

European Journal of Breast Health

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Aims and Scope

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

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

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

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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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Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *Br Med J* 1983; 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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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
Current Opinion	300	No abstract	5	No tables	No media
BI-RADS: Breast imaging, report and data systems					

titled as Background, Present Study, and Implications. Authors are expected to describe the background of the subject/study briefly, critically discuss the present research, and provide insights for future studies.

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

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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.

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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)"

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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.

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

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

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The Adventure of Axillary Treatment in Early Stage Breast Cancer

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ABSTRACT

Axillary lymph node dissection (ALND) which was an essential part of breast cancer treatment and the gold standard in evaluation of the status of axillary lymph node had notorious with increased arm morbidity and reduction of quality of life. Sentinel lymph node biopsy (SLNB) accurately stages the axilla in early breast cancer and ALND is omitted in SLNB negative patients. In patients with positive SLNB the omission of ALND with or without replacement of axillary radiotherapy has also been recommended by guidelines. The neoadjuvant chemotherapy (NAC) which has been increasingly used for large breast cancers to downstage the tumours for allowing breast conserving surgery and decreasing mastectomy rate has also been used in axillary node positive patients to reduce the need for ALND. The issues surrounding the treatment of axilla in patients treated with NAC; application and false negative rate of SLNB, number of identified sentinel lymph nodes, and axillary radiotherapy instead of ALND are currently the discussed and practiced hot topics. The quests for decreasing arm morbidity without compromising outcome in breast cancer treatment which have begun with the invention of SLNB continue for axilla conserving surgery. This article reviews the adventure of axillary treatment in breast cancer patients treated with or without NAC.

Keywords: Breast cancer, axillary treatment, axillary lymph node dissection, sentinel lymph node dissection, neoadjuvant chemotherapy

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Introduction

Axillary lymph node dissection (ALND) was an essential part of breast cancer treatment and erstwhile for a lengthy period was the sole gold standard in evaluation of the status of axillary lymph node. The benefits of ALND were staging the axilla, providing important prognostic information, improving of axillary regional control, and the probable improvement of survival and disease-free survival (DFS) (1-3). As to the harms of ALND; they are known as increased arm oedema, restrictions in the arm movements, and reduction of quality of life. Arm oedema which is the most known complication after ALND could sometimes be very severe, increase by axillary radiotherapy and may even lead to the disability of arm (4-7).

Larson et al. (8) reported that extent of ALND (full ALND vs lower or level 1, 2 ALND) was a significant predictor of subsequent lymphoedema. In that study, in addition to level 1, 2 ALND, the stripping of axillary vein was described as full ALND and the dissection of axillary content between latissimus muscle, axillary vein and pectoralis minor muscle was described as lower or level 1, 2 ALND. Lymphoedema rate was reported as 37% for full ALND, and 8% for level 1, 2 ALND. In reference to the article by Larson et al. (8), other articles claimed that the risk of lymphoedema is directly related to the extent of axillary surgery as level 1, 2 ALND vs full ALND (7, 9). The approval of full ALND as level 1-3 ALND based on the description of Larson et al. (8) is misleading, because level 1-3 ALND does not include the stripping of axillary vein which was known as a major cause of lymphoedema by disrupting the lymphaticovenous anastomoses (10, 11).

The extent of axillary dissection had been argued and whether level 1-2 axillary dissection instead of level 1-3 axillary dissection could decrease the arm morbidity had been investigated (12, 13). The two randomised studies showed that the extent of ALND (level 1, 2 or level 1 versus level 1-3) was not associated with arm morbidity in cT1-3cN0-1 invasive breast cancer (12, 13). In the study by Kodama et al. (12), level 1 was compared with level 3 dissection and 58% and 68% were clinically and histologically axillary node negative,

respectively. Tominaga et al. (13) compared level 1, 2 with level 1-3 dissection, and 74% were clinically and 65% were histologically axillary node negative. These studies proved that the 10-year survival, DFS or axillary recurrence-free survival were not significantly different for level 1 and level 1, 2 or level 1-3 ALND. Arm oedema and restrictions in arm movements were also not significantly different for level 1 or level 1-3 in the study by Kodama et al. (12). Tominaga et al. (13) reported that there were no significant differences for level 1 or level 1-3 ALND in regard to arm pain, motor function or social functioning. In both of these trials patients were randomised to level 1, level 1, 2 or level 1-3 ALND without performing sentinel lymph node biopsy (SLNB). While it was clear that ALND has no benefit for axillary recurrence or survival in patients with negative axillary lymph node, the power of these studies was also not sufficient to evaluate the advantage of level 1-3 ALND over level 1 or level 1, 2 ALND. Although the extent of ALND has been shown to be not effective for survival, DFS, axillary recurrence and arm morbidity in breast cancer, arm morbidity continued to remain high after either level 1, 2 or full (level 1-3) ALND (4-6). Findings from a systematic review and meta-analysis suggest that more than one in five women with breast cancer will develop arm oedema (4). The quests for decreasing arm morbidity without compromising outcome in breast cancer treatment which began with the invention of SLNB continue for axilla conserving surgery. This article reviews the adventure of axillary surgery in breast cancer patients treated with or without NAC.

Clinical and Research Consequences

Sentinel lymph node biopsy in clinically axillary node negative patients

Following the first successful report of SLNB (14, 15), this technique was rapidly introduced to clinical practice in cT1-2 patients with clinically axillary node negative (16-21). Overall identification rate of SLNB and the false negative rate (FNR) of SLNB are over 90% and under 10%, respectively (Table 1) (22-30). High FNR is of clinical concern because of probability of higher axillary recurrence and inappropriate staging. Therefore, surgeons who perform SLNB are recommended to have figures close to or not worse than these.

Long term results of studies in patients with negative SLNB who did not undergo ALND, demonstrated that axillary recurrence rate was low and less than 2% (range, 0.4-1.7%) (Table 2) (31-38) and there was not significant difference between SLNB without ALND and with completion ALND in respect to axillary recurrence, DFS or survival (Table 2) (28, 31, 32, 34, 37, 39). Arm morbidity and/or quality of life were also shown to be improved significantly in patients with SLNB alone compared with completion ALND (Table 2) (4, 25, 28, 31, 32, 40-45). However, one study reported that SLNB is not associated with a better quality of life than ALND (46). SLNB was associated with low risk of arm oedema compared with ALND (47). As the results of sentinel node trials revealed no difference in terms of survival and axillary recurrence between SLNB and ALND (23), SLNB has been accepted as a standard procedure for early-stage breast cancer with cT1-2 clinically axillary node negative patients (21, 48). The American Society of Clinical Oncology (ASCO) guideline updated on 2014 recommended that women without SLNB metastases should not receive ALND (21).

Axillary treatment in patients with metastasis on sentinel lymph node biopsy

Until 2011, axillary lymph node dissection (ALND) had been the standard treatment in breast cancer patients with metastasis on SLNB

(32, 49). However, ALND stood on to be associated with high arm morbidity (5, 50).

Many retrospective studies which reported the outcomes in patients with positive SLNB have observed no axillary recurrences (51-54) or between 0.2% and 1.7% in patients with SLNB alone (Table 3) (34, 55, 56). The others which compared the outcomes after SLNB alone with completion ALND demonstrated that the axillary recurrence rate was $\leq 2\%$ (Table 3) (43, 57, 58). However, in a cohort study from the Netherlands, 1,028 patients with sentinel lymph node (SLN) micro-metastases who did not undergo ALND were shown to have a significantly higher risk of axillary recurrence of 5.6% at 5 years follow-up compared with 0% in 94 patients who received axillary radiotherapy after SLNB or 1.1% in 793 patients who underwent ALND ($p < 0.001$) (Table 3) (59, 60). All patients in that study had a tumor size of ≤ 1 cm and only 52% of the patients with no axillary therapy received systemic therapy. Two retrospective studies with metastasis on SLNB reported that axillary recurrence was 0% with a median follow-up of 30 months and 48% and 32% of patients had radiotherapy for breast and 22% and 29% of patients received additional radiotherapy for nodal fields, respectively (Table 3) (52, 53).

Naik et al. (57) reported that 210 SLNB-positive/no ALND patients had either refused completion ALND or were felt to be at low risk of having residual axillary disease. In the study by Naik et al. (57) although axillary recurrence was higher in 210 SLNB positive/no ALND patients compared with SLNB positive/ALND group, it was not significant and of the 149 patients who underwent breast conserving surgery (BCS) 53 had radiotherapy. In this group, 43% (23/53) had radiotherapy for the breast only, and 57% (30/53) received additional radiotherapy for the axilla. No patients in this subset developed axillary recurrence (58).

In the study by Park et al. (58) which included an expanded number of patients from Memorial Sloan Kettering Cancer Center (MSKCC), among 287 SLNB positive/no ALND patients, none of the 6 patients who developed axillary recurrences had radiotherapy for axilla and/or supraclavicular region. They reported that in SLNB (+)/no ALND patients, axillary recurrence was significantly higher compared with SLNB (+)/ALND group (2% vs 0.4%, $p = 0.004$). However, 31% of their patients underwent mastectomy, and only 15% of all patients with SLNB (+)/no ALND had additional radiotherapy for axilla or supraclavicular region.

These show that uncontrolled omission of ALND could result in increased rate of axillary recurrence and the importance of radiotherapy as part of BCS and/or as additional tangent fields to axilla in patients treated with BCS or mastectomy. Although, none of the retrospective trials and meta-analyses revealed any significant difference in survival or DFS in patients with positive SLNB/no ALND compared with ALND, the impact of axillary recurrence should never be overlooked. The Early Breast Cancer Trialists' Collaborative Group reported that for every 4 locoregional recurrences avoided, about 1 breast cancer death over the next 15 years is prevented (61). Harris and Morrow (62) reported that with increasing use of chemotherapy this ratio changed from 4:1 to 2:1.

The meta-analysis by Bilimoria et al. (63) showed that axillary recurrence and survival were not significantly different for patients who underwent SLNB alone versus SLNB with completion ALND for microscopic nodal disease and, in selected patients, for macroscopic nodal metastases. On the other hand meta-analysis by Yi et al. (64) reported that axillary recurrence was significantly higher in patients with SLNB alone compared

Table 1. Identification and false negative rates of SLNB in clinical node negative patients

Study	Patient numbers	SLNB identification rate %	False negative rate%*
Before adjuvant chemotherapy			
Veronesi et al. (1999)	371	98.7	6.7
Tafra et al. (2001)	535	87	13
		Surgeon experience	Surgeon experience
		<10 cases: 82	<30 cases: 15.5
		≥10 cases: 92	≥30 cases: 4
			1 node: 20.8
			≥2 nodes: 9.2
McMasters et al. (2000)	806	Single agent: 86	Single agent: 11.8
		Dual agent: 90	Dual agent: 5.8
ALMANAC trial (2006)	815	96	6.7
		Single agent: 85.6	
		Dual agent: 96	
Kim et al. (2006) Meta-analysis of 69 studies	8059	96 (41-100)	7.3 (0-29)
NSABP B-32 (2007)	5536	97.2	9.8
Sentinella/GIVOM (2008)	697	95	16.7
Hunt et al. (2009)	3171	98.7	4.1
Kuru et al. (2011)	232	91	7
After neoadjuvant chemotherapy			
Tafra et al. (2001)	29	93	0
NSABP B-27 (2005)	343	85	10.7
		Lymphazurin: 78	Lymphazurin: 14
		Radioisotope: 89	Radioisotope: 8
Xing et al. (2006) Meta-analysis of 21 studies	1273	90 (72-100)	12 (0-33)
Hunt et al. (2009)	575	97.4	5.9
Classe et al. (2019)	589	97.6	11.9
Kelly et al. (2009) Meta-analysis of 24 studies	1799	89.6 (63-100)	8.4 (0-33)
Fontein et al. (2013) Meta-analysis of 21 studies	1738	95	11.4
Geng et al. (2016) Meta-analysis of 16 studies	1456	96	6
*Detected by axillary lymph node dissection after SLNB			
NSABP: National Surgical Adjuvant Breast and Bowel Project; SLNB: sentinel lymph node biopsy			

with those with ALND in macroscopic nodal disease. However, axillary recurrence rate of 0.2% in selected patients with SLNB alone is very low and an acceptable figure. Yi et al. (64) considering the axillary radiotherapy as an alternative to ALND in SLNB-positive patients, noted that patients who underwent BCS were more likely to undergo SLNB alone. Because patients who underwent BCS would have already been candidate for adjuvant radiation, the use of high tangents or the addition of an axillary field during whole breast radiotherapy could readily be applied to avoid axillary recurrence and ALND (63, 64).

