2/4.7ms; matrix, 246x252; NEX, 3; FOV, 200x210 mm) was obtained after the administration of contrast in the 3D array.

The MR imaging, US and MG findings were characterized by consensus reading according to the American College of Radiology's Breast Imag-

ing Reporting and Data System (BI-RADS) Atlas 5th edition (15). Two radiologists with six and four years of experience in breast imaging interpreted the MR images of TCs by processing in Extended MR workstation. Lesions were categorized as follows: focus, mass and non-mass enhancement. Masses were interpreted as margin (smooth, spiculated or irregular), shape (oval, irregular, round), and internal enhancement pattern (rim enhancement, non-enhancing internal septation, heterogeneous, homogeneous). Non-mass enhancement was evaluated as the internal enhancement pattern (homogeneous, heterogeneous, clumped, clustered ring) and distribution (focal, linear, regional, segmental or diffuse). The time-signal intensity curves (progressive, plateau, washout) with early (initial) enhancement findings (fast, medium, slow) of lesions were obtained. Apparent diffusion coefficient (ADC) maps were generated on the Extended MR Workspace 2.6.3.5 workstation. ADC values were calculated using whole-measurement method. A freehand region of interest was drawn above the enhancing component of the mass throughout the entire dynamic series and included not more than 3-4 pixels. Regions of interest were drawn on the b = 800 s/mm² images round the mass, with reference to the information from T2-W and subtraction sequences of breast MR study. ADC value of the TC and contralateral normal parenchyma of the breast were measured three times. Measurement of ADC of normal breast parenchyma was compared with ADC of TC.

US and MG findings of ten patients were analyzed. The mammographic findings were analyzed for asymmetry and masses. Masses were analyzed for density (high, equal and low), shape (irregular, oval, round) and margins (circumscribed, spiculated, obscured, indistinct and microlobulated). Accompanying architectural distortions and calcifications were also analyzed. Ultrasonography was used to evaluate lesion shape, margin characteristics, echogenicity and posterior acoustic features.

Patients underwent breast-conserving surgery (n=7) or mastectomy (n=3) with sentinel lymph node sampling. Preoperatively, the nonpalpable lesions were localized sonographically in seven patients. Three patients underwent mastectomy because of patient preference, the presence of invasive ductal carcinoma and the presence of ductal carcinoma in situ in the different quadrant of the same breast.

Table 1. Sonographic and mammographic features of tubular carcinoma

Mass	US-Echogenicity	US-Shape, Border	US-Attenuation	MG Findings
1	hypoechoic	irregular, indistinct	acoustic shadowing	high-density irregular mass with indistinct margin
2	hypoechoic	irregular, indistinct	acoustic shadowing	asymmetric density
3	hypoechoic	irregular, microlobulated	acoustic shadowing	high-density irregular mass with obscured margin
4	hypoechoic	irregular, angular	normal sound transmission	high-density irregular mass with indistinct margin
5	hypoechoic	irregular, microlobulated	acoustic shadowing	asymmetric density
6	hypoechoic	irregular, microlobulated	acoustic shadowing	dense parenchyma
7	hypoechoic	irregular, spiculated	acoustic shadowing	dense parenchyma
8	hypoechoic	irregular, indistinct	acoustic shadowing	dense parenchyma
9	hypoechoic	irregular, spiculated	acoustic shadowing	high-density irregular mass with spiculated margin
10	hypoechoic	irregular, angular	normal sound transmission	not visible
11	hypoechoic	irregular, angular	normal sound transmission	not visible
12	hypoechoic	irregular, microlobulated	shadowing	high-density oval mass with indistinct margin

US: ultrasonography; MG: mammography

Table 2. MR imaging features of tubular carcinoma

masses	Age	Right/ left	Size-MR (mm)	Size- Pathology (mm)	T2		T1		Shape	pattern	Enhancement		Initial phase	Delayed phase	ADC-m,ADC-p	ln-p	satellite	adc-m	adc-p
					weighted	weighted	weighted	weighted			Margin								
1	47	upper- outer	right	8	9	hyperintense septation	hypointense	hypointense	irregular	heterogeneous	spiculated	fast	persistent	0.9–1.3	0	0	0.9	1,3	
2	48	upper- inner	left	7	6	hypointense	hypointense	hypointense	irregular	heterogeneous	irregular	medium	persistent	0.8–1.2	0	0	8	1,2	
3	49	upper- outer	right	16	15	hyperintense	hypointense	hypointense	irregular	heterogeneous	irregular	fast	plateau	0.9–1.1	1, microme- tastasis	0	0.9	1,1	
4	45	upper- inner	left	8	8	hyperintense septation	hypointense	hypointense	irregular	homogeneous	irregular	fast	washout	0.8–1.4	0	0	0.8	1,4	
5	58	upper- outer	right	9	7	hypointense	hypointense	hypointense	irregular	heterogeneous	irregular	fast	plateau	0.6–1	0	1	0.6	1	
6	58	upper- outer	right	10	10	hypointense	hypointense	hypointense	irregular	heterogeneous	irregular	fast	plateau	0.6–1	0	1	0.6	1	
7	48	lower- outer	right	9	10	hyperintense	hypointense septation	hypointense septation	irregular	homogeneous	irregular	fast	plateau	1.1–1.8	0	0	1.1	1,8	
8	48	upper- outer	left	7	6	hyperintense septation	hypointense	hypointense	irregular	heterogeneous	irregular	fast	plateau	1.1–1.5	0	0	1	1,5	
9	42	upper- inner	left	15	25	hyperintense septation	hypointense	hypointense	oval	heterogeneous	spiculated	fast	plateau	0.8–1	0		0.8	1	
10	42	upper- inner	left	10	11	hyperintense septation	hypointense	hypointense	irregular	heterogeneous	irregular	fast	plateau	0.7–1	0	0	0.7	1	
11	37	upper- outer	right	5	5	hyperintense septation	hypointense	hypointense	oval	heterogeneous	irregular	medium	plateau	1–1.4	0	0	1.1	1,4	
12	48	lower- outer	left	5	4	hypointense	hypointense	hypointense	oval	heterogeneous	irregular	fast	persistent	1–1.4	0	0	0.9	1,4	
MR: magnetic resonance; ADC: apparent diffusion coefficient; Size-MR: size-magnetic resonance; Size-P: Lesion size-histopathology																			

MR: magnetic resonance; ADC: apparent diffusion coefficient; Size-MR: size-magnetic resonance; Size-P: Lesion size-histopathology

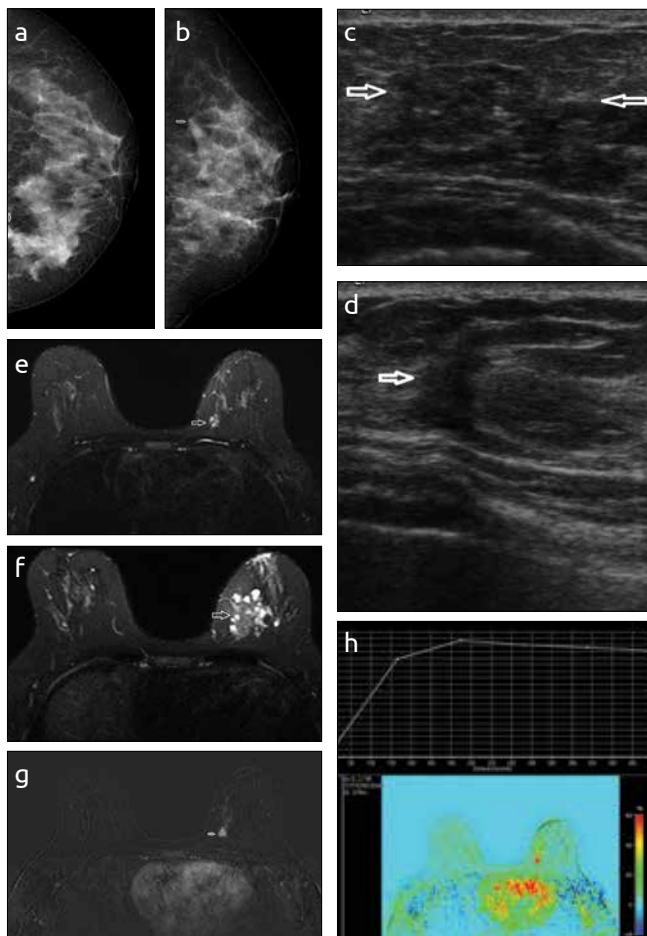


Figure 1. a-h (mass 4). A 45-years-old woman with palpable mass in the lower-inner quadrant of the left breast. Craniocaudal (a) and mediolateral (b) oblique mammography images showed not only a 30x15 mm high-density irregular mass with amorphous calcification in the lower-inner quadrant, but also 8x7mm high-density irregular mass with indistinct margins (arrow), which proved to be tubular carcinoma in the upper-inner quadrant of heterogeneous dense parenchyma. Sonography (c) of that palpable area showed a predominantly solid mass with internal cystic spaces and calcification (arrows). Tubular carcinoma was an irregular hypoechoic mass (d) with angulated border (arrow). Axial T2-weighted images with fat suppression shows 8 mm hyperintense lobulated tubular carcinoma with dark internal septation (arrow) (e) and hypointense mass with milimetric cysts that proved to be stromal fibrosis (f). TC shows homogenous contrast enhancement with Type-3 dynamic analysis on T1-weighted gadolinium-enhanced subtraction image (2.second) (g), (h)

Statistical Package for Social Sciences (SPSS) software version 17 (SPSS Inc, Chicago, IL, US) was used for statistical analyses. Data are presented as follows: mean±standard deviation or median with range, as appropriate. The frequencies of involvement in each quadrant, additional lesion, the presence of suspicious lymph nodes and magnetic resonance imaging findings were also analyzed. The Mann-Whitney U test was used for comparing the continuous variables of two samples. $p < 0.05$ was considered as a sign of a significant difference. Each eligible woman was informed and signed the consent form.