That the occurrence of significantly higher axillary recurrence in patients with the axilla left untreated after omitting ALND, the pres-

ence of no significant difference in axillary recurrence and survival or DFS in patients without undissected axilla but received axillary radiotherapy compared with ALND prove the evidence that ALND could be omitted should the axilla be treated with radiotherapy in SLNB-positive breast cancer patients undergoing BCT or mastectomy. Lack of significant difference in axillary recurrence and survival or DFS in cT1-2 patients with 1, 2 metastases on SLNB and without ENE who undergo BCS without ALND and receive whole breast radiotherapy compared with those undergoing ALND is attributed to the tangential radiotherapy for axillary region during whole breast radiotherapy. Thus omitting of ALND in those pa-

Table 2. Outcomes in observational studies with SLNB negative patients and in studies which compared SLNB with ALND in SLNB negative patients in clinical axillary negative patients

Prospective studies Follow-up	Number SLNB, ALND	Axillary recurrence % SLNB vs ALND	Survival % SLNB vs ALND	Arm morbidity % SLNB vs ALND	Quality of life SLNB vs ALND
ALMANAC trial (2006) Mansel et al. 18 months	515, 516	NR	NR	At 12 months Lymphedema: 5 vs 13 Arm function: Favours SLNB (p<0.01)	Favours SLNB p<0.01
Chen et al. (2009) 6/12 months	140, 81	NR	NR	Lymphedema: Favours SLNB (p=0.04) Arm movement: Favours SLNB (p<0.001-0.038)	Favours SLNB p=0.037
NSABP 32 (2010) 8 years	2011, 1975 All SLNB (-)	0.4 vs 0.1 NS	90.3 vs 91.8 NS	At 36 months Lymphedema: 8 vs 14 and Arm functions favour SLNB (p< 0.001)	Favours SLNB p<0.002
Veronesi et al. (2010) 10 years	259, 257 All SLNB (-)	0.8 vs 0 NS	93.5 vs 89.7 NS	At 24 months Any lymphedema: 7 vs 75 Arm mobility: 0 vs 21 Favour SLNB (p<0.01)	NR
Sentinella/GIVOM (2008) 56 months	336, 341	NR	DFS 88 vs 90 NS	At 6 months, lymphedema and movement restriction favour SLNB (p<0.01, 0.016)	PGWBI: Favours SLNB Significantly p=0.015
Purushotham (2005) 12 months	86, 155	NR	NR	Lymphedema 20 vs 60 (p=0.007) Arm restriction favours SLNB	Psychological morbidity: Significantly less in SLNB
Kootstra et al. (2008) 24 months	61, 134	NR	NR	NR	NS
Dabakuyo et al. (2009) 12 months	222, 296	NR	NR	Arm symptoms scale favours SLND (p=0.013)	GHS favours SLND, p=0.018
Hunt et al. (2012) ACOSOG z0010. 8.4 years	3904 SLNB All SLNB (-)	0.5	Surv.: 93	NR	NR
Kell et al. (2010) 5 RT 6 months	Arm swelling: 1997, 1967 Paraesthesia: 1596, 1613	NR	NR	Arm swelling and Paraesthesia: Favours SLNB (p=0.0028, 0.0018)	NR
Pepels et al. (2011) 47 months	6,664, 1878 All SLNB (-)	0.4 vs 0.3 NS	NR	NR	NR
Pepels et al. (2011) 50 studies, 36 months	26,000, SLNB All SLNB (-)	0.6	NR	NR	NR
Petrelli et al. (2012) 4 RT, 5-10 years	2699, 2725 All SLNB (-)	NS	NS	NR	NR
Galimberti et al. (2014) 7 years	5,262, SLNB All SLNB (-)	1.7	10 years Surv.: 91	NR	NR
Matsen et al. (2016) 10.4 years	1529 SLNB All SLNB (-)	0.9	Surv.: 84	NR	NR
Houvenaeghel et al. (2016) 55 months	8386, 945 All SLNB (-)	0.4 vs 0.5 NS	NS in MVA	NR	NR
De Boniface et al. (2017). 10.5 years	2216 SLNB All SLNB (-)	1.6	Surv.: 94	NR	NR

SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; LRR: locoregional recurrence; Surv.: survival; Neg.: negative; RT.: randomised trials; PGWBI: Psychologic General Well Being Index; GHS: general health status, NR: not reported; NS: not significant; MVA: multivariate analysis

Table 3. Characteristics and outcomes of studies that compared SLNB with or without axillary RT versus ALND for patients with SLN metastasis

Prospective studies (Follow-up)	Year/ Number (SLNB, ALND)	Outcome of SLNB	Axillary treatment	Micr. %	Axillary recurrence % SLNB vs ALND	Survival or DFS %	Arm morbidity %
ACOSOG Z0011 (9 years)	2011/420, 436	SLN 1-2 (+) SLN >2 (+) or ENE (+)	SLNB vs ALND	35	1.5 vs 0.5 NS	Similar NS	25 vs 70 p< 0.01
AMAROS (6.1 years)	2014/681, 744	SLN (+)	SLNB+ART vs ALND	40	1.7 vs 2 NS	Similar NS	5 vs 13 p< 0.01
OTOASOR 8 years	2017/230, 244	SLN (+)	SLNB+ART vs ALND	40	1.2 vs 0.43 NS	Similar NS	5 vs 15 p< 0.01
IBCSG 23-01 (10 years)	2018/469, 465	SLN 1-2 (+) SLN >2 (+) or ENE (+)	SLNB vs ALND	100	0.8 vs 0.2 NS	DFS Similar NS	18 vs 39 p< 0.01
AATRM (5 years)	2013/121, 112	SLN (+) 93.3% BCS	SLNB vs ALND	100	0.8 vs 0.9 NS	Similar NS	NR
Meta-analyses							
Bilimoria et al. NCDB (5 years)	2009/1988, 20,290	SLN (+)	SLNB vs ALND	18 vs 8.5	Mic.: 0.6 vs 0.2 NS, Mac.: 1.2 vs 1, NS	Similar NS	NR
Yi et al. SEER database (50 months)	2010/4425, 22,561	SLN (+)	SLNB vs ALND	51 vs 20	Mic.: 0.13 vs 0.09, NS Mac.: 0.2 vs 0.08 (p<0.002)	Similar NS	NR
Pepels et al. 30 months	2011/962, 15 studies	SLN (+)	SLNB±ART	Mic.: 61 Itc.: 25 Mac.:14	1.7	NR	NR
Retrospective studies							
Naik et al. (31 months)	2004/210, 1132	SLN (+)	SLNB vs ALND	NR	1.4 vs 0.35 p=0.08	NR	NR
Houvenaeghel et al. (55 months)	2016/282, 2923	SLN (+)	SLNB vs ALND	66 vs 40	Mic.: 1.6 vs 0.4, p=.05, Mac.: 0 vs 0.9 (NS)	NR	NR
Takei et al. (34 months)	2007/120, 402	SLN (+)	SLNB vs ALND	NR	0 vs 1 NS	NR	NR
Zakaria et al. (30 months)	2007/86, 421	SLN 1-3 (+) SLN (+)	SLNB±ART vs ALND	80 vs 24	0 in SLNB	NR	NR
Hwang et al. (30 months)	2007/196	SLN (+)	SLNB±ART	85	0 in SLNB	NR	NR
Park et al. (26 months)	2007/287, 1673	SLN (+)	SLNB vs ALND	NR	2 vs 0.4 p=0.004	NR	NR
Tjan-Heijnen et al. (60 months) MIRROR	2009/235, 793	SLN (+)	SLNB vs SLNB+ART ALND	100	5.6,0, 1.1 (p<0.01)	NR	NR
Spiguel et al. (95 months)	2011/123	SLN (+)	SLNB	67	0.8	DFS: 85	NR
Morrow et al. (37 months)	2017/484	SLN 1-2 (+) All BCT	SLNB	NR	0.2	DFS: 93	NR
Kuru et al. (37 months)	2019/81, 28	SLN 1-2 (+) SLN >2 (+) or ENE (+)	SLNB+ART vs ALND	0	0 vs 1 NS	Similar NS	6.2 vs 17.8 p< 0.01

BCT: breast conserving therapy; OS: overall survival; DFS: disease-free survival; Mic.: micrometastasis; Mac.: macrometastasis; Itc.: isolated tumor cells; SLN: sentinel lymph node; SLNB: SLN biopsy; ART: Axillary radiotherapy; NS: not significant. NR: not reported

tients does not create any unfavourable status in respect to axillary recurrence, survival or DFS.

These retrospective studies are crippled with the selection bias, because as in the study by Pepels et al. (34), 25% of patients had isolated tumor cells on SLNB which was accepted as pN0 in the current Guidelines. In three other studies patients with low risk of non-sentinel node metastasis by various nomograms was selected to omit ALND (53, 57, 58). In the two largest series with SLNB positive/no ALND from MSKCC and MD Anderson cancer center, the patients were at low risk for having additional positive non-SLNs and probably low probability of developing axillary recurrence with a median risk of <10% for non-SLN metastasis based on MSKCC nomogram (53, 57). Two meta-analyses reported that patients with older age and smaller size of breast tumor were more likely to undergo SLNB alone (63, 64). Many randomised trials have been conducted to overcome the selection bias by retrospective studies (65-70).

The American College of Surgeons (ACOSOG) Z0011 trial was carried out to assess whether omitting ALND would decrease the high arm morbidity following ALND in patients with 1-2 metastases on SLNB who underwent breast-conserving therapy (BCT) (65, 66). This trial showed that in women with clinically node-negative axilla who underwent BCT, the omission of ALND in T1-2 breast cancer patients with 1, 2 metastases on SLNB and without extra nodal extension (ENE) did not decrease survival, not increased axillary recurrence, and reduced arm morbidity compared with ALND. The ACOSOG Z0011 study changed the practice of axillary treatment and breast surgeons in some main breast centers began to omit the ALND in patients with T1-2 tumor and with 1, 2 metastases on SLNB and without ENE who underwent BCT (71-73). The National Comprehensive Cancer Network (NCCN) recommends the consideration of not performing ALND following SLNB in patients who match the ACOSOG Z0011 eligibility criteria (74).

The American Society of Clinical Oncology also does not recommend routine ALND, based on the ACOSOG Z0011 study (75). However, the Z0011 study had been criticized for its design and for its very favourable and low risk patient and tumor characteristics (76). The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) study compared ALND with SLNB plus axillary and supraclavicular radiotherapy in T1-2 early breast cancer patients with positive SLNB (67). The finding of this study revealed that the five-year axillary recurrence rate was not significantly different for the regional radiotherapy following SLNB without ALND compared with ALND following SLNB (1.2% vs 0.43%). However, the lymphoedema rate at five years was significantly lower in the radiotherapy group (13% vs 6%, $p=0.0009$) (67). The IBCSG 23-01 trial also showed that the DFS and axillary recurrence rate were not significantly different between the SLNB-only group and the ALND group in T1-2 patients with 1, 2 micrometastases on the SLNB who underwent BCT (68). In the OTOASOR (The Optimal Treatment of the Axilla - Surgery or Radiotherapy) study, 474 patients had positive SLNB. Two hundred and forty four patients with positive SLNB underwent completion ALND and 230 received axillary radiotherapy (69). There was no significant difference in axillary recurrence (2% in the ALND arm and 1.7% in the radiotherapy arm), and overall survival between the arms at the mean follow-up of 97 months. The arm morbidity was higher in the ALND group (15.3%) than in the radiotherapy (axillary levels, and supraclavicular, and $\pm$ internal mammary nodes) group at one year (4.7%). Considering that arm morbidity is important after surgery for breast cancer, and the

prevention of arm morbidity, together with a low axillary recurrence rate are among the major objectives of breast cancer treatment without worsening the oncologic outcome, the findings from these 4 randomised trials seemed to achieve these aims.

In the study by Kuru et al. (54), patients with 1-2 metastases on SLNB without ENE were assigned to the SLNB-only plus radiotherapy for the axillary levels I-III and to supraclavicular fossa or ALND groups (plus radiotherapy for undissected axillary level III and to the supraclavicular fossa). However, contrary to the randomised trials micrometastases were not included in this study, and all patients had macrometastases on the SLNB (66-69). This study also showed that lymphoedema and arm morbidity were significantly lower in SLNB-only arm compared with the ALND arm (54).

In patients with metastasis on SLNB, residual non-sentinel node metastases could be left in the axilla in many patients, and this is expected to be higher in patients with macrometastases on the SLNB than in micrometastasis on SLNB (77, 78). That residual disease left in the axilla could be responsible for axillary recurrence is the main argument for performing ALND or axillary radiotherapy in SLNB-positive patients, especially in patients with macrometastases on SLNB. As in systemic therapy adjuvant radiotherapy can be regarded as a treatment modality for any remaining axillary lymph node metastases. Radiotherapy for the breast as part of BCT includes the lowest portion of the axilla. In several studies it has been confirmed that the clip marking the SLN fell within the standard tangential fields of the whole breast radiotherapy in 78-94 % of the patients (79, 80). Veronesi et al. (81) reported that radiotherapy for the breast is one of the possible explanations for the lower than expected numbers of axillary metastases in the no axillary radiotherapy arm of their randomised trial that assessed the role of axillary radiotherapy. Axillary radiotherapy, tangentially or directly, is associated with low axillary recurrences (65, 67, 82, 83). What is important is the associated arm morbidity of the radiotherapy for the axilla levels.

As demonstrated in the AMAROS, OTOASOR studies, and the study by Kuru et al. (64, 67, 69) radiotherapy for three axillary levels resulted in significantly lower or no axillary recurrence in SLNB-only arm compared with ALND. These studies supported that the addition of radiotherapy for breast or chest wall was associated with a significantly higher risk of lymphoedema in patients who underwent ALND, but there was no association with lymphoedema in patients treated with SLNB plus radiotherapy (84). Sanuki et al. (85) reported that in 104 cT1-T2N0M0 breast cancer patients with positive SLNB who underwent BCT without ALND; the five-year axillary recurrence and lymphoedema were 0%. In that study, macrometastasis was found in 33% of patients. In one of the two studies which looked like the design of the ACOSOG Z0011 study, Dengel et al. (71) reported that there was no axillary recurrence after omitting ALND for T1-2 invasive breast cancer patients with 1, 2 metastases on SLNB with a median follow-up of 13 months. However, 27% of patients had micrometastases, and the median tumor size was under 2 cm (71).

Briefly, in all of the above randomised studies, survival, DFS or axillary recurrence were not significantly different; and the arm morbidity rates were significantly lower in SLNB-positive patients treated with breast surgery and radiotherapy for three axillary levels and/or to the whole breast. Axillary dissection could safely be omitted in patients with 1, 2 metastatic SLNB and without ENE who undergo BCS or in patients with metastatic SLN who undergo BCS or mastectomy and have ad-

juvant radiotherapy for the all three axillary levels, the supraclavicular fossa, and $\pm$ mamma interna and/or the whole breast or chest wall.

Axillary treatment after neoadjuvant chemotherapy in clinically axillary negative patients

Sentinel lymph node biopsy after neoadjuvant chemotherapy (NAC) in clinically axillary negative patients is recommended by current guidelines (74, 75). While ALND is recommended in patients with metastasis on SLNB, omitting ALND in patients with negative SLNB is increasingly being used after NAC (86). The identification and false negative rates of SLNB after neoadjuvant therapy in clinically axillary negative patients are over 90% and under 10%, respectively (Table 1). These figures justify the use of SLNB in this setting. Many studies and meta-analyses including NSABP B-27 showed that the identification and false negative rates of SLNB were similar to the rates of upfront surgery (29, 87-93) (Table 1).

Four hundred and nineteen patients who had cT1-3 and clinically and radiologically axilla negative breast cancer proved with fine needle aspiration biopsy (FNAB) and had negative SLNB after NAC had been treated with SLNB alone in GANEA 2 study (90). Only one axillary recurrence occurred during a median follow-up of 36 months and 3-year overall survival was 97.2% (90). In the MD Anderson study, among 3,746 clinically axillary negative cT1-3 patients, 3,171 patients underwent surgery first and 575 patients underwent SLNB after NAC (29). SLNB identification rates before and after NAC were 98.7% and 97.4%, respectively. False negative rate of SLNB before and after NAC were also similar as 4.1% and 5.9%, respectively. Of the 444 patients with negative SLNB after NAC, 409 did not undergo ALND. Regional recurrence rates for patients treated with and without NAC were 1.2% and 0.9% with a median 47 months of follow-up, respectively, and not significantly different (29). This study also demonstrated that in patients with clinically axillary node negative T2-3 tumours treated with NAC, the axillary disease could be reduced and could lead to decreased ALND without impairment in locoregional control. These findings showed that NAC could eradicate non-palpable axillary nodal disease (94). Outcomes in two studies including patients with clinically node negative who received NAC showed that axillary/regional recurrence rate was 0% and 1.2% with a follow up time of between 47 and 51 months, respectively in SLNB negative patients who underwent SLNB only (29, 95). Axillary recurrence rate, DFS or survival was not significantly different in patients with SLNB alone compared with patients with ALND (96, 97) (Table 4).

Considering all, these data show that SLNB after NAC is accurate and feasible in clinically axillary node negative breast cancer and NAC could spare patients the morbidity of ALND and adjuvant treatment suggestions without impairing locoregional control by decreasing the number of patients with a positive SLNB (29). These findings also led to the questioning of the current recommendations that all axillary suspicious lymph nodes on axillary ultrasound in patients undergoing NAC should be biopsied (98). All data show that SLNB could be performed with more or less similar identification rate and similar FNR compared with upfront surgery (99).

Nguyen et al. (86) from Mayo clinic reported that overall, the proportion of patients undergoing ALND ($\pm$ SLNB) in node positive patients treated with NAC decreased from 100% in 2009 to 38% in 2017 ($p < 0.001$), and the use of axillary surgery limited to SLNB only increased from 0 to 62% over this time period (86). Further stratified, the use of ALND only without SLNB dropped from 72% to 14%,

while SLNB without ALND for negative sentinel node (s), increased significantly over 50%.

Axillary treatment after neoadjuvant chemotherapy in clinically axillary positive patients

Sentinel lymph node biopsy after NAC for cN (+) axilla at presentation was in the past contentious and not recommended by guidelines even if axilla was converted to negative axilla either by clinical examination or imaging (21). The rationale for this was that the FNR of SLNB may be unacceptably high ranging from 10% to 30% (100-106) (Table 5). However, 3 randomised clinical trials (107-109) (Table 5) and other studies conducted in patients with biopsy proven positive axilla or clinically positive axilla that converted to clinically negative axilla showed that FNR rate was under 10% or could be decreased below 10% if 3 or more SLN removed, using dual mapping technique of SLNB or targeted SLNB methods by clipping of positive nodes before NAC (90, 107-113) (Table 5). These studies led to the conclusion that ALND was not required in all patients with clinically positive axilla that converted to clinically negative axilla, and SLNB without completion ALND is accurate and feasible if three or more negative SLN is removed or at least one negative SLN is removed by dual mapping technique with blue dye and radioisotope is used (107-109, 114).

Therefore, in patients with cN1-2, NAC may achieve complete axillary response (cN0) detected by clinical examination and imaging studies and may achieve pathological complete response (pCR). In fact in one forth or more or up to 83% of node-positive patients, axilla become cN0 after NAC (101, 107, 108, 115, 116) and in HER2 and triple negative tumors up to three forth of axillary metastasis can completely be cleared pathologically (pCR) (114, 116). Thus ALND and the associated morbidity could be avoided. The extent of disease at presentation, and tumor biologic subtype should also be considered in the selection of axillary approach (86). HER2 and triple negative tumors have been shown to respond to NAC more successfully with pCR rates that could exceed 50% (86, 117).

Current NCCN guidelines have incorporated SLNB after NAC as an accepted part of management and state that SLNB can be performed on selected patients with clinically N1 breast cancer who have clinically negative axilla after NAC, and that the SLNB false-negative rate can be improved by removing more than two lymph nodes, using dual tracers or marking biopsied lymph nodes to document their removal (74). The proportion of patients with positive SLNB who did not undergo ALND after NAC increased from 0% in 2009 to 10% 2017 (86).

Outcomes in many studies with clinically or biopsy proven node positive patients who converted to clinically negative after NAC showed that in SLNB negative patients, axillary recurrence rate, DFS or survival were not significantly different in patients with SLNB alone compared with patients with ALND (26, 86, 118, 119) (Table 4). Axillary recurrence rates were between 0% and 3.3% with a follow up time of between 9 and 51 months (Table 4).