Results

Ten patients with twelve masses of TC were evaluated. Our patients were aged between 37 and 58 years (mean age, 47) at the time of the

diagnosis. There was no positive risk factor for breast cancer in any patient. Three patients were considered to be diagnostic for firm-palpable mass on physical examination. In seven patients, TC was diagnosed on screening mammography and additionally on ultrasonography; the other cases were symptomatic and were evaluated diagnostically. MG was negative in 5 (42%) patients. US and MR imaging was positive in all patients (TC could be seen with second look US in two patients). Six of the twelve masses were in the left breast (50%). The quadrant frequency in the twelve breasts was upper-outer (50%), upper-inner (33%), and lower-outer (17%).

Mammography showed TC as a high-density mass in 5 (42%) patients and as asymmetry in 2 (16%) patients. No architectural distortion or suspicious calcification was seen in any patients on MG. Masses were irregular shaped with microlobulated margin in 1 patient, indistinct margin in 2 patients and spiculated margin in 1 patient. An oval shaped mass with indistinct margin was seen in only one patient. US was positive in all patients of 12 masses (1 multifocal and 1 bilateral). All masses were hypoechoic ($n=12$) with nine of them with posterior acoustic shadowing. All patients had masses with irregular shapes. The margins of the masses were microlobulated in 4 (33%) patients, angular in 3 (25%) patients, indistinct in 3 (25%) patients, and spiculated in 2 (17%) patients. US and MG imaging findings are presented in Table 1.

The amount of fibroglandular tissue in patients with TC on MRI was almost entirely fat in 1/12, scattered fibroglandular tissue in 2/12, heterogeneous fibroglandular tissue in 4/12, and extreme fibroglandular tissue in 5/12 of patients. All TCs were visible as masses with a total of twelve (1 bilateral and 1 multifocal) on MR imaging. The size of the masses on MR imaging varied from 5 to 16 mm (mean, 9 mm). The masses were irregular ($n=9$) and oval shaped ($n=3$). The margins of the masses were irregular in 10 patients, and spiculated in 2 patients on MR imaging. The patterns of internal enhancement were found to be homogeneous in 2 patients and heterogeneous in 10 patients. The time-signal intensity curve (delayed enhancement phase) showed progressive enhancement (Type-1) in 3 (25%) masses, a plateau enhancement (Type-2) in 8 (67%) masses, and a washout enhancement (Type-3) in 1 (8%) mass. Initial enhancement phase was fast in ten masses and medium in two masses. All TCs showed a hypointense signal on T1-W images. Mass signals were variable on T2-W, hypointense in 4 masses, and hyperintense in 8 masses. The hypointense internal septation-like appearance was observed in seven of the hyperintense masses on T2-W images (Figure1). The mean ADC value of tubular carcinoma was calculated ($0.85 \pm 0.16 \times 10^{-3} \text{ mm}^2/\text{s}$) as lower than the mean ADC value of normal parenchyma ($1.25 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$) (Figure 2). The difference between TC and normal parenchyma ADC values was significant ($p < 0.05$). MR imaging findings are provided in Table 2. MR imaging did not provide additional contribution to MG and US in our study (multifocality, suspicious lymph node (LN) or different findings).

Histopathological examination of the tumor size ranged from 4 to 25 mm (mean, 9.6 mm). A total of 12 masses were seen in the 10 patients. One patient had bilateral tubular carcinoma (Figure 3). The tumor was multifocal in one patient, who also showed DCIS in another quadrant of the same breast. Axillary lymph node metastasis was present in only one patient as micrometastases; the tumor size was 15mm in that patient (Figure 4).

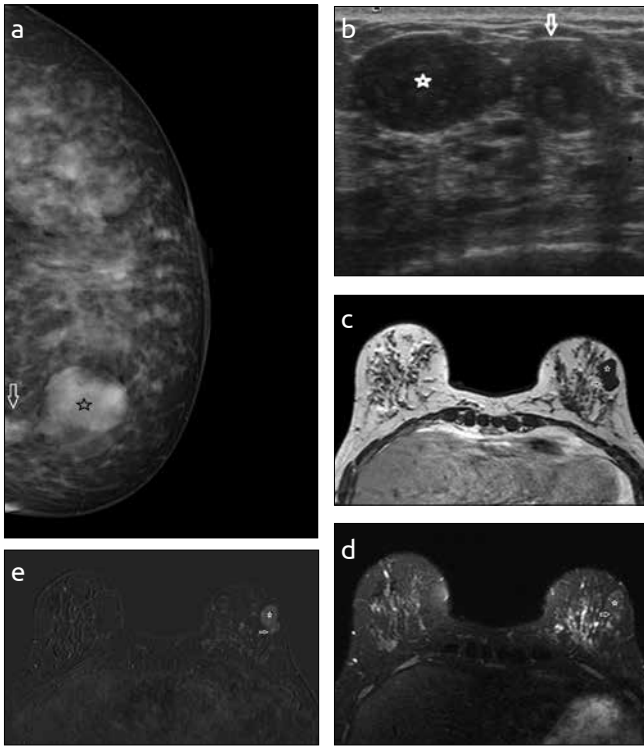


Figure 2. a-e (mass 12). A 48-years-old woman with tubular carcinoma. Craniocaudal mammography (a) shows high-density oval mass with indistinct margins (arrow) adjacent to fibroadenoma (asterisk) on outer quadrant of left breast. Tubular cancer cannot be seen on mediolateral oblique projection. Sonographically, irregular shaped, heterogeneous, microlobulated tubular carcinoma with posterior shadowing (arrow) and oval shaped hypoechoic fibroadenoma with well-defined margins (asterisk) were detected (b). Also a thin fat plane was seen between masses. Axial T1-weighted without fat suppression (c) and T2-weighted with fat suppression (d) images show 5mm hypointense tubular carcinoma (arrow) and fibroadenoma (asterisk). TC (arrow) shows heterogeneous contrast enhancement on T1-weighted gadolinium-enhanced subtraction image (2.second) (e)

Discussion and Conclusion

A few articles have been reported regarding the MR findings of TC (13, 14). Because tubular carcinoma was only partially mentioned in these articles, little information was provided and MR imaging features for this type of tumor were nonspecific. MR imaging is performed very rarely in patients who are diagnosed with TC because of typical malignant features on MG and US and due to small size. In our series, all of the TC appeared as mostly irregular shaped masses with indistinct margin classified according to the BI-RADS 5th edition (15). Tubular carcinoma sizes were too small in general to evaluate margins accurately on MR imaging compared to MG and US. So, spiculated margins, which constitute a common finding for this type of cancer, were not observed frequently on MR imaging. TC showed hypointense signal on T1-W images in all masses just like other breast carcinomas, but in seven of the masses there was hyperintense signal with dark internal septations on T2-W images in our study. Breast carcinoma with high signal intensity on T2-W was reported many times in the literature, but there is no information about TC (16, 17). In our series, high signal intensity on T2-W images was considered to be a MR feature of tubular carcinoma. Meanwhile hypointense internal septation-like appearance was seen in most of the hyperintense tubular carcinomas,

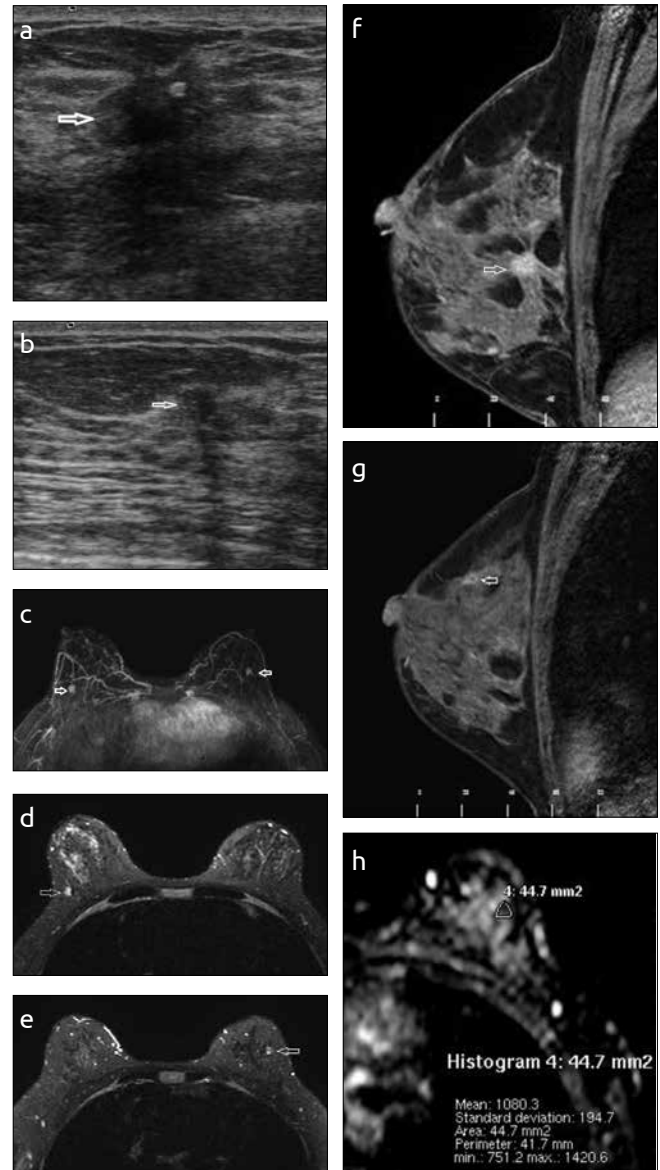


Figure 3. a-i (mass 7 and mass 8). A 48-years-old woman with bilateral tubular carcinoma that was negative on MG. Sonography detected an irregular shaped mass with spiculated margins on the right breast (a) and irregular shaped mass with indistinct margins on the left breast (b). Axial maximum intensity projection of a contrast enhanced T1-weighted three-dimensional spoiled gradient-echo image (c) shows bilateral tubular carcinomas (arrows). Axial T2-weighted with fat suppression images show 9mm hyperintense mass with slightly visible internal septation on the right breast (arrow) (d) and 7 mm hyperintense mass with prominent hypointense internal septation on the left breast (e). In the sagittal plane of post-contrast fat suppression images, mass on the right breast enhanced homogeneously (arrow) (f) and mass on the left breast enhanced heterogeneously (arrow) (g). Apparent diffusion coefficient (ADC) map reveals $1.12 \times 10^{-3} \text{ mm}^2/\text{s}$ within mass on the right breast (h) and $1.08 \times 10^{-3} \text{ mm}^2/\text{s}$ on the left breast (i)

which was a different finding from most of the other cancers. The pattern of internal enhancement was heterogeneous in most of the tubular carcinomas. Consistent with other breast cancers, our results showed that the kinetic curve obtained from contrast enhanced MR imaging of TC exhibits a fast initial contrast enhancement pattern, followed by a plateau pattern. Linda et al. (13) reported spiculated shape, ill-defined margin, low-intermediate signal on T2-W and heterogeneous

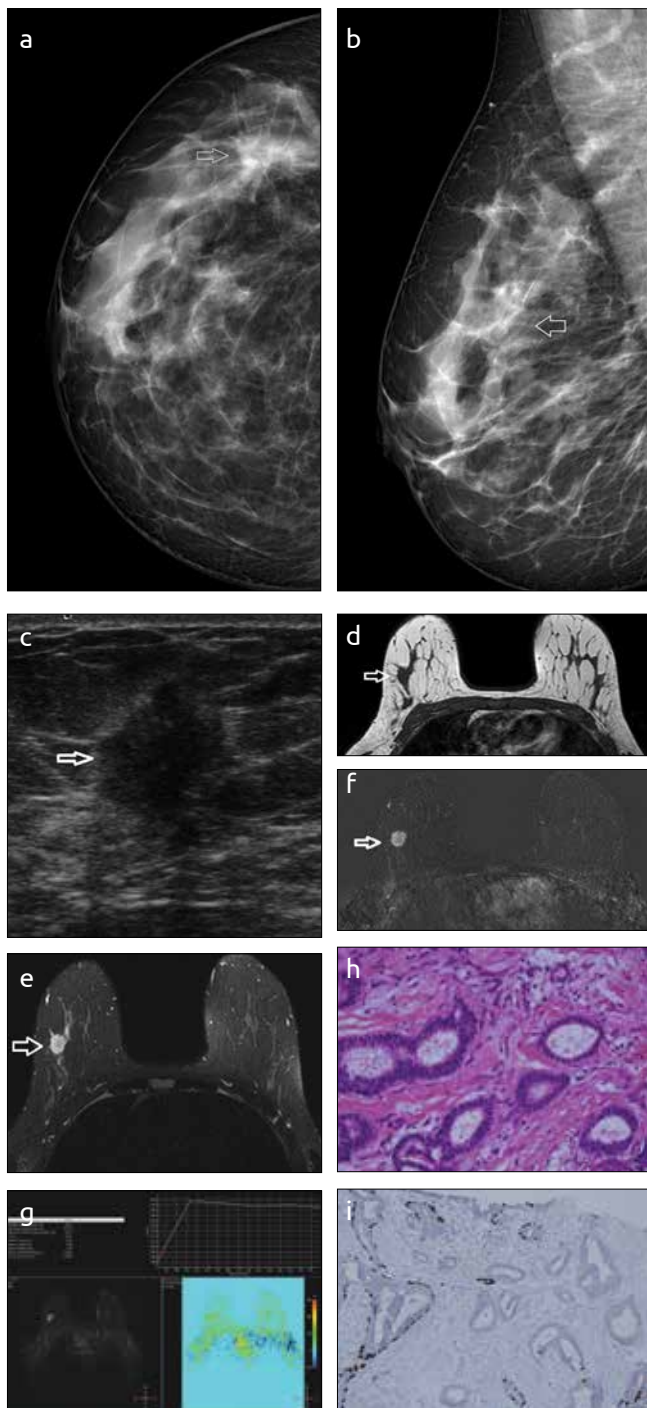


Figure 4. a-i (mass 3). A 49-years-old woman with tubular carcinoma who had axillary lymph node metastasis. Craniocaudal (a) mammography shows high-density mass with obscured margins in the outer quadrant of the right breast (arrow), but the mass was unclear on mediolateral oblique (b) MG. Ultrasonography (c) image reveals irregularly shaped tubular carcinoma with microlobulated margins (arrow), also posterior shadowing is seen. Axial T1-weighted image without fat suppression (d) shows a 16 mm irregularly shaped hypointense tubular carcinoma (arrow). Mass (arrow) is heterogeneous hyperintense on T2-weighted fat suppression image (e). TC shows heterogeneous contrast enhancement (arrow) (f) with Type-2 dynamic analysis on T1-weighted gadolinium-enhanced subtraction image (2. second) (g). Infiltrating tubules with angular shape in a desmoplastic stroma (H.E, x20, original magnification) (h). No myoepithelial cells were detected with p63 immunostaining in tubular carcinoma (p63, x10, original magnification) (i)

enhancement with persistent kinetic curve in their article about MR features of tubular carcinoma. Ghai et al. (14) reported three tubular carcinomas that did not enhance on MR imaging. These were the only findings reported in the imaging literature about TC characteristics on MR imaging. We had difficulty in defining morphologic, kinetic and diffusion characteristics of lesions smaller than 7 mm. US findings were useful for characterization of subcentimeter lesions on MR imaging. In one patient, we decided to designate a 5 mm lesion as a mass because of its space occupying nature on axial and sagittal images, hypointense signal on T2-W images and its visibility on US.

Diffusion-weighted MR imaging demonstrates high accuracy in differentiating malignancy from benignancy by measuring the ADC in breast lesions (18, 19). We measured the mean ADC values of TC and ADC of normal contralateral parenchyma and compared each other. According to our results, the mean ADCs of the TC ($0.85 \pm 0.16 \times 10^{-3} \text{ mm}^2/\text{s}$) were lower than breast parenchyma ($1.25 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$). Previous studies have shown that ADC values of malignant lesions are significantly lower than benign lesions and parenchymal values (18, 20-22). However, there are no reports about ADC values to differentiate breast carcinomas from one other. Our results on calculated ADC values demonstrated that TC had similar ADC values with previously studied invasive breast carcinomas (18-22). Even though hyperintense signal with dark internal septations of TC on T2-W images of MR imaging is similar to fibroadenoma, dynamic analysis with early and delayed enhancement patterns, ADC values and advanced age help to differentiate TC from this benign entity on MR imaging.

Tubular carcinoma has been reported to be related with other types of carcinomas and associated with other histologic entities (4, 23, 24). In this study, one patient with DCIS in another quadrant of the same breast and one patient with invasive ductal carcinoma in the same quadrant were reported. TC has been reported to have a low recurrence rate (25). No deaths as a result of distant metastasis or cancer were seen in our study. Axillary LN metastases are rare in patients with TC. Only one patient had LN micrometastasis, and that patient had a higher mean tumor size (15 mm) in our study.

The mammography and sonography characteristics of this rare tumor have been discussed in several reports (5, 9, 10, 11, 23). The described features on MG and US were not specific for TC with suspicion of malignancy. Common finding of the breast tubular carcinoma is the irregular shaped mass with spiculated margin on both US and MG (9, 11, 23). In our series, on mammography, tubular carcinomas were usually high-density, irregular shaped masses with indistinct or spiculated margins. Almost all tubular carcinomas in the literature are hypoechoic masses with posterior acoustic shadowing (9, 11). In our study all tubular carcinomas were irregular shaped with hypoechoic echotexture. Most of them (73%) had posterior acoustic shadowing on US.

Several limitations of this study should be acknowledged. This study was retrospective in design and a case collection study. There is no a case control study, therefore it remains unclear whether or not these MR characteristics are specific findings. New studies with larger populations and a comparative-prospective nature are required for further evaluation of MR imaging features in TC, maybe to differentiate them from other breast carcinomas and fibroadenomas.

In conclusion, the present study was the first to report two important MR imaging features of pure tubular carcinomas. Tubular carcinomas may exhibit high signal intensity and dark internal septation-like ap-

pearance on T2-W images. In such cases low ADC values from DW imaging may useful differentiating TC from hyperintense benign breast lesions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University Faculty of Medicine.

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Breast Injuries in Female Collegiate Basketball, Soccer, Softball and Volleyball Athletes: Prevalence, Type and Impact on Sports Participation

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ABSTRACT

Objective: In 2015-2016, over 214,000 female athletes competed at the collegiate level in the United States (U.S.). The National Collegiate Athletic Association (NCAA) collects injury data; however, breast-related injuries do not have a specific reporting category. The exact sequelae of breast injury are unknown; however, a relationship between breast injury and fat necrosis, which mimics breast carcinoma, is documented outside of sports participation. Breast injuries related to motor vehicle collisions, seatbelt trauma, and blunt trauma have been reported. For these reasons, it is important to investigate female breast injuries in collegiate sports. The objectives of this study are to report the prevalence of self-reported breast injuries in female collegiate athletes, explore injury types and treatments, and investigate breast injury reporting and impact on sports participation.

Materials and Methods: A cross-sectional study of female collegiate athletes at four U.S. universities participating in basketball, soccer, softball, or volleyball. Main outcome measure was a questionnaire regarding breast injuries during sports participation.

Results: Almost half of the 194 participants (47.9%) reported a breast injury during their collegiate career, less than 10% reported their injury to health personnel with 2.1% receiving treatment. Breast injuries reported by sport include softball (59.5%), basketball (48.8%), soccer (46.7%), and volleyball (34.6%).

Conclusions: The long-term effects and sequelae of breast injuries reported by female collegiate athletes during sport play are unknown. Nearly 50% of participants had a breast injury during sports activities. Although 18.2% indicated that breast injury affected sports participation, only 9.6% of the injuries were reported to medical personnel with 2.1% receiving treatment.