Axillary treatment in pathological node positive patients after neoadjuvant chemotherapy

In locally advanced and axilla positive breast cancers (cT $\geq$ 4 cm N1-2M0), DFS was 51% versus 87%, respectively in patients who have residual disease with metastasis on SLNB following NAC compared with those who had negative SLNB ($p < 0.001$) (116). In patients who have not received NAC, the size of the SLN metastasis is associated

Table 4. Outcomes in studies with clinical node negative and with clinical or biopsy proven node positive patients who converted to clinical negative after neoadjuvant chemotherapy

Studies Follow-up	Number/ Characteristics	SLNB and Groups	Axillary surgery SLNB vs ALND	Axillary recurrence % SLNB vs ALND	Survival or DFS% SLNB vs ALND
Hunt et al. (2009) 47 months	575 cT1-3cN0	409 neg.	SLNB	Regional recurrence: 1.2	NS compared with ALND
Galimberti et al. (2016) 61 months	396 cT1-4cN0-2 All ycN0 after NAC 260 Quart 136 mast.20% RT	1. 227 neg. 2. 169 pos.	1. SLNB 2. ALND	0.4 vs 0.6 NS	5-year survival cN0: 93.3 cN1-2: 86.3 NS
Nogi et al. (2017) 51 months	147 cN0	147 neg.	SLNB	0	5-year DFS 96%
Martelli et al. (2017) 72 months	216 cT2cN0-1	1. 77 neg. 2. 99 pos.	SLNB ALND	0	DFS NS
Choi et al. (2018) 51 months	213 cT1-4 pN1 (biopsy proven) All ycN0 after NAC	Groups 1.85 neg. 2. 49 pos.	1. SLNB 2. ALND 3. 79 ypN0 with ALND no SLNB	(Group 1 vs 3) 2.6 vs 1.3, NS	NS
Kim et al. (2015) 20 months	199 pN1 (biopsy proven)	Groups 1. 31 neg. 2. 20 neg. 3. 69 pos. or UD SLNB	1. SLNB 2. ALND 3. ALND 4. 79 ypN0 with ALND no SLNB	3.3 vs 5 vs 1.3 (Group 1 vs 2 vs 4) NS	Survival NS (Group 1 vs 2 vs 4)
Kang et al. (2017) 48 months	1247 cN1 (58% biopsy proven)	Groups 1a. 165 neg. 1b. 263 pos.	1a. SLNB 1b. ALND 2. 819 ALND no SLNB	1.2 vs 1 (Group 1a+1b vs 2) NS	DRFS 98 vs 99 NS for Group 1 vs 2
Nguyen et al. (2017) 9 months	430 cN1 (246 ALND 184 SLNB)	1. 82 neg. 2. 18 neg. 3. 73 pos. 4. 11 pos.	1.SLNB 2.ALND 3.ALND 4.SLNB+ART	0 vs 3.3 NS	NR
Kuru et al. (2019) 20 months Unpublished data	124 cN0-1 (99 SLNB 25 ALND)	1. 55 neg. 2. 25 pos. 3. 19 pos.	1. SLNB 2.SLNB+ART 3. ALND+ART	0, 0, 0 NS (Group 1 vs 2 vs 3)	NS

SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; LRR: locoregional recurrence; Surv.: survival; UD: undetected; DRFS: Distant recurrence-free survival; Neg.: negative; Rand.: randomised; PGWB: Psychologic General Well Being Index; GHS: general health status, NR: not reported; NS: not significant; MV: multivariate; RT: radiotherapy; ART: Axillary RT.

with the probability of the non-sentinel nodal metastasis, and low-volume SLN disease (that is, isolated tumour cells [ypN0i+, <0.2 mm], and micrometastasis [ypN1mi, 0.2-2.0 mm]) does not always require completion ALND (32, 66). However, the potentially chemoresistant disease that persists in the axilla after NAC could not have the same outcomes as in the ACOSOG Z0011, AMAROS, OTOASOR and IBCSG 23-01 trials of upfront surgery (66-69). Thus ALND remains as a standard procedure in patients with low-volume disease and macrometastasis on SLNB who received NAC.

The status of residual disease after NAC is also important for the decision of adjuvant radiotherapy. An updated analysis of NSABP B-18 and B-27 trials demonstrated that 10-year rate of locoregional recurrence (LRR) in patients with clinically axillary positive who remained pathological node positive after NAC was high as between 15% and 22% following ALND and lumpectomy and radiotherapy for breast or mastectomy (120). This finding showed that adjuvant regional radiotherapy in addition to whole breast radiotherapy after lumpectomy and adjuvant radiotherapy for the chest wall and regional radiother-

apy after mastectomy should be considered in these patients (120). Whether ALND could be omitted in favour of axillary radiotherapy in patients with positive SLNB after NAC is currently being investigated in ongoing phase III A011202 Alliance trial (121). In contrast, 10-year LRR in NSABP trials has been found 0% in clinically node positive patients who had pCR after mastectomy and had pathological negative node after NAC (ypT0N0) (120). This excellent LRR suggest that the response to NAC could be used in selection of patients for postmastectomy radiotherapy (120). This concept is currently being researched in NSABP B-51/Radiation Treatment Oncology Group (RTOG) 1304 (NRG 9353) phase III randomised trial (122). In this trial, the indication of radiotherapy for axillary or supraclavicular region in addition to whole breast or chest wall in patients with clinically axillary node positive who converted to pathological axillary lymph node negative and had negative SLNB after NAC is being investigated (122).

Axillary treatment is controversial in patients with positive axillary node either by physical examination, axillary ultrasound or fine needle aspiration biopsy. In French GANEA 2 trial, 307 patients from 19

Table 5. False negative rates of SLN biopsy in clinical and biopsy proven node positive patients who converted to clinical negative after neoadjuvant chemotherapy

Prospective studies (Number)	SLN identification rate %	False negative rate %	SLN number and false negative rate %			SLN technique and false negative rate %	Single agent	Dual agent
			1	2	≥3			
SENTINA (592)	80.1	14.2	24.3	18.5	7.3	16	8.6	
ACOSOG Z1071 (649)	92.9	12.6	31.5	21	9.1	20.3 6.8 (107 clipped nodes removed as SLN)	10.8	
SN FNAC (153)	87.6	8.4	18.2	4.9 *	NR	16	5.2	
GANEA2 (307)	80	11.9	19.3	7.8 *	NR		< 10	
Enokido et al. (143)	90.9	16						
Donker et al. (100)								
MARI procedure	97	7						
Retrospective studies								
Cabioglu et al. (98)	88	16.7				4.2 (clipped nodes removed as SLN)		
Caudle et al. (208)	NR	10.1				2.4 (with addition of clipped nodes removed as SLN)		
Alvarado et al. (150)	93	20.8	FNR associated with <2 SLN number					
Park et al. (121)	96.7	7.8	NS	22.2	6.1			
Takahashi et al. (46)	87	27.3						
cN1 converted to cN0								
Shen et al. (64)	93	25						
Meta-analyses								
Fu et al. (2,471) 15 studies	89	14				with IHC 8.7	without IHC 16	
El Hage (3,398)	91	13						
Chehade et al. 19 studies								
Tee et al. (1921) 13 studies	90	14	20	12	4	Single agent 19	Dual agent 11	
*Reported as ≥2 NR: not reported; SLN: sentinel lymph node; N: not significant								

centers with T2-3 breast cancer who had axillary node positive proved by axillary ultrasound and FNAB and converted to axillary node negative, the SLN detection rate after NAC was 80%, false negative rate (FNR) was 19.3% for 1 SLN and <10% for combined technique or for 2 SLNs (90) (Table 5).

In the three meta-analyses, 2,471, 3,398, and 1,921 patients with metastatic axillary nodes by clinical examination or FNAB who converted to clinically node negative axilla and underwent ALND following SLNB after NAC, the SLNB detection rates were 89%, 91% and 90%, and FNR rates were 14%, 13%, and 14% respectively (104-106) (Table 5). FNR rate dropped under 10% with dual agent or with ≥3 SLN or with IHC (104, 106). The authors reported that SLNB was a viable alternative to ALND (104-106) (Table 5). In the study from Korea which included the data of 5 hospitals, 1,247 patients with

positive axillary node by clinically or FNAB who converted to axillary node negative by clinically or ultrasound imaging underwent SLNB or ALND. Of the 428 patients, 263 with positive SLNB underwent ALND, 165 with negative SLNB did not undergo ALND, and 819 patients underwent ALND without SLNB. Comparison of patients with or without SLNB revealed no significant difference in regard to axillary recurrence and distant metastasis-free survival. The findings of this study also demonstrated that SLNB is valid for patients with positive axillary nodes before NAC (119) (Table 4). So far, only one published study by Nguyen et al. (123) reported that axillary recurrence was 0 with a median 9 months of follow-up for 11 patients with metastatic SLNB after NAC who did not undergo ALND and received axillary radiotherapy. In the unpublished study by Kuru et al., there was no axillary recurrence with a median 20 months of follow-up in 19

patients with positive axillary nodes on SLNB after NAC who did not undergo ALND but received axillary radiotherapy (Table 4).

The approaches of SLNB application after NAC according to the current Guidelines are as follows: ASCO early stage breast cancer SLNB Guidelines recommend SLNB in T1/2 tumours, and do not recommend SLNB in T3/T4 patients after NAC (15). NCCN Guidelines recommend SLNB in clinical axillary node negative patients or in patients with clinically axillary node positive before NAC who converted to clinically node negative (74). According to NCCN, SLNB is not feasible for clinical axillary node positive patients after upfront surgery or after NAC. 15. St Gallen Breast Cancer Conference reported the conditions that SLNB is feasible in patients treated with NAC; clinically axillary node negative at initial diagnosis or after NAC and if 2 or more sentinel nodes removed at SLNB in patients with clinically axillary node negative (124). The conclusions from Guidelines are that SLNB is feasible in patients with clinically axillary node negative or in patients with clinically or histologically node positive before NAC who are clinically (by physical examination or radiological imaging) node negative after NAC.

Ongoing trials

Sentinel Node Vs Observation After Axillary Ultra-sound (SOUND) trial at the European Institute of Oncology was designed to investigate whether ultrasound staging of the axilla could replace with SLNB to improve patients' quality of life. Breast cancer patients with clinically node negative axilla by axillary ultrasound or axillary FNAB (cT1N0) were randomised to SLNB ± ALND or axillary observation without axillary staging. Patients with negative SLNB or micrometastasis will not undergo ALND, whereas patients with macrometastasis on SLNB will undergo ALND (125). The POSNOC randomised trial aimed in women with early stage breast cancer with 1 or 2 sentinel node macrometastases, to assess whether adjuvant therapy alone is no worse than adjuvant therapy plus axillary treatment, in terms of axillary recurrence within 5 years. The study will compare adjuvant therapy alone with adjuvant therapy plus axillary treatment (axillary node clearance or axillary radiotherapy) (126).

In patients treated with NAC, two randomised studies began to investigate the role of SLNB and radiotherapy. The AMAROS trial demonstrated that radiotherapy for axilla had similar efficiency as with ALND in the treatment of patients with positive SLNB. The ongoing A011202 Alliance trial is addressing the same question in T1-3 breast cancer patients with biopsy proven axillary node positive who converted to clinically negative after NAC. Patients who had positive SLNB after NAC were randomised to axillary radiotherapy or ALND. This trial investigates whether axillary radiotherapy could replace with ALND in patients with positive SLNB after NAC (121). In NSABP B-51/Radiation Treatment Oncology Group (RTOG) 1304 (NRG 9353) phase III randomised trial, patients with biopsy proven positive axillary node who converted to clinically axillary node negative after NAC underwent SLNB and patients with negative nodes on SLNB were randomised to observation or regional radiotherapy (axillary and supraclavicular). Whether axillary or supraclavicular radiotherapy in addition to breast or chest wall after lumpectomy or mastectomy is required in patients with negative SLNB is being investigated in this trial (122).