Keywords: Chest injury, breast trauma, sport injury

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Introduction

In 2015-2016, there were over 214,000 women competing in collegiate athletics in the United States and this number continues to rise (1). The exact sequelae of breast injury are unknown; however, a relationship between breast injury and fat necrosis, which can mimic breast carcinoma in manual exams and/or ultrasound and mammogram findings, has been documented outside of sports participation (2-6). Fat necrosis can occur following trauma to the breast, leading to persistent and sometimes painful masses in the breast (7). Breast injuries related to motor vehicle collisions and resultant blunt breast trauma with the seat belt (3-5, 8-11) and breast blunt trauma as a result of a fall (11-12) have been reported; however, only one study has been found that explored female breast injury during competitive sports participation (13). For these reasons, it is important to investigate the prevalence, reporting, treatment and implications of female breast injuries in collegiate sports. The primary purpose of this study is to report the prevalence of self-reported breast injuries in female collegiate athletes. A secondary purpose is to explore the injury reporting, the severity and type of breast injury. The treatment of breast injuries including the impact of breast injury on sports participation in female collegiate athletes was also explored.

Materials and Methods

Study Design: Cross-sectional. The questionnaire's face value was established by three experts in survey research methodology not involved in the study and the questionnaire was piloted on a subset of participants.

Subjects: Participants included female collegiate athletes over the age of 18 who were currently participating on a sanctioned basketball, soccer, softball, or volleyball sports team during the 2015-16 season. These teams were selected because they were identified by the primary researchers as popular women's sports. All the participants provided written consent and the study was approved by an ethics committee, University of Michigan-Flint Institutional Review Board (IRB), prior to recruitment. Twenty-six schools representing the National Collegiate Athletic Association (NCAA), National Association of Intercollegiate Athletics (NAIA), and Mid-America Intercollegiate Athletics Association (MIAA) universities from four different states were invited via email and telephone to participate in this study. Four schools agreed to participate in this study, 13 schools declined, and nine did not respond. The IRB guidelines for data collection were also completed at each of the four institutions where data were collected. For the four schools represented in this study, there were seven male and three female athletic trainers. Once approved by the IRB, an invitation to participate in the study was sent via e-mail to university coaches and was posted for the athletes with the day and time of data collection.

Procedures: On the day of data collection, one of the primary researchers of the study met with the athletes who were potentially interested in participating in the study in a room at their university. Those who attended were given the informed consent form and the questionnaire, and those who wished to participate completed both

forms. The paper-based questionnaire had 12 questions which included demographic information and questions about their sports-related breast injury history, including injury reporting, severity, treatment, participation, and protective equipment.

Statistical Analyses

Statistical Package for Social Sciences (SPSS) version 23 (SPSS Inc., Chicago, IL, USA) was used to determine the prevalence of self-reported breast injuries in female collegiate athletes during their collegiate career.

Results

A total of 194 female collegiate athletes participated in this study. There was no indication why athletes elected to participate in the study or not. Participants represented basketball, soccer, softball, and volleyball as their primary sport (Table 1). The mean age was 19.3 years. Although almost half (47.9%) of the athletes reported a trauma/injury to their breast during their collegiate career, less than 10% of all the injured females reported their injury to an athletic trainer, coach, physician, team captain or other person and 2.1% reported having received treatment for their injuries.

Breast injuries were the most prevalent (59.5%) among softball athletes. The reported injuries ranged in severity: ten women with mild injuries, eight with moderate injuries, six having abrasions or scrapes, seven with bruising or discoloration, three with swelling and three with scar tissue development. Only 4.6% of the injuries were reported with two athletes not specifying whether they did or did not report their injury to a healthcare professional. Three athletes reported that their play was affected, but only one of them received treatment for swelling. The treatment received for this injury was ice. No athletes reported missing any trainings or competitions. (Table 2).

Table 1. Survey Responses by Sport and Institution

Sport	Institution A		Institution B		Institution C		Institution D		Total Response Rate
	Roster Size	Responses n (%)	Roster Size	Responses n (%)	Roster Size	Responses n (%)	Roster Size	Responses n (%)	
Basketball	11	11 (100%)	-	-	30*	30 (100%)	-	-	100%
Soccer	22	18 (81.8%)	23	23 (100%)	28	28 (100%)	24	21 (87.5%)	92.8%
Softball	16	6 (37.5%)	18	15 (72.2%)	-	-	20	16 (80%)	68.5%
Volleyball	14	3 (21.4%)	-	-	16	16 (100%)	14	7 (50%)	59.1%

*Institution C had two teams, a varsity and a junior varsity, which were combined here for the response rate.

Table 2. Breast Injury Results by Sport

Sport	Total participants per sport (n)	Number of individuals injured n (%)	Total number of injuries n (%)	Reported injury n (%)	Injury affected play n (%)	Wearing protective equipment n (%)	Received treatment n (%)
Basketball	41	20 (48.8%)	50	1 (5%)	5 (25%)	0	1 (2.4%)
Soccer	90	42 (46.7%)	113	2 (4.8%)	5 (11.9%)	1 (1.1%)	0
Softball	37	22 (59.5%)	34	4 (18.1%)	3 (13.6%)	1 (2.7%)	1 (2.7%)
Volleyball	26	9 (34.6%)	55	2 (22.2%)	4 (44.4%)	0	0
Total	194	93 (47.9%)	252	9 (9.6%)	17 (18.2%)	2 (2.1%)	2 (2.1%)

Breast injuries were the second most prevalent (48.8%) among basketball athletes. Of the breast injuries, one was considered to be severe, nine were moderate and two were mild. Eight of these injuries had subsequent bruising and three had swelling of the breast tissue. One athlete reported bruising of her breast and received an unspecified treatment but did not miss trainings or competitions. Three of the participants did not specify whether they reported their injury to a healthcare professional. (Table 2)

A similar percentage (46.7%) in soccer athletes indicated on the questionnaire a history of breast injury. Of these injured players, 25 reported mild injuries, 11 reported moderate injuries and two reported severe injuries with 16 reporting bruising or discoloration and four with scar tissue developing following the injury. Of these injuries, two were reported, four did not specify if they reported their injury or not, and none of the athletes received treatment. None of the injuries resulted in missing trainings or competitions. (Table 2)

Approximately one-third of volleyball athletes (34.6%) indicated breast injury; seven of the injuries were mild, two were moderate, five of them reported bruising or discoloration and two reporting swelling. Two of these injuries were reported and one athlete did not state whether they reported their injury to a healthcare professional or not. Four of the injuries affected play or competition and none of the athletes received any types of treatment or resulted in missing trainings or competitions. (Table 2)

Participants (97.8%) who experienced a breast trauma/injury reported not wearing any protective breast/chest equipment beyond normal bra/support worn during daily activities when the breast trauma/injury occurred. Approximately 18.2% of the participants who sustained an injury indicated that their participation or performance in trainings or competitions was affected by mild or moderate pain. Of the two athletes who received treatment for their injuries, only one received follow-up care/instruction for ice treatment (softball athlete) and the other respondent (basketball) did not specify.

Discussion and Conclusion

The results from this study indicate that 47.9% of all the female collegiate athletes in this study experienced a breast injury during sports participation during their collegiate career, yet research specific to sports-related breast injuries in females is limited, making it difficult to capture the prevalence and sequelae of these injuries (7, 14-30). In this study, there was relatively no association (less than 10%) between the number of women who sustained a breast injury ($n=93$) and the number of women who reported the injury to a healthcare professional ($n=9$), which is a reason for concern. A previous report on collegiate athletes found that when reporting gender-specific injuries and conditions to their athletic trainer, athletes were more comfortable in reporting and receiving care from those of the same sex (31). Also, at the collegiate level, approximately 30% of athletic trainers are female (32). These factors may contribute to the lack of injury reporting identified in the current study.

In this study, approximately one-third ($n=36$) of the female athletes who reported breast injury classified their injury as bruising or discoloration and nine reporting swelling. These symptom reports are consistent with previous studies of females who suffered a seat belt injury (3-5, 9, 11) and/or blunt breast trauma (8, 11, 33). In a study of female boxers, nine out of the 61 athletes (14.7%) had signs of fibrocystic breast tissue, two out of 61 had developed breast fibroadenomas

and one female had three small cystic lesions (14). Previous reports suggest that traumatic injury to the breast often led to hematomas (3, 4, 8, 11, 12, 33-36). This trauma often led to palpable nodules, months or years following the injury, that were diagnosed as lipid cysts and/or fat necrosis (3, 4, 9, 11, 36). Other studies revealed that breast trauma may be linked to the development of breast cancer (12, 37), breast deformity (10), hematoma with extraversion (8, 36), and breast asymmetries (38). Fat necrosis is a common theme in research and case studies related to breast trauma. Following breast injury, the development of masses or nodules in the breast tissue is common, and may be a sign of fat necrosis (3, 4, 6, 9, 11, 36). Fat necrosis often begins as lipid cysts and can become calcified as time progresses and are often difficult to distinguish from breast carcinoma (36). Fat necrosis has also been linked to chronic pain and anxiety, both affecting the female for months to years following injury (6, 9). Hence there is an obvious need for specific classification, thorough documentation, treatment, and follow-up for females who experience breast injury during collegiate athletics.

In the present study, only two athletes of the 93 injured (2.1%) received treatment for their breast injuries. While the mechanism of injuries reported by participants in this study are different than high velocity seat belt injuries and other traumas, the physiological response to these injuries remains the same, that being contusions, bruising, hematomas, edema and pain. The lack of treatment reported by participants in this study may be concerning because of similar information reported on breast injury resulting from seat belt trauma (3-5, 8-11, 39) including classification systems for breast injury due to seat belt trauma (5, 9) and others for blunt breast trauma (33). Following a seat belt related breast injury, it is recommended that the female have a physical breast exam three-six months post-injury as well as yearly mammograms and breast examinations (9). This is primarily to monitor for complications such as fat necrosis, a possible result of breast trauma, which can mimic the presentation of breast cancer (7). Despite some recommended treatment approaches for blunt breast trauma (9, 33-35) and seat belt injuries (5), previous reports suggest that there is lack of consistency with the standard of care for individuals with blunt breast trauma (33).

Recommendations for the management of breast trauma in adolescents during sports participation include cold application, firm support, and surgical aspiration in the presence of hematoma (35). It is imperative that healthcare professionals distinguish between scar tissue and fat necrosis of the breast tissue and carcinoma of the breast to prevent misdiagnoses of cancer (34). Proper management should include a thorough physical exam as well as mammograms and biopsies as needed (34). The authors of this study recommend that an athlete with a past history of breast trauma report their injury history when getting routine breast exams and mammograms in the future. Information regarding previous breast trauma could be helpful to the physician in interpreting mammograms and determining a diagnosis when fat necrosis is present.

The use of chest protection in female college sports is rare and more exploration is needed. Investigation into other female sports is warranted. This study revealed that only 2.1% of the female college athletes were wearing any type of protection beyond their normal sports bra. Protection is needed at all levels of female sports, including in adolescents. It has been found that in pre-menarchal females, breast trauma can potentially lead to future breast asymmetries during development (38).

Almost 20% of the female athletes who reported a breast injury in this study reported that their performance/participation during sports play was affected by mild or moderate pain; yet none of the injured athletes reported that they did not compete because of their injuries. This finding is most likely explained by the lack of breast injury reporting to a healthcare professional. It is possible that if these injuries were reported, the management of the injury would include time-off from competitive play or modifications to activity.

Participants were informed that they did not have to answer any question that they did not wish to, or that made them uncomfortable, which likely explains any missing responses. Limitations to this study include possible recall bias for the self-reported history of breast injuries. Also, this study included participants representing four sports, which makes it difficult to generalize results to all female college athletes. Additional longitudinal research is needed to investigate reporting systems, training of healthcare professionals that work with female athletes to address specific breast issues, as well as standardization of classification and treatment for sports-related female breast injuries.

In conclusion, the long-term effects and sequelae of breast injuries reported by female collegiate athletes during sport play are unknown. In this study, almost half (47.9%) of the athletes reported a trauma/injury to their breast during their collegiate career, less than 10% of all the injured females reported their injury to a healthcare professional and 2.1% received treatment for their injuries. From a clinical perspective, this information can be used to heighten the awareness related to female breast injuries and encourage healthcare professionals to create an environment that encourages disclosure of injuries that may be perceived as personal or embarrassing to discuss.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the University of Michigan-Flint.

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

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Juvenile Papillomatosis of the Breast in a Pre-Pubertal Girl: An Uncommon Diagnosis

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ABSTRACT

Juvenile papillomatosis of the breast represents a rare benign proliferative disorder that affects women younger than thirty years of age. Although it is a localized lesion, it does not have well-demarcated margins. These patients tend to have a strong family history for cancer. As it has similar clinical presentation with that of a fibroadenoma, it usually receives the diagnosis of the latter in the preoperative period. Nonetheless, it has distinct microscopic features such as ductal papillomatosis and cysts that are helpful in the diagnosis. In this article, a case of juvenile papillomatosis diagnosed in a young girl who presented due to a mass of the breast was presented. For the fairly rare case, a total mass excision was performed with preserved breast tissue. The exact diagnosis was made by postoperative histopathological examination.

Keywords: Breast, juvenile, papillomatosis

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Introduction

Juvenile papillomatosis (JP) of the breast was diagnosed as Swiss cheese disease due to multiple cystic formations on the fraction based on the macroscopic examination. Some of the epithelial ducts demonstrated apocrine metaplasia and papillary formations expanding toward the lumen, which were dilated in cystic formation as typical characteristics upon macroscopic examination. This lesion usually causes a mass of the breast. They are similar to fibroadenoma in clinical and macroscopic aspects. Carcinoma of the same of the opposite breast has also been observed besides JP. In addition, it has been observed that breast carcinoma developed during follow-up of patient diagnosed with JP in the past (1). In this article, a 11-year-old female patient who was operated on due to preliminary diagnosis of fibroadenoma of the right breast was presented.

Case Presentation

A 11-year-old female patient presented to the General Surgery outpatient clinic due to rapidly growing mass of the right breast without pain for about two months. During the physical examination, a hard mass with irregular contour and with a dimension of approximately 7 cm, which infiltrated the right breast almost completely, was palpated (Figure 1a). No pathology was noted for the left breast and bilateral axillary regions. No specific characteristics were noted in the patient's familial medical history and laboratory test results. She had no nipple or skin changes associated with the mass, and there were no symptoms suggestive of a history of an abscess. A solid lesion in dimensions of 7x6 cm that infiltrated the right breast almost completely was seen on the breast ultrasonography (US). A Tru-cut biopsy of the right breast was performed because of suspected fibroadenoma at the first stage. The result of the pathological examination was reported as fibroglandular proliferation and an operation was decided upon. Under general anesthesia, the mass was totally excised preserving the breast tissue (Figure 1b). The resulting deformity was filled using the patient's own breast tissue. The patient was discharged on the post-operative first day without complications and no further treatments were provided. The patient was seen to have recovered

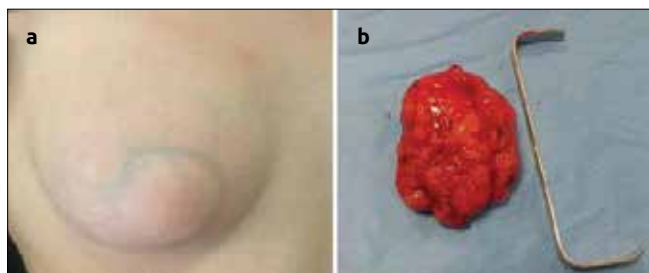


Figure 1. a,b . Preoperative view of the patient (a), macroscopic view of the excised specimen (b)

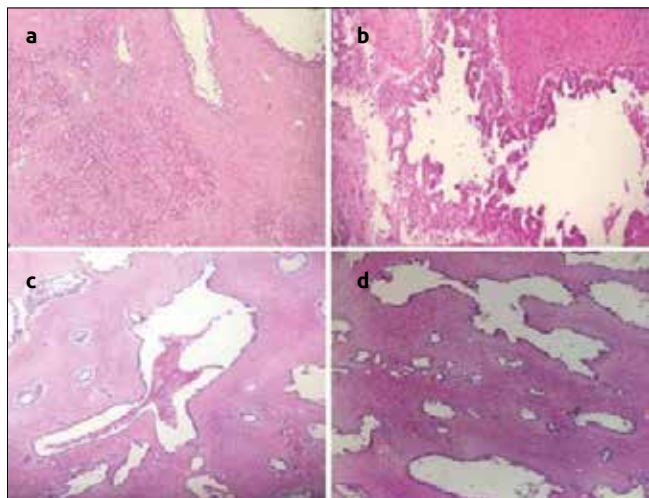


Figure 2. a-d . Cystic enlarged ductus accompanied by adenosis foci (H&E:100x) (a), ductal epithelial hyperplasia forming papillary structures (H&E:200x) (b), decreased secretion in cystic ducts and inflammatory cells mixed with histiocytes (H&E:40x) (c), microscopic view of cysts and enlarged ducts (H&E:40x) (d)

with a better cosmetic outcome during the control visit 1 month later. Post-operative histopathological examination of the mass was considered to show juvenile papillomatosis (Figure 2). Informed consent was obtained from the father of the patient who participated in this case.

Discussion and Conclusion

Juvenile papillomatosis is a clinicopathological entity first described by Rosen et al. This lesion, which causes a mass of the breast containing dilated ducts with some of them in papillary formations on macroscopic examination and cystic spaces, is similar to fibroadenoma. Microscopically, the main diagnostic criteria have been determined as papillary epithelial hyperplasia, ductal stasis, cysts with apocrine and non-apocrine epithelium, sclerosing adenosis, fibroadenomatoid hyperplasia and lobular hyperplasia (2). In our patient, there were cystic spaces with lumens with single or several epitheliums located between the connective tissue elements, which appeared to be partially hyalinized. There were papillary formations in some of the cysts. No mitotic activity and necrosis was seen.

Juvenile papillomatosis is seen at the ages of 10 to 48 (average 23). It is seen equally in bilateral breasts. Although it is most commonly seen in the upper-outer quadrant, it has also been reported inferior to the areola. Its average dimension ranges from 1 to 8 cm. Based on Rosen's series of 180 cases, where the patients' menarche, parity, marital status and hormones were measured during pregnancy of the mother, no relationship was found between JP and endocrinological variations (3).

Our patient had not yet menstruated and the patient's mother did not take any medication during pregnancy.

When family members of patients with JP are questioned for breast diseases, breast carcinoma has been found to have a ratio of 58% in their first and second degree relatives. However, the presence of carcinoma in the relatives of patients with JP can be considered as a tumor marker of JP, allowing the possibility of following up their close relatives without waiting until they are over 50 years of age where the cancer risk is most (2). No specific characteristics in terms of breast carcinoma were found in our patient's familial medical history. Bazzocchi et al. (3) have found a familial history of breast carcinoma in 33% of patients with JP.

Patients present usually with the complaint of a mass in the breast regarding JP. Hemorrhagic discharge and pain of the nipple are rarely seen (4). The reason of presentation of our patient was the presence of a single, unilateral and growing mass of the breast. In situ or invasive carcinoma at a ratio of 4% was diagnosed in the same or opposite breast regarding JP (5). During 59- to 274-month follow-up of patients with JP, breast carcinoma was diagnosed in 5 patients within about 14 years. In all of these patients, the lesion was bilateral with recurrence or multifocal and all patients had positive familial history (6).

Juvenile papillomatosis is a clinical entity different from childhood papillary ductus hyperplasia of the breast. Papillary ductus hyperplasia is commonly seen above 30 years of age. It has three types including intraductal papilloma, intraductal papillomatosis and sclerosing papillomatosis (7). All characteristics such as the patient's age being below 30, identification of a mass with regular contours in the breast (although it is considered fibroadenoma in clinical setting), presence of ductal formations with some of them being cystic by dilation in the connective tissue areas on macroscopic examination, and the lumens of ducts containing partial papillary formations lined with epithelium that demonstrates single or several apocrine metaplasia are consistent with the diagnosis of juvenile papillomatosis as it was in our patient. In a 18 years of follow-up of patients with papillary ductal hyperplasia, carcinoma was found in none of them. However, when all the papillary lesions of the breast are considered, it is estimated that papillary carcinoma will emerge later on in 14% of the patients with papillomatosis in average (8).