In SENOMAC trial, T1-3N0M0 breast cancer patients who underwent upfront surgery or surgery after NAC and had 1, 2 macro-

metastatic lymph nodes on SLNB were randomised to observation or ALND. The effects of omitting ALND on survival, LRR and morbidity in patients with positive SLNB are being investigated (127). In the study which is being conducted by Kuru et al., whether axillary dissection could safely be omitted in cT1-3N0-1M0 invasive breast cancer patients who had clinically negative axilla (ycN0) and metastatic nodes on SLNB after NAC and received adjuvant radiotherapy for the whole breast or the chest wall, to three axillary levels and the supraclavicular region is investigated (Table 4).

Conclusions

Sentinel lymph node biopsy is the standard procedure for early-stage breast cancer with cT1-2 clinically axillary negative patients. Women without SLNB metastases should not receive ALND. In patients with micro- or macrometastasis on SLNB, axillary radiotherapy successfully replaces the ALND. The arm morbidity rate was significantly lower in patients with positive SLNB treated with breast surgery and radiotherapy for three axillary levels and/or to the whole breast. Axillary dissection could safely be omitted in patients with 1, 2 metastatic nodes on SLNB and without extranodal extension who undergo BCS and whole breast radiotherapy or in patients with metastatic nodes on SLNB who underwent BCS or mastectomy and have adjuvant radiotherapy for the all three axillary levels, the supraclavicular fossa, and ± mamma interna and/or the whole breast or chest wall. Treatment of breast cancer patients with NAC reduces the need for ALND and surgical morbidity without increasing the risk of LRR. Neoadjuvant chemotherapy often downstages the axillary disease in patients with clinically axillary node negative or positive at initial diagnosis. SLNB after NAC accurately represent the status of axillary lymph node and therefore, could guide the indication of ALND and this approach is associated with a low risk of LRR. In patients with clinically axillary node positive who converted to clinically axillary node negative, SLNB is feasible if more than 2 SLNs are removed or performed with dual tracer, but long term results from patients treated with SLNB alone in this setting are missing. While ALND could be avoided in clinically axillary node negative or in clinical or biopsy proven axillary positive patients who converted to clinical node negative and had at least three negative SLNs or had any negative sentinel node if SLNB is performed with dual tracer after NAC, ALND is the standard treatment for patients with positive SLNB after NAC. In patients with positive SLNB after NAC, axillary radiotherapy instead of ALND according to the ongoing trials could lead to conservation of the axilla and thus could avoid the probable morbidities of ALND.

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Atypical Lesions of the Breast and Lobular Carcinoma in Situ in Pregnancy – Surgeons' Practice

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ABSTRACT

Objective: Approach to precancerous and high-risk breast lesions occurring in pregnancy has received little attention in the literature. We carried out a study to investigate the practice of surgeons in the management of these cases.

Materials and Methods: A short survey was sent to surgeons, including a multiple-choice questionnaire about their practice for atypical hyperplasia or lobular carcinoma in situ presenting in each trimester of pregnancy or at time of breastfeeding. Answer options included observation, immediate vacuum biopsy, immediate surgery, surgery in next trimester, surgery after delivery, and surgery after end of breastfeeding; based on the time of presentation.

Results: Out of the 671 practitioners invited, 97(14.5 %) responded to the survey. Participants were from 23 countries. Answers showed that management of gestational Atypical Ductal Hyperplasia (ADH) and Lobular Neoplasia (LN) was readily postponed by surgeons in favor of fetus safety while being cautious about risks of conservative management alone.

Conclusion: Various methods of treatment are selected by surgeons for managing high-risk breast lesions during pregnancy. In the absence of relevant literature, decision making in a multidisciplinary team would be the best approach in these cases.

Keywords: Atypical ductal hyperplasia, lobular carcinoma in situ, pregnancy, lactation, survey

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Introduction

Some benign breast lesions are unique to the gestational period, and some others undergo alterations due to elevated levels of sex hormones during pregnancy (1, 2). Pregnancy associated breast cancer (PABC) may also occur, embracing many diagnostic and treatment challenges (3-5). All these have been thoroughly described, and many studies have covered, and are still investigating, different aspects of care of these diseases.

Conversely, issues concerning precancerous and high-risk breast lesions occurring in pregnancy have seldom been contemplated in the literature. There are several plausible reasons for this: overall low incidence, occurrence in ages higher than usual age of pregnancy, presentation as non-mass, non-palpability, and image-dependent detection. It might be that these lesions have been less studied in non-pregnancy periods as well.

Nonetheless, ultrasonography (US) of the gravid breast might be carried out for the follow-up of previous breast lesions, or for assessment of a new clinical finding. With the advent of highly accurate US which allows for detailed assessment, many structural deformities, microcalcifications, or other abnormalities of breast tissue are discovered; many of which would expectedly undergo biopsy, and histologic evaluation of the specimen. In this setting, reports of atypical hyperplasia (AH) or lobular carcinoma in situ (LCIS) by the pathologist create a therapeutic dilemma in the prenatal period.

The approach to atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and LCIS in the general woman has undergone continuous modifications since they were first described, till recent times (6-8). Recommended treatment has extended from most invasive procedures such as bilateral mastectomy to plain observation (9, 10). Because of the lack of recorded evidence, physicians would presumably rely on that literature and their common sense for making therapeutic decisions when facing such diagnoses in the gestational period.

We carried out the following study in order to find out what the practice of surgeons would be in management of such cases.

Materials and Methods

A short survey involving a brief account of the purpose of the investigation, a short description of the cases, three optional blanks for the surgeon email address, specialty/subspecialty, and country where they practice, followed by a multiple choice questionnaire (Figure 1), was designed. The questionnaire included two parallel sets of questions. The first set described a pregnant or lactating patient whose supposed lesion was a mass, and the second consisted of a non-mass lesion. In

both sets, surgeons were asked to determine their approach for each trimester of pregnancy and during breastfeeding individually. ADH, ALH, and LCIS were considered separately in the questions.

Participants could choose for the first and second trimester among following variables: observation, immediate vacuum biopsy, immediate surgery, surgery in next trimester, and surgery after delivery.

For the third trimester, participants could choose among following variables: observation, immediate vacuum biopsy, immediate surgery, and surgery after delivery.

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High-Risk Breast Lesions in Pregnancy

When atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), or lobular carcinoma in situ (LCIS) is seen in a specimen of core needle biopsy of the breast, the routine practice is to excise the specimen. Depending on several factors like previous history or other known breast cancer risk factors of the patient, type of breast abnormality, accompanying lesions, size of biopsy specimen... this may be substituted by other practice such as simple observation or risk-reducing options.

Only two sets of questions are asked in the following text to see how you would manage one of the above breast lesions when detected on core needle biopsy during pregnancy, supposing that you and your patient have access to any equipment or facility that may be needed.

Please write your email:

Specialty/Subspecialty:

Country where you practice:

Q1: Core needle biopsy of a breast MASS LESION, palpable or not, in following trimesters of pregnancy or during lactation in a woman less than 45 years old with no other risk factor for breast cancer:

Trimester/Lactation	ADH	ALH	LCIS
1st Trimester: ADH			
2nd Trimester: ADH			
3rd Trimester: ADH			
Lactation: ADH			

Please add any comment you wish:

Q2: Core needle biopsy of a breast NON-MASS LESION, in following trimesters of pregnancy or during lactation in a woman less than 45 years old with no other risk factor for breast cancer:

Trimester/Lactation	ADH	ALH	LCIS
1st Trimester: ADH			
2nd Trimester: ADH			
3rd Trimester: ADH			
Lactation: ADH			

Please add any comment you wish:

Management Options:

- Observation
- Immediate vacuum biopsy
- Immediate surgery
- Surgery after Lactation

Submit

Figure 1. Multiple choice questionnaire for survey of surgeons' choice regarding management of AH and LCIS in pregnant and lactating women

For the lactation period, the variables included: observation, immediate vacuum biopsy, immediate surgery, and surgery after end of breast-feeding.

The survey was sent to general, breast, and oncologic surgeons, as well as gynecologists who were known to practice breast surgery. Methods of contacting practitioners consisted of sending the link with an invitation to take part in the survey and a brief description of the work through emails, LinkedIn network, Short Message Service (SMS) and WhatsApp mobile application. Furthermore, members of the International Network on Cancer, Infertility and Pregnancy (INCIP) (www.cancerinpregnancy.org) were both contacted by email and invited to the survey personally via printed questionnaires handed out in an INCIP meeting.

The ethics committee approval was not needed for this study and participation in this study was volunteer.

Table 1. Countries of practice of the participants

Country	Number of participants	Country	Number of participants
Belgium	1	Malaysia	2
Bosnia and Herzegovina	1	Pakistan	5
Brazil	1	Panama	1
Bulgaria	1	Peru	1
Egypt	2	Poland	1
France	1	Russia	1
Germany	1	Saudi Arabia	1
Greece	3	UAE	3
India	3	UK	5
Iran	35	USA	10
Italy	6	Venezuela	2
Jordan	2		
Total : 97			

Statistical analysis was performed using Statistical Package for Social Sciences software version 18 (SPSS Inc.; Chicago, IL, USA). Categorical variables were summarized as N (%). Categorical variables were compared using the chi-square test or Fisher exact test, when appropriate.

Results

Overall, we offered the survey to 671 practitioners. Seven of them proposed to send the link to their colleagues, and we do not have the number of these invited doctors. Of all queried surgeons, 24 (3.5 %) answered that they did not practice breast diseases anymore and so would not participate in the survey. One surgeon replied that he was displeased with the work and believed the question was incorrect, around 550 (82%) of the directly invited surgeons did not answer at all, and 97 (14.5 %) took part in the survey.

The country where they practiced had been marked by 97 of the participants and is demonstrated in Table 1. Also, 88 participants wrote their specialty or subspecialty; this is shown in Table 2. Answers of participants to questions regarding their practice in different trimesters of pregnancy and in breastfeeding time is presented in Tables 3, 4 and 5 respectively. Colored cells show the highest values in each row, and p-values in last columns show the significance of different attitudes toward mass and non-mass presentations.