As patients affected by these lesions are usually young, US appears to be the optimal tool for their diagnosis and follow-up. Ultrasonography is useful for differentiating it from other cystic masses, fibroadenomas, intracystic papillomas, phyllodes tumors, and breast cancer. Although mammography is usually not routinely used for women younger than 35 years of age, its findings in rare cases that present include a homogenous opacity with sharp borders, which is also common in fibroadenomas and cysts. Magnetic resonance imaging also aids in the diagnosis by showing multiple small internal cysts on T2-weighted sequences (9).

Treatment of juvenile papillomatosis is usually accomplished by complete excision followed by histologic confirmation. Prognosis is uncertain. No additional treatments are necessary if no carcinogenic lesions exist simultaneously. Recurrence is inevitable following incomplete excision. Annual monitoring for possible breast cancer development should be done until studies on this subject would determine the value of this practice. Breast carcinoma most commonly develops in those who had a family history for breast cancer and recurrent bilateral JP lesions (10).

In conclusion, juvenile papillomatosis of the breast is rarely encountered in clinical practice. Although it is a benign lesion, monitoring of the patient and her family is an appropriate practice given that there is an association between family history and the risk of future development of breast cancer. In order to decrease the rate of recurrence, JP lesions should be excised completely.

Informed Consent: Informed consent was obtained from the father of the patient who participated in this study.

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Silicone Granuloma Associated with Pectoral Muscle Involvement after Ruptured Breast Implant: a Novel case report

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ABSTRACT

In this study, an unusual case of a patient who was previously operated on a ruptured breast implant following silicone granuloma associated with pectoral muscle involvement is reported. A 72-year-old woman had undergone breast augmentation surgery when she was 52-year-old and silicone implant rupture 10 years later. After 10 years of ruptured silicone implant, her mammography showed diffuse, multiple high-density nodules in the left breast. The pectoral muscle was significantly hypertrophic. The magnetic resonance imaging showed that the pectoral muscle was quite hypertrophic and had heterogeneous enhancement. In clinical consideration and the presence of the suspected malignancy, a biopsy was performed. The histological analysis identified pectoral muscle and breast tissue, which had been mainly replaced by giant cells, along with an apparent foreign body response. Silicone granuloma can present itself as a soft tissue mass. Malignancy is the most important differential diagnosis. Meticulous follow-up is recommended for these patients.

Keywords: Breast implant, pectoral muscle, silicone granuloma

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Introduction

Silicone has rapidly become one of the most commonly used prosthetic for breast implants over the last 30 years. Therefore, we have been witnessing more silicone-related disease. Silicone implant rupture, one of the most common silicone-related diseases, occurs more frequently with the implant's age. After implant rupture, silicone leakage can remain within the breast parenchyma or spread to regional lymph nodes first (1). Case studies report silicone migration to distal parts of the body, such as the arm, subcutaneous soft tissues of the abdominal wall and the inguinal area and even to the liver, where silicone causes foreign body inflammation and sometimes mimics malignancy (1). Silicone granuloma associated with pectoral muscle involvement has not been published before.

In this study, an unusual case of a patient who was previously operated on a ruptured breast implant following silicone granuloma associated with pectoral muscle involvement is reported, and all imaging modality pattern are shown.

Case Presentation

A 72-year-old woman was referred to breast radiology department with a pain and hardness in her left breast. The patient had undergone bilateral subglandular breast augmentation surgery when she was 52-year-old. Ten years later, she had silicone implant rupture of left breast, required breast revision surgery and the breast implant and free silicone is removed without replacement. Her right breast was normal. After 10 years of ruptured silicone implant, she complained of pain, hardness, and swelling on her left breast. First of all, to determination of breast cancer and evaluation of the breast parenchyma changes after open removal surgery, a mammography (MG) and breast ultrasonography (US) were performed (IMS Giotto MD digital radiography and Tomosynthesis, Bologna, Italy). The MG showed; diffuse, multiple high-density nodules in the left breast, some with a thin rim of calcifications (Figure 1). The pectoral muscle was signifi-

cantly hypertrophic, including the same diffuse multiple high-density rim-calcified nodules, and was extended into the left breast. High-frequency grey scale US of the breast using a linear probe (6–13 MHz) (Hitachi Medco's Digital Ultra Sound Examination Device, HI VISION Avius, Tokyo, Japan) revealed several multiple cystic lesions that have well-defined borders and posterior acoustic shadows, a so-called 'snowstorm' appearance with no visible pectoral muscle (Figure 2).

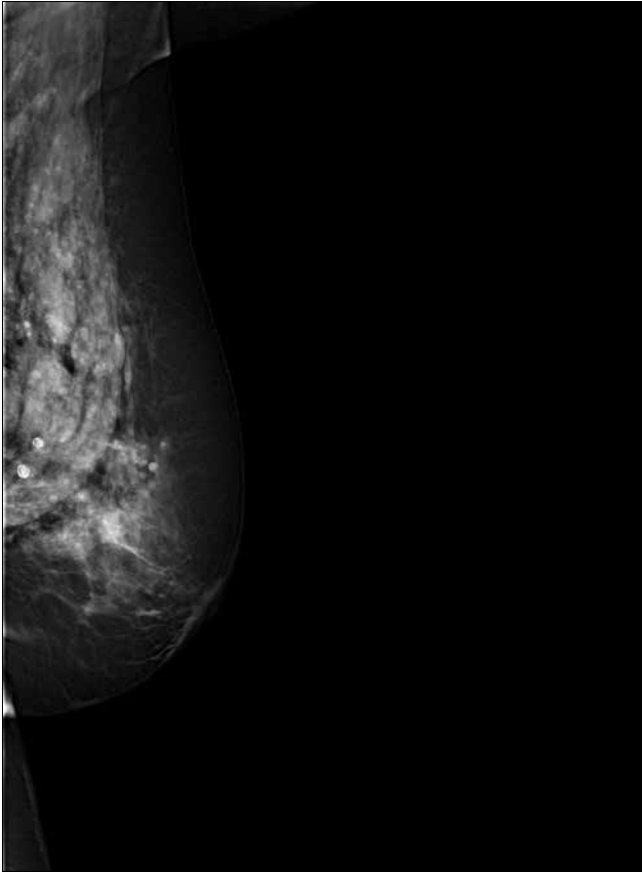


Figure 1. Left MLO mammography shows diffuse, multiple high-density nodules (siliconomas) in the left breast, some with a thin rim of calcifications. Pectoral muscle was significantly hypertrophic, including the same diffuse multiple high-density rim-calcified nodules and was extended into the left breast

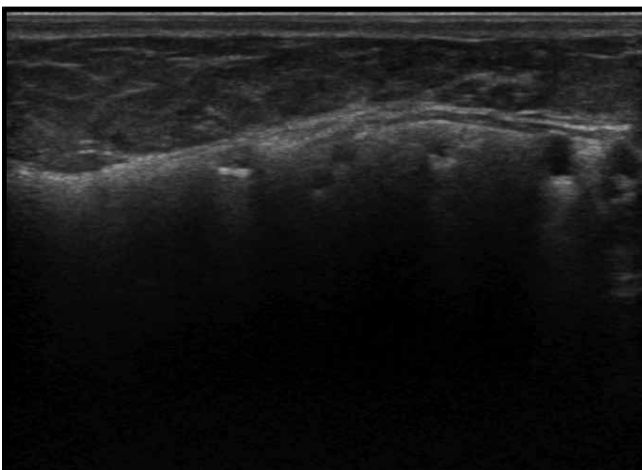


Figure 2. Ultrasound image shows multiple globules of silicone appearing as small anechoic cystic lesions that have ill-defined borders and posterior acoustic shadowing; so-called 'snowstorm' pattern

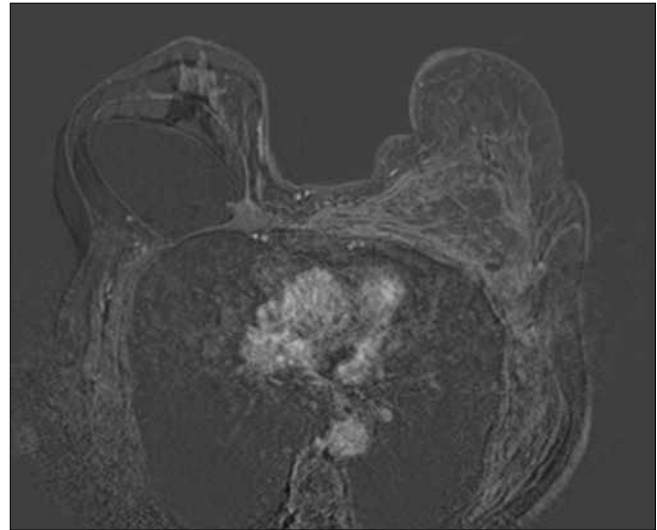


Figure 3. Axial post-contrast subtracted MRI image shows that the pectoral muscle and surrounding breast tissue showed heterogeneous early and delayed enhancement

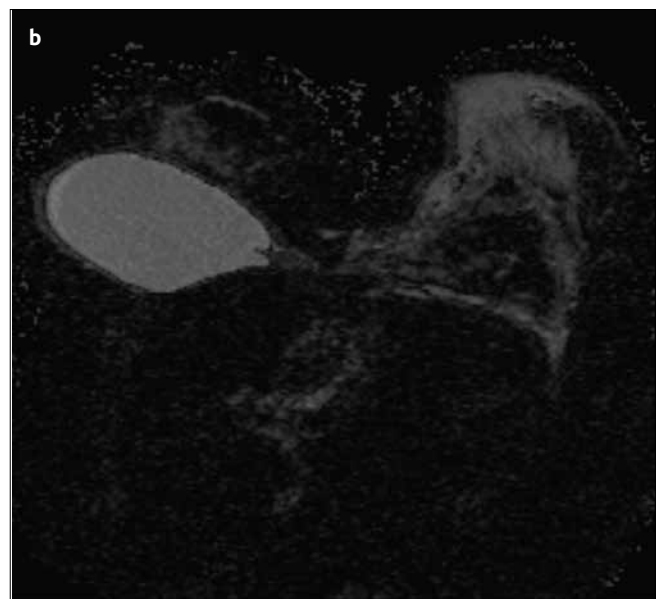
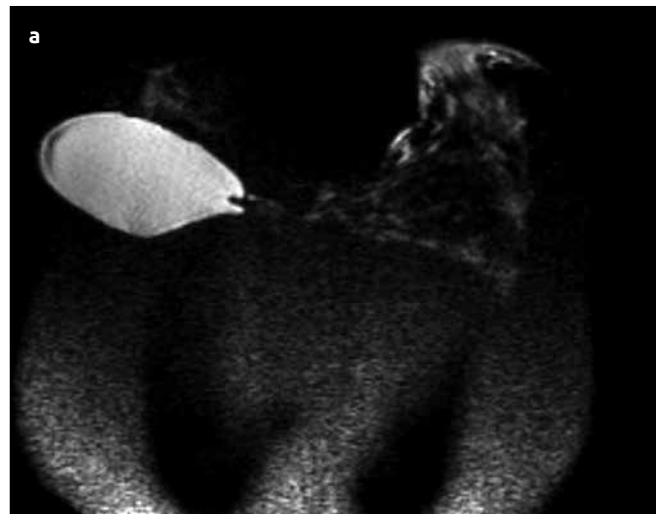


Figure 4. a, b. DWI (a) and ADC (b) showed that the left breast and pectoral muscle exhibited high SI due to the unrestricted diffusion

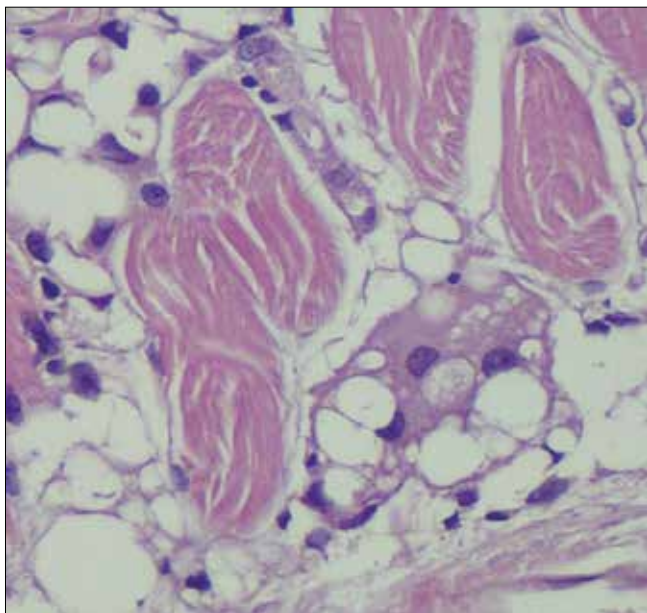


Figure 5. Pathological specimen identified infiltration giant cells with vacuoles, consistent with silicone granuloma

Dynamic contrast-enhanced magnetic resonance imaging (MRI) was then performed (1.5T MR system, Achieva Philips, The Netherlands). T1-weighted images showed low signal intensity and T2-weighted images showed heterogeneous-hyperintensity. Pectoral muscle was quite hypertrophic and had heterogeneous, non-mass like parenchymal enhancement (Figure 3). The kinetic curve not observed.

In diffusion-weighted images (Figure 4a, b), neither pectoral muscle nor breast tissue exhibited high SI, which means unrestricted diffusion.

In clinical consideration and the presence of the suspected malignancy, a biopsy was performed to upper outer quadrant of left breast and pectoral muscle under sonographic guidance using 16-gauge automatic core-needle biopsy (GEOTEK, Ankara, Turkey). Histological analysis identified pectoral muscle and breast tissue, which had been mainly replaced by giant cells and along with an apparent foreign body response (Figure 5). No evidence of malignancy within the breast and pectoral muscle was seen. We diagnosed the patient with silicone granuloma associated with pectoral muscle involvement.

An informed consent was obtained from the patient for the publication of this manuscript.

Discussion and Conclusion

Silicone granuloma (SG) or siliconoma, by definition, is a type of tissue reaction from silicone. SG was first described in 1964 by Winer et al. (2) after an injection of free silicone used for breast augmentation, SG which occurred after ruptured implants were first described in the 1980s. The use of implants for breast augmentation has been increasing in recent years. However, in many cases, we have to take into consideration the risk from unknown foreign body reactions and complications. The major complications involve hematoma, infection, asymmetry in the early postoperative period, capsule contracture, rupture, and SG in long-term period (2).

Silicone leaking from a ruptured implant increases the risk for silicone to transmigrate to different areas. The well-timed removal of an extracapsular silicone is the best treatment because delayed surgery may

increase silicone leakage and migration, therefore making complete removal of silicone very difficult or sometimes impossible. When silicone leaks out from an implant, the silicone particles spread to local areas, such as to the ipsilateral chest wall, axillary regions and lymph nodes (3). Moreover, silicone can spread to the whole body, sometimes mimicking malignancy (2). In our case, the SG seemed a granulomatous reaction within the breast, but the appearance of pectoral muscle was quite different, and malignancy could not be excluded.

Detection of silicone by imaging methods is challenging for radiologists because presence of silicone implant may cause difficulties for breast cancer diagnosis. In addition, breast implant complications can mimic breast cancer.

Mammography demonstrates free or residual silicone in the breast parenchyma. Silicone from incomplete removal surgery of a ruptured implant can be seen as well-circumscribed or ill-defined densities (3). Calcification, architectural distortion, lipid-cyst formation such as fat necrosis, and the thickening and calcification of the skin can be seen as well (4). If MG is suspected or the result is inconclusive, further evaluation may be needed.

The classic appearance of silicone on sonography is a high echogenic pattern which shows posterior echoes with a well-defined anterior margin and a loss of detail posterior margin. This pattern has been described as “echo-dense noise” or “snowstorm” (5).

Magnetic resonance imaging provides a great overview of the breast implant and surrounding anatomic areas. MRI findings of free silicone include separated foci of low signal intensity on fat-suppressed T1-weighted images and high signal intensity on the water-suppressed T2-weighted images.

Diffusion weighted imaging (DWI) and ADC maps are opening up new screening possibilities for the identification of malignant breast lesions and help exclude malignancy in women with suspicious MG (3).

Breast carcinoma rarely occurs in the form of a foreign body granuloma following liquid silicone injection. This concern has not been substantiated yet. But breast carcinoma originating from a silicone granuloma has been reported (6). Considering so many women that have breast implants every year; the compiled data show that there is a very small risk of developing non-Hodgkin's lymphoma and anaplastic large cell lymphoma (7). Moreover, the relationship between breast augmentation and angiosarcoma of the breast remains unclear, but a few cases has been reported in the literature. T-cell mediated autoimmune reactions may have some relationship with the silicone implants. But clinical case reports still have been unable to establish a correlation (8). In our case, biopsy was required because of the appearance of the pectoral muscle and suspected malignancy.

In conclusion, SG can present itself as a soft tissue mass. Malignancy is the most important differential diagnosis. Meticulous follow-up is recommended for these patients.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.I., G.G.; Design - T.I.; Supervision - T.I., G.G.; Resources - T.I.; Materials - T.I., I.A.; Data Collection and/or Processing - T.I., I.A.; Analysis and/or Interpretation - T.I.; Literature Search - T.I.; Writing Manuscript - T.I.; Critical Review - T.I.; Other - G.G., J.L.

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Granulomatous Mastitis Concurrence with Breast Cancer

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ABSTRACT

Idiopathic Granulomatous Mastitis (IGM) is a rare, chronic, non-malignant and non-life-threatening breast disease. IGM may mimic carcinoma of the breast. This case report is about concurrence of chronic granulomatous mastitis with breast cancer. The important aspect of this case is that it is the 4th case where IGM and breast cancer are present concurrently.

Keywords: Granulomatous Mastitis, breast, cancer, carcinoma in situ

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Introduction

Idiopathic Granulomatous Mastitis (IGM) is a rare, chronic, non-malignant and non-life-threatening breast disease (1). Clinically and radiologically, it mimics carcinoma of the breast. The most common complaints of patients are unilaterally emerging breast pain or painless masses (2, 3). This case highlights the possibility that the concurrence of chronic granulomatous mastitis with breast cancer may be explained just as an adjunct situation or a coincidence and may be the difficulty in distinguishing one from the other.

Case Presentation

A 77-year-old female was admitted to our clinic with complaints of breast pain, accompanied by edema and thickening of the skin at 9 o'clock of the right breast, close to the areola. Initial physical examination revealed axillary lymphadenopathy approximately 2 cm in diameter. The breast ultrasound and mammography studies were performed. The ultrasonography revealed a fibroglandular tissue increase with no distinctive borders and an inflammatory appearance and right axillary 2x2 cm non-reactive lymphadenopathy (Figure 1). Mammography showed amorphous mass, axillary lymphadenopathy and focal asymmetric opacity with calcifications in the retroareolar and outer quadrant of right breast (Figure 2, 3). A core biopsy of the right breast was then done. Microscopic examination displayed chronic inflammation and macrophage, giant histiocyte and epithelioid-like cellular infiltration, with cytologic features suggestive of a granulomatous process (Figure 4). Further histopathological analysis showed an evidence of invasive ductal carcinoma 5 mm in diameter and extensive high grade in situ ductal carcinoma foci (Figure 5, 6). The invasive tumor was estrogen and progesterone receptor negative; e-cadherin and c-erb positive (+++). Also, the following methods were performed on the tissue samples obtained from the patient; alkaline-acid resistance factors for tuberculosis bacteria (AARB) and Lowenstein-Jensen culture, Ehrlich Ziehl-Neelsen (EZN) staining and Periodic acid-Schiff (PAS) staining for the investigation of fungal infections. All culture and stains for infectious organisms remained negative. Later, modified radical mastectomy performed because there were widespread high degree carcinoma in situ foci in the non-tumor areas. 18 axillary lymph nodes were present in the axillary dissection specimen, ductal carcinoma metastasis was reported in 2 lymph node which was 2.3 cm in diameter (Figure 7). No granulomatous structures were observed in the axillary lymph nodes. The patient is being followed in an adjuvant chemotherapy program.