Discussion and Conclusion

Results of this study disclosed that surgeons were mostly inclined toward extraction of ADH histology, either by vacuum-assisted biopsy

Table 2. Specialty or subspecialty of the participants

Specialty/subspecialty	Number (%)
Breast/Breast Oncology Surgeon	51 (52.6)
General /Plastic surgeon	12 (12.4)
Gynecologist/Gynecologic Oncologist	4 (4.1)
Oncological Surgeon	21 (21.6)
Unknown	9 (9.3)

Table 3. Practice of surgeons in ADH presenting during pregnancy or breastfeeding

Period	Presentation	Observation	Im VAB	Im Sx	Sx next T	Sx after	p*
T1	Mass	21 (21.6)	31 (32)	11 (11.3)	23 (23.7)	8 (8.2)	0.08
	Non-mass	30 (30.9)	38 (39.2)	7 (7.2)	12 (12.4)	10 (10.3)	
T2	Mass	15 (15.5)	28 (28.9)	36 (37.1)	3 (3.1)	15 (15.5)	0.05
	Non-mass	28 (28.9)	34 (28.9)	20 (20.6)	2 (2.1)	13 (13.4)	
T3	Mass	16 (16.5)	26 (26.8)	22 (22.7)	-	33 (34)	0.07
	Non-mass	27 (27.8)	33 (34)	15 (15.5)	-	22 (22.7)	
Lactation	Mass	12 (12.4)	25 (25.8)	37 (38.1)	1 (1)	22 (22.7)	0.77
	Non-mass	16 (16.5)	29 (29.9)	29 (29.9)	1 (1)	22 (22.7)	

ADH: Atypical Ductal Hyperplasia; Im: immediate; VAB: Vacuum assisted biopsy; Sx: surgery; T: trimester; after: after delivery/end of breastfeeding
Data are presented as number with percentage in parenthesis

Table 4. Practice of surgeons in ALH presenting during pregnancy or breastfeeding

Period	Presentation	Observation	Im VAB	Im Sx	Sx next T	Sx after	p
T1	Mass	41 (42.3)	30 (30.9)	6 (6.2)	6 (6.2)	14 (14.4)	0.50
	Non-mass	48 (49.5)	32 (33)	4 (4.1)	6 (6.2)	7 (7.2)	
T2	Mass	32 (33)	25 (25.8)	26 (26.8)	2 (2.1)	11 (11.3)	0.07
	Non-mass	46 (47.4)	28 (28.9)	13 (13.4)	0 (0)	10 (10.3)	
T3	Mass	16 (16.5)	26 (26.8)	21 (21.6)	-	34 (35.1)	<0.001
	Non-mass	45 (46.4)	27 (27.8)	8 (8.2)	-	17 (17.5)	
Lactation	Mass	24 (24.7)	25 (25.8)	28 (28.9)	-	20 (20.6)	0.32
	Non-mass	35 (36.1)	25 (25.8)	21 (21.6)	-	16 (16.5)	

ALH: Atypical Lobular Hyperplasia; Im: immediate; VAB: Vacuum assisted biopsy; Sx: surgery; T: trimester; after: after delivery/end of breastfeeding
Data are presented as number with percentage in parenthesis

Table 5. Practice of surgeons in LCIS presenting during pregnancy or breastfeeding

Period	Presentation	Observation	Im VAB	Im Sx	Sx next T	Sx after	p
T1	Mass	31 (32)	34 (35.1)	9 (9.3)	16 (16.5)	7 (7.2)	0.09
	Non-mass	45 (46.4)	32 (33)	2 (2.1)	11 (11.3)	7 (7.2)	
T2	Mass	14 (14.4)	30 (30.9)	37 (38.1)	1 (1)	15 (15.5)	<0.001
	Non-mass	40 (41.2)	30 (30.9)	17 (17.5)	0 (0)	10 (10.3)	
T3	Mass	15 (15.5)	27 (27.8)	21 (21.6)	-	34 (35.1)	<0.001
	Non-mass	41 (42.3)	25 (25.8)	9 (9.3)	-	22 (22.7)	
Lactation	Mass	24 (24.7)	18 (18.6)	35 (36.1)	-	20 (20.6)	0.40
	Non-mass	33 (34)	20 (20.6)	26 (26.8)	-	18 (18.6)	

LCIS: Lobular Carcinoma in Situ; Im: immediate; VAB: Vacuum assisted biopsy; Sx: surgery; T: trimester; after: after delivery/end of breastfeeding
Data are presented as number with percentage in parenthesis

(VAB) or surgery. The approach was more invasive where it presented a mass, and more conservative with other findings. This could be anticipated because ADH usually does not present as a mass. This also shows that surgeons are highly concerned about the rate of upgrade of ADH and prefer to make sure the lesion is only high risk benign one or not malignant because when it has ADH in core biopsy, it is not a really benign one. However, in the third trimester, most of the surgeons chose to operate on the patient after delivery in case of mass lesions, and to perform VAC for non-mass lesions. In addition, among the 4 suggested treatment options, the “immediate surgery” ranks third for mass lesions, and fourth (15.5%) for non-mass lesions in the practice of participating surgeons. This is interesting considering that part of literature claims that ADH can be managed with no surgical excision at all. The approach of most surgeons to ALH was conservative. The only situations which pushed physicians toward surgical excision were lumps harboring ALH detected in the last trimester, with the decision to operate the patient after delivery; or found during breastfeeding. These results, however, might be interpreted as a tendency to excise unusual presentations of biopsy-detected ALH (lumps) as soon as the gestational state is safe enough. This also might be related to the small percentage of respondents to the survey, which brings in mind the possibility that surgeons who are more determined to extract borderline lesions during gestation might have answered the survey more frequently than others.

In LCIS, surgeons observed non-mass cases, while mass lesions were chosen to be excised; either by VAB or surgery. This complies with protocols that suggest excision of pathologic-radiologic non-concordant lesions, and observation of others. Time and method of excising the lesion depended on the gestational stage and was in accord with rules of mother and fetus safety.

All aspects of breast tissue atypia and LCIS including histologic definition, incidence, risks, and management have been discussed in the literature for non-pregnant women. ADH is defined as a borderline lesion which carries some of the histologic features of Ductal Carcinoma in Situ (DCIS), but not all of them (6, 7). Lobular neoplasia (LN) is proliferation of atypical epithelial cells within the terminal duct lobular units and comprises ALH and LCIS, which are very similar except for quantitative difference in abnormal and atypical characteristics. These are infrequent lesions that have been diagnosed more frequently since mammographic screening has taken place. ADH is seen in 0.5 to 17% of biopsied breast specimens with benign results (8-13). The incidence of LN is very different in various studies, from 0.1% for ALH alone, to 0.5% -7.8% for LCIS with or without ALH. ADH is more frequently diagnosed around 45- 46 years of age (12), and LN between 40 and 55 years (12-14). The most frequent mode of presentation is through mammographically-detected microcalcifications, nonetheless it may very occasionally present as a palpable or an US-

detected mass (6, 12, 15-18). LN is usually not associated with any image finding, but may infrequently cause a “shadowing, avascular, irregular, hypoechoic mass” on US (14).

There are two major concerns about AH and LCIS. The first consists of the probability to upgrading to malignancy when excised, this is due to the presence of adjacent cancer. The second concern is future risk of malignancy in the breast. When ADH is diagnosed by core needle biopsy, the rate of upgrade to DCIS or invasive disease has been reported from 0% to as high as 65% (6-8, 10, 19, 20). Rate of upgrade for biopsy-detected LN has been from 9% to 33% (8, 21). For subsequent risk of cancer in AH, figures up to 3- to 4-fold increase in risk have been detected, mostly in same but also in opposite breasts, more frequent in younger ages, and more frequently invasive than in situ (9, 22-24). The risk of future cancer in ALH is around 4- to 5- fold, and 8- to 10-fold in LCIS. In both lesions, the cancer might be ductal or lobular invasive, and in same or opposite breast, with a predilection for the same breast (11-13, 18, 22).

Management of ADH detected on image-guided biopsy has been subject to various suggestions. At present, because of the high rate of upgrading, excision of the lesion is mostly recommended (6, 7, 9, 10, 16-18, 20, 25-27), except for very small microcalcifications which have excised by VAB (8, 18, 26, 27). For LN found in core needle biopsy specimens, the optimal therapeutic approach is still debated. The most recent approach is to keep lesions under observation whenever the radiologic and pathologic results are concordant; if not, excision is advised (9, 13, 18, 20, 21, 23, 27). Counseling for risk-reduction with tamoxifen should also be considered in AH and LCIS (14, 18, 23, 27, 28).

Issues regarding incidence, risks, and management of these lesions during pregnancy have not been considered in the literature. Whether the same approach as non-pregnant women should be undertaken, or should physicians avoid any treatment because of low risks of malignancy and indolent nature of lesions; and whether the highly modified hormonal milieu of pregnancy would affect the course of the disease are not known. Our study scanned the practice of surgeons in various countries of the world in regard to these matters.

Overall and in contrast with PABC which infers immediate action, management of gestational ADH and LN was easily deferred by surgeons because of their relative benignity; in favor of fetus safety. Nevertheless, most surgeons stood vigilant toward these borderline lesions in selecting type of management.

This study also revealed some supplementary points. For example, the diversity of answers and heterogeneity in practice of surgeons was very interesting. One surgeon who believed the survey was inappropriate wrote: “No one in their right mind will operate on a pregnant patient with ADH, ALH, or LCIS”, and stated that ABS and ASCO guidelines have clearly defined the suitable management. Nonetheless the survey shows that many skilled and experienced surgeons chose to operate on the patient, which should not be considered incongruous for a high-risk lesion, where there is no specific guideline or consensus over the subject.

Our study shows that in the lack of specific evidence and absence of guidelines, decision-making varies significantly among practitioners. Yet, guidelines do not cover rare instances, and cases in the survey are probably rare enough not to deserve being discussed in an international consensus. The best approach to these cases is to have the disorder managed by a multidisciplinary team comprising related specialty or subspecialties.

Our study had some limitations. Because we planned to design a concise survey that would take a short time to complete, we did not ask participants about their years of expertise, their statistics about yearly number of breast surgeries or management of pregnant cases with breast complaints; and also if they worked in a referral center, or if they had ever managed cases similar to our questions. In addition, around one third of the participants were from Iran, because we knew who worked on breast diseases in our country, and we also called them and asked to participate. However they were from different centers, and different cities, where practices are not based on same guidelines.

In conclusion, in the absence of relevant literature and guidelines, approach of surgeons to high-risk lesions of the breast that could occur in pregnancy differs to some extent; but follows those common scientific bases that concern safety of pregnant mothers and their fetuses. Decision-making in a multidisciplinary team would be the best option in these cases.

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A Comparison of the Clinicopathological Features, Metastasis Sites and Survival Outcomes of Invasive Lobular, Invasive Ductal and Mixed Invasive Ductal and Lobular Breast Carcinoma

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ABSTRACT

Objective: We compared the breast cancer patients with invasive lobular carcinoma (ILC), invasive ductal carcinoma (IDC) and mixed invasive ductal and lobular carcinoma (IDLC) in terms of clinicopathological and treatment features, metastatic patterns and long-term survival.

Materials and Methods: In a 10 years patient cohort, 3412 patients with unilateral breast carcinoma were enrolled in the study. Tumors were classified histologically according to criteria described by World Health Organization classification.

Results: The highest rate of T3 tumors were found in IDLC patients, the lowest in IDC patients, and the difference between groups was significant only in comparison of IDC vs IDLC. Axillary positivity rate was highest in IDLC, lowest in ILC; differences were significant in comparisons of IDLC vs ILC and IDLC vs IDC. There was no significant difference between the patient groups in terms of surgical treatment, mastectomy and breast conserving surgery. Rate of bone metastasis was highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. Locoregional recurrence-free survival (LRFS) rate was 90.9% in ILC patients, 92.5% in IDC patients, 92.9% in IDLC patients, with no significant difference between the groups; in multivariate Cox analysis, histological type had no prognostic significance ($p=0.599$). Distant metastasis-free survival (DMFS) rate was 66.2% in ILC patients, 66.7% in IDC patients, 57.1% in IDLC patients; in multivariate Cox analysis, histological type had no prognostic significance ($p=0.392$).

Conclusion: Although these results suggest that IDLC may have a worse prognosis than IDC and ILC, in multivariate analysis LRFS and DMFS were not significantly different among the histological type groups.

Keywords: Breast cancer, Invasive lobular carcinoma, Invasive ductal carcinoma, mixed invasive ductal and lobular carcinoma, survival

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Introduction

Invasive breast cancer is a histologically heterogeneous disease; among numerous histological types, invasive ductal carcinoma (IDC) is the most common, present in 70%-75% of the cases (1, 2), followed by invasive lobular carcinoma (ILC), present in 5%-15% of the cases (1-3). Mixed invasive ductal and lobular carcinoma (IDLC), which has characteristics of both invasive ductal and lobular carcinoma, is present in approximately 5% of the cases (2). Lately, the prevalence of the lobular breast tumors has been on the rise, particularly in postmenopausal women; this increase has been linked with evidence suggesting that frequent use of hormone replacement therapy in recent years has increased the risk of ILC and IDLC development more than that of IDC (4-6). Clinicopathological characteristics and survival outcomes of ILC and IDC have been compared in numerous studies with conflicting results. On the other hand, few studies have compared IDLC with ILC and IDC.

In this study, we compared ILC, IDC and IDLC in terms of clinicopathological and treatment features, metastatic patterns and long-term survival retrospectively in a 10 years patient cohort.

Materials and Methods

Ethical standards

The research protocol of this clinical study was approved by the Ethics Committee of the University of Health Sciences, İstanbul Okmeydanı Training and Research Hospital (the date/protocol number: 04.24.2019/1236). The study was conducted according to the

principles of the Helsinki Declaration and its later amendments or comparable ethical standards. In addition, all patients were routinely informed about the procedures and their written informed consent was obtained.

Patients

We reviewed the file records of women who underwent surgery for breast carcinoma between January 1993 and December 2002 who were then followed up in Istanbul Okmeydanı Training and Research Hospital. Inclusion criteria for the patients were a histological diagnosis of unilateral breast ILC, IDC and IDLC; tumors were classified histologically according to criteria described by World Health Organization classification; no previous or concomitant malignant disease; known pathological tumor size (patients with T4 tumor were not included), for multifocal/multicentric (MFMC) tumors, largest dimension of the largest tumor was accepted as the tumor size; at least one lymph node removed by axillary dissection; no metastasis in ipsilateral internal mammary or supraclavicular lymph nodes and distant sites at the time of diagnosis; microscopically tumor-free surgical margins; completion of adjuvant therapy planned according to standard therapy protocols (patients received neoadjuvant therapy were not included); and a follow-up period at least five years in patients without disease recurrence. A total of 3412 patients (including 668 patients who underwent surgery at the study hospital) who met these criteria were enrolled in the current study.

Removal of at least six nonmetastatic lymph nodes is required to describe the axillary lymph node status as “negative” according to TNM classification (7). Thus, within the node-negative patient group, 132 patients (nine patients with ILC, 118 patients with IDC, five patients with IDLC) with one to five lymph node(s) removed by axillary dissection were not included in the analyses of axillary status assessment and survival.

Follow-up data were obtained from file records and, in some patients, through telephone calls. The endpoint of the study was first disease recurrence. Locoregional recurrence was defined as the recurrence involving the chest wall or tumor excision site in the breast (local) or/and ipsilateral axillary, supraclavicular and internal mammary lymph nodes (regional). Locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) times were defined as the time interval between tumor excision and detection of first locoregional recurrence or distant metastasis, respectively, or the date of last follow-up. In 147 patients who developed a second malignancy (excluding three patients with basal cell carcinoma), the diagnosis date of second malignancy was considered as the last follow-up date. In 66 patients whose death was unrelated to cancer, the date of death was considered as the last follow-up date.

Statistical analysis

The chi-squared and Fisher's exact tests were used to evaluate the differences between proportions and Student's t-test was used to evaluate the continuous data for comparisons of the clinicopathological and treatment features, metastatic pattern and metachronous contralateral breast cancer development of the patient groups. Kaplan-Meier method was used for calculation and plotting of the LRFS and DMFS curves of the patient groups, and log-rank test was used for the comparison of the survival curves. The relative importance of the prognostic features was investigated using the Cox proportional hazards model; prognostic parameters present in all patients were included in the Cox analysis. All comparisons were two-tailed, and p

value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinicopathological features

Among 3621 patients, including 209 patients with invasive carcinoma of other histological types (mucinous, medullary, papillary, metaplastic and other) who were in the patient cohort during the same period but not included in this study, 272 (7.5%) had ILC, 2981 (82.3%) had IDC, and 159 (4.4%) had IDLC. Clinicopathological features of 3412 patients are shown in Table 1. Patients with ILC had the highest mean age, while patients with IDLC had the lowest; significant age difference was found for comparisons of ILC vs IDC and ILC vs IDLC. Considering age status according to the cutoff of 35 years, there was no significant difference among the histological types in the rates of the patients below 35 years and 35 and above 35 years. The rate of postmenopausal patients was highest in ILC group and lowest in IDLC group; no significant difference was detected in comparison of ILC vs IDC, while the rate of postmenopausal women in IDLC group was significantly lower than those in the ILC and IDC groups. Mean tumor size was largest in IDLC patients, smallest in IDC patients; the difference was borderline significant for comparison of ILC vs IDC ($p=0.051$), significant for IDC vs IDLC, not significant for ILC vs IDLC. According to TNM classification, the highest rate of T1 tumors were found in IDC patients, lowest in IDLC patients; the highest rate of T3 tumors were found in IDLC patients, the lowest in IDC patients, and the difference between groups was significant only in comparison of IDC vs IDLC. The rate of MFMC tumors was highest in IDLC patients, and the difference was statistically significant compared with both ILC and IDC; there was no significant difference between ILC and IDC.

During the examination period of this study patients, vascular invasion, perineural invasion, estrogen receptor (ER) and progesterone receptor (PR) evaluations were not performed routinely in our hospital and in our country. Even though the number of patients having these evaluations was not high, we analyzed the available data. Vascular invasion rate was lowest in ILC, highest in IDC; the difference was significant for comparison of ILC vs IDC, while other group comparisons showed no significant difference. Perineural invasion rate was highest in IDLC, lowest in IDC; the difference was significant in comparison of IDLC vs IDC, while IDLC vs ILC difference was close to the level of significance ($p=0.076$). ER positivity rate was highest in IDLC, lowest in IDC; the difference between groups was significant only in comparison of IDLC vs IDC. PR positivity rate was highest in IDLC, lowest in IDC; this rate was significantly higher in IDLC compared with ILC and IDC. In the evaluation of axillary lymph node status, axillary positivity rate was highest in IDLC, lowest in ILC; differences were significant in comparisons of IDLC vs ILC and IDLC vs IDC, but not significant for ILC vs IDC.

Treatment features

Surgery and adjuvant treatment features of patients are presented in Table 2. There was no significant difference among histological type groups in terms of surgery, adjuvant hormonal therapy, and radiotherapy. Adjuvant chemotherapy application was highest rate in IDLC patients, lowest rate in ILC patients; the difference was significant in comparison of ILC vs IDC and ILC vs IDLC, but not significant for IDC vs IDLC.

Table 1. Clinicopathological features of the patients

Feature	ILC		IDC		IDLC		p		
	n	%	n	%	n	%	ILC vs IDC	ILC vs IDLC	IDC vs IDLC
Age, years							0.023	0.008	0.119
Mean (SD)	50.9 (11.2)		49.3 (11.0)	47.9 (11.3)					
Median	49.5		48.0		47.0				
Range	24.0-84.0		20.0-86.0	22.0-80.0					
Age, years							0.377	0.305	0.602
<35	17	6.3	237	8.0	15	9.4			
≥35	255	93.7	2744	92.0	144	90.6			
Menopausal status							0.188	0.006	0.021
Premenopausal	129	47.4	1538	51.6	97	61.0			
Postmenopausal	143	52.6	1443	48.4	62	39.0			
Tumor size, cm							0.051	0.132	0.002
Mean (SD)	3.3 (2.0)	3.1 (1.8)	3.6 (2.1)						
Median	3.0	2.9	3.0						
Range	0.3-13.0	0.2-15.0	0.7-11.0						
Tumor size, TNM							0.204	0.367	0.008
T1	86	31.6	966	32.4	42	26.4			
T2	143	52.6	1654	55.5	85	53.5			
T3	43	15.8	361	12.1	32	20.1			
MFMC tumors							0.790	0.001	<0.001
Yes	17	6.3	205	6.9	26	16.4			
No	255	93.7	2776	93.1	133	83.6			
Vascular invasion							0.047	0.521	0.292
Negative	65	52.4	751	43.3	56	48.3			
Positive	59	47.6	985	56.7	60	51.7			
Unknown	148		1245		43				
Perineural invasion							0.371	0.076	0.001
Negative	52	66.7	759	72.1	40	52.6			
Positive	26	33.3	294	27.9	36	47.4			
Unknown	194		1928		83				
Estrogen receptor							0.288	0.149	0.008
Negative	45	34.9	631	39.6	24	25.8			
Positive	84	65.1	961	60.4	69	74.2			
Unknown	143		1389		66				
Progesterone receptor							0.122	0.047	<0.001
Negative	42	33.9	636	41.0	18	20.5			
Positive	82	66.1	917	59.0	70	79.5			
Unknown	148		1428		71				
Axillary lymph node status							0.391	0.029	0.046
Negative	103	39.2	1045	36.5	44	28.6			
Positive	160	60.8	1818	63.5	110	71.4			

ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma; SD: standard deviation; MFMC: Multifocal or Multicentric

Table 2. Treatment features of the patients

Feature	ILC		IDC		IDLC		p		
	n	%	n	%	n	%	ILC vs IDC	ILC vs IDLC	IDC vs IDLC
Surgery							0.998	0.904	0.829
Mastectomy	244	89.7	2674	89.7	144	90.6			
Breast-conserving	28	10.3	307	10.3	15	9.4			
Chemotherapy							0.009	0.010	0.200
Yes	202	74.3	2409	80.8	135	84.9			
No	70	25.7	572	19.2	24	15.1			
Hormonal therapy							0.161	0.742	0.484
Yes	199	73.2	2059	69.1	114	71.7			
No	73	26.8	922	30.9	45	28.3			
Radiotherapy							0.502	0.086	0.116
Yes	184	67.6	2075	69.6	120	75.5			
No	88	32.4	906	30.4	39	24.5			

ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma

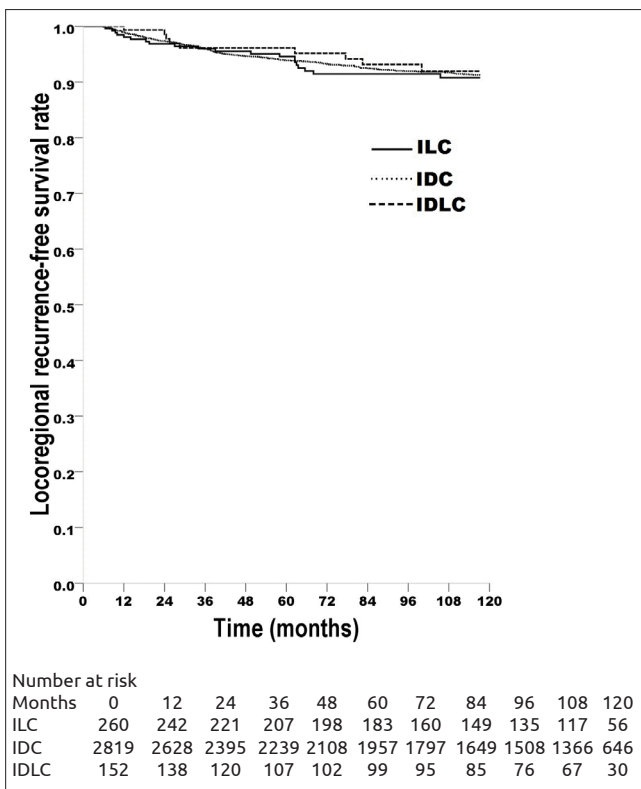


Figure 1. Locoregional recurrence-free survival (LRFS) rates of the breast carcinoma patients with invasive lobular carcinoma (ILC, 263 patients, LRFS rate 90.9%), with invasive ductal carcinoma (IDC, 2863 patients, LRFS rate 92.5%), with mixed invasive ductal and lobular carcinoma (IDLC, 154 patients, LRFS rate 92.9%). ILC vs IDC, log-rank $\chi^2=0.842$, $p=0.359$; ILC vs IDLC, log-rank $\chi^2=0.295$, $p=0.587$; IDC vs IDLC, log-rank $\chi^2=0.000$, $p=0.993$.