Figure 1. Ultrasonography revealed a fibroglandular tissue increase and axillar lymphadenopathies

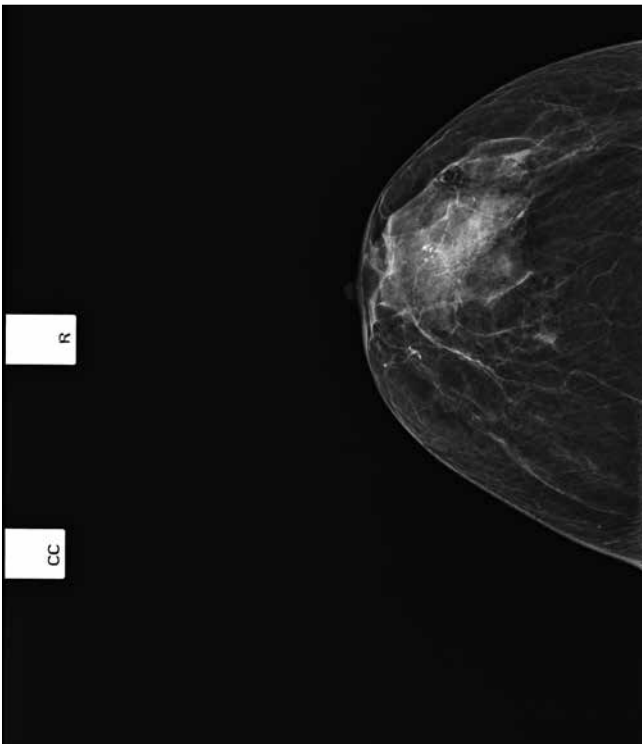


Figure 2. Mammography showed opacity with calcifications in the retroareolar and outer quadrant

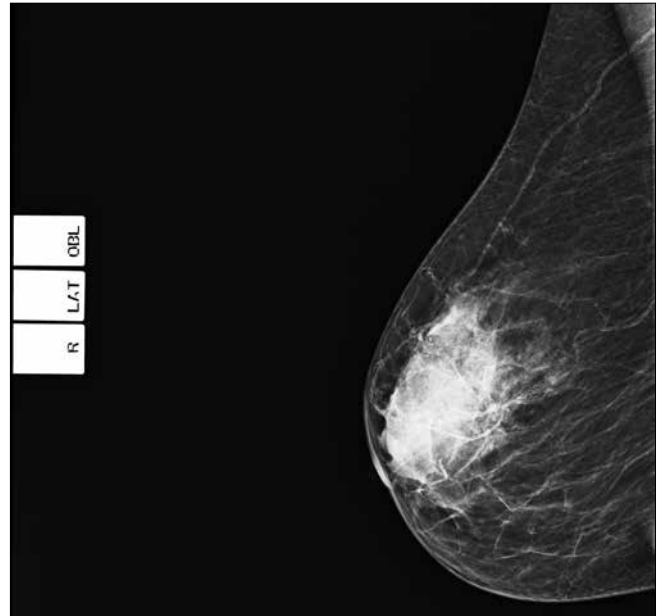


Figure 3. Mammography showed opacity with calcifications in the retroareolar and outer quadrant

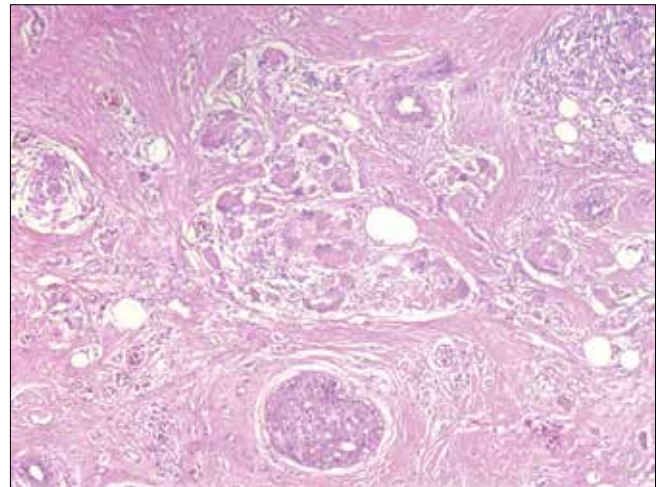


Figure 4. The presence of multinucleated giant cells within non-caseating granulomatous inflammation (H&E, X50)

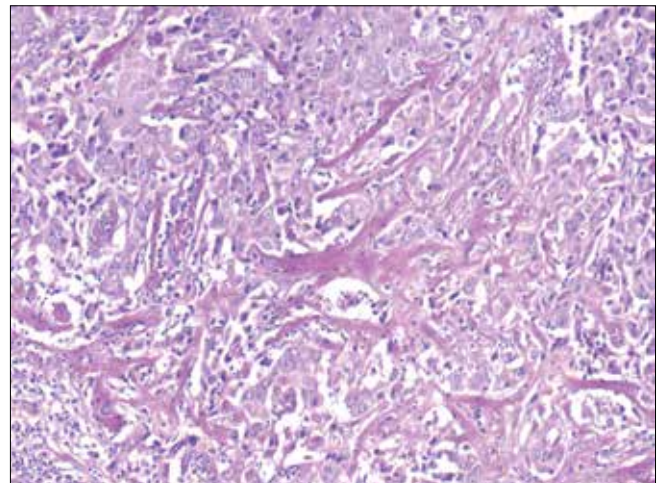


Figure 5. Foci of invasive breast carcinoma and high grade in situ ductal carcinoma (H&E, X100), (H&E, X50)

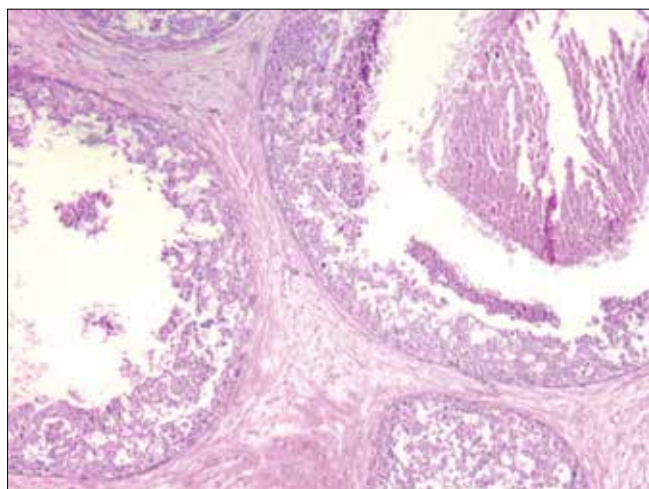


Figure 6. Foci of invasive breast carcinoma and high grade in situ ductal carcinoma (H&E, X100), (H&E, X50)

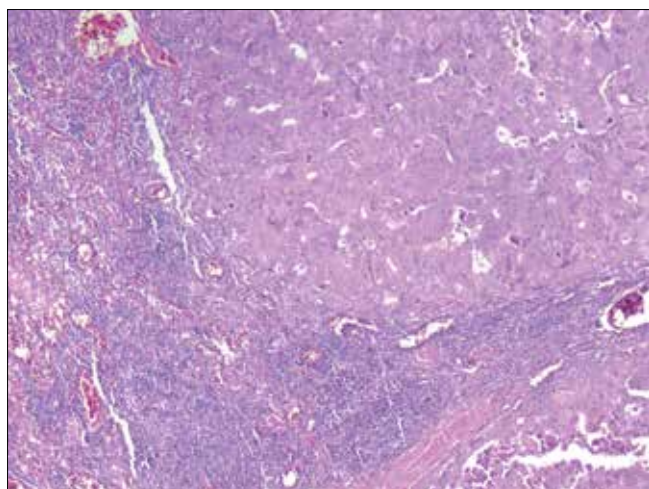


Figure 7. Invasive breast carcinoma metastasis in lymph node (H&E, X50)

Discussion and Conclusion

Idiopathic Granulomatous Mastitis is a non-malignant, chronic, non-life-threatening and rare breast disease (1). The patients visit us mainly due to a mass in one breast. They may consult us due to hyperaemia, sensitivity, areolar retraction, fistula and ulceration complaints in the breast as well (2, 4). The mass may mimic breast cancer by pulling the skin tissue above it, or may penetrate the pectoralis major muscle via nipple retraction and may cause lymphadenopathy. Routine radiologic evaluation, ultrasound and mammography may not discern IGM from breast cancer. Similarly, the probability of MRG discerning the inflammatory process from a tumoral process is very low (4, 5). Our patient's ultrasonographic evaluation revealed a fibroglandular tissue increase with no distinctive borders and an inflammatory appearance and right axillar 2x2 cm metastatic lymphadenopathy. Mammography showed focal asymmetric opacity with calcifications in the retroareolar and outer quadrant of right breast. Inflammatory breast carcinoma and IGM were considered during the pre-diagnosis. The excisional biopsy

result was reported as invasive ductal carcinoma, high grade ductal carcinoma in situ and granulomatous mastitis. Only 3 cases in, which IGM and breast cancer were present concurrently, have been presented in the literature (6-8). The important aspect of this case is that it is the 4th case where IGM and breast cancer are present concurrently.

On the other hand, granulomatous mastitis is usually seen in women during their reproductive or breast feeding period (9). Our patient is 77 years old and that is another important point.

We must be careful in identifying and diagnosing breast cancer in a patient with background history of IGM. Clinical, radiological and pathological investigations have to be performed together for breast cancer developing due to the chronic progresses of IGM or concurrent breast cancer.

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