Metastasis sites and metachronous contralateral breast carcinoma
Table 3 presents data regarding the location of metastases (in one site or more sites concomitantly) and the development of metachronous contralateral breast carcinoma for the whole series encompass-

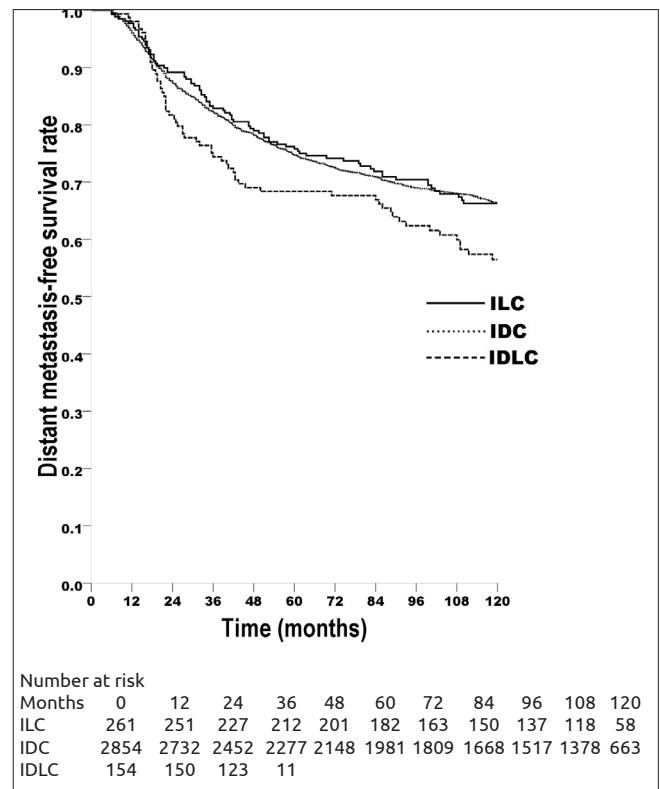


Figure 2. Distant metastasis-free survival (DMFS) rates of the breast carcinoma patients with invasive lobular carcinoma (ILC, 263 patients, DMFS rate 66.2%), with invasive ductal carcinoma (IDC, 2863 patients, DMFS rate 66.7%), with mixed invasive ductal and lobular carcinoma (IDLC, 154 patients, DMFS rate 57.1%). ILC vs IDC, log-rank $\chi^2=0.040$, $p=0.842$; ILC vs IDLC, log-rank $\chi^2=3.065$, $p=0.080$; IDC vs IDLC, log-rank $\chi^2=5.867$, $p=0.015$.

ing 3412 patients. There was no significant difference among the histological type groups in terms of metastasis to unilateral axillary lymph nodes. Distant metastasis sites were not significantly different among the groups except for the bone. Development rate of

Table 3. Metastasis sites and metachronous contralateral breast carcinoma in patient groups according to histological types

Metastasis sites	ILC		IDC		IDLC		p		
	n	%	n	%	n	%	ILC vs IDC	ILC vs IDLC	IDC vs IDLC
Axillary lymph nodes							0.929	0.410	0.325
Yes	4	1.5	52	1.7	5	3.1			
No	268	98.5	2929	98.3	154	96.9			
Bone							0.162	0.085	0.001
Yes	54	19.9	493	16.5	43	27.0			
No	218	80.1	2488	83.5	116	73.0			
Lung							0.429	1.000	0.700
Yes	25	9.2	320	10.7	15	9.4			
No	247	90.8	2661	89.3	144	90.6			
Pleura							0.961	0.591	0.306
Yes	4	1.5	51	1.7	5	3.1			
No	268	98.5	2930	98.3	154	96.9			
Liver							0.779	0.519	0.574
Yes	18	6.6	217	7.3	14	8.8			
No	254	93.4	2764	92.7	145	91.2			
Central nervous system							0.071	1.000	0.235
Yes	3	1.1	98	3.3	2	1.3			
No	269	98.9	2883	96.7	157	98.7			
Gynecologic							1.000	1.000	1.000
Yes	1	0.4	6	0.2	0	0.0			
No	271	99.6	2975	99.8	159	100.0			
Distant lymph nodes							0.146	1.000	0.265
Yes	10	3.7	63	2.1	6	3.8			
No	262	96.3	2918	97.9	153	96.2			
Skin-subcutaneous							0.545	1.000	1.000
Yes	1	0.4	8	0.3	0	0.0			
No	271	99.6	2973	99.7	159	100.0			
Adrenal							1.000	-	1.000
Yes	0	0.0	5	0.2	0	0.0			
No	272	100.0	2976	99.8	159	100.0			
Peritoneum							0.354	1.000	0.229
Yes	1	0.4	4	0.1	1	0.6			
No	271	99.6	2977	99.9	158	99.4			
Contralateral breast carcinoma							0.496	0.252	0.405
Yes	3	1.1	56	1.9	5	3.1			
No	269	98.9	2925	98.1	154	96.9			

ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma

bone metastasis was highest in IDLC patients, lowest in IDC patients; the difference was significant in comparison of IDC vs IDLC, but not significant for ILC vs IDC and ILC vs IDLC. In addition to metastasis sites reported in Table 3, metastases developed in cecum, pancreas, urinary bladder, thyroid, pericardium, retroperitoneal soft

tissue in one patient each and in the eye in two patients. Due to their low numbers, these locations were not considered in the statistical analysis. The rates of metachronous contralateral breast carcinoma were not significantly different among the three histological type groups.

Table 4. Cox proportional hazards model analysis of the clinicopathological and treatment features in terms of locoregional recurrence-free survival

Feature	Relative risk	95% CI	p
Age, years			0.009
<35	1.00		
≥35	0.57	0.38-0.87	
Menopausal status			0.103
Premenopausal	1.00		
Postmenopausal	1.26	0.95-1.67	
Tumor size			<0.001
T1	1.00		
T2	1.72	1.27-2.33	
T3	2.18	1.40-3.41	
Multifocality/multicentricity			0.031
Yes	1.00		
No	0.62	0.40-0.96	
Histological type			0.599
ILC	1.00		
IDC	0.80	0.52-1.23	
IDLC	0.80	0.39-1.63	
Axillary lymph node status			0.018
Negative	1.00		
Positive	1.51	1.07-2.12	
Surgery			0.001
Mastectomy	1.00		
Breast-conserving	1.92	1.29-2.85	
Chemotherapy			0.863
Yes	1.00		
No	1.03	0.70-1.52	
Hormonal therapy			<0.001
Yes	1.00		
No	1.82	1.39-2.38	
Radiotherapy			0.001
Yes	1.00		
No	1.87	1.31-2.66	

CI: confidence interval; ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma

Survival

Survival analyses were conducted on 3280 patients, excluding 132 node-negative patients who had 1-5 lymph node(s) removed by axillary dissection. Until the end of the study on November 2017, 251 patients developed locoregional recurrence, 1107 patients developed distant metastasis, and 57 patients developed concomitant locoregional recurrence and distant metastasis. In patients without disease recurrence, the median follow-up time was 148 months (range:60-297 months).

LRFS rate was 90.9% in ILC patients, 92.5% in IDC patients, 92.9% in IDLC patients, with no significant difference between the groups

(Figure 1); in multivariate Cox analysis, histological type had no prognostic significance ($p=0.599$) (Table 4). DMFS rate was 66.2% in ILC patients, 66.7% in IDC patients, 57.1% in IDLC patients, with no significant difference between the ILC patients and IDC patients (log-rank $\chi^2=0.040$, $p=0.842$); DMFS of IDLC patients was significantly worse than IDC patients (log-rank $\chi^2=5.867$, $p=0.015$); it was also worse than that of ILC patients, but the difference was outside the limit of significance (log-rank $\chi^2=3.065$, $p=0.080$) (Figure 2); in multivariate Cox analysis, histological type had no prognostic significance ($p=0.392$) (Table 5).

Table 5. Cox proportional hazards model analysis of the clinicopathological and treatment features in terms of distant metastasis-free survival

Feature	Relative risk	95% CI	p
Age, years			<0.001
<35	1.00		
≥35	0.68	0.56-0.84	
Menopausal status			0.263
Premenopausal	1.00		
Postmenopausal	1.08	0.94-1.23	
Tumor size			<0.001
T1	1.00		
T2	1.55	1.33-1.82	
T3	2.49	2.05-3.03	
Multifocality/multicentricity			0.001
Yes	1.00		
No	0.72	0.59-0.88	
Histological type			0.392
ILC	1.00		
IDC	0.96	0.77-1.19	
IDLC	1.14	0.83-1.57	
Axillary lymph node status			<0.001
Negative	1.00		
Positive	2.41	1.99-2.93	
Surgery			0.661
Mastectomy	1.00		
Breast-conserving	0.95	0.76-1.19	
Chemotherapy			0.301
Yes	1.00		
No	0.89	0.71-1.11	
Hormonal therapy			<0.001
Yes	1.00		
No	1.36	1.20-1.55	
Radiotherapy			0.068
Yes	1.00		
No	0.83	0.67-1.01	

CI: confidence interval; ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma

Discussion and Conclusion

In our study, comparison of clinicopathological features of patients with ILC, IDC and IDLC revealed highest mean age in ILC, lowest mean age in IDLC, with significant difference in comparisons of ILC vs IDC and ILC vs IDLC. When patients were analyzed in two groups according to 35-year cutoff, no significant difference was found among the histological types. In some studies, significantly advanced age was found in ILC compared with IDC (8-13). In other studies, no significant age difference was found between ILC and

IDC (14-18). In one study, the rate of patients below the age of 50 years was significantly lower in IDLC compared with ILC, while no significant difference was seen between IDLC and IDC (19). In a study comparing IDLC with ILC and IDC, the rate of women over the age of 50 years was significantly higher in ILC (20). In our series, the rate of postmenopausal women was highest in ILC, lowest in IDLC, with significant difference for IDLC vs ILC and IDLC vs IDC comparisons. In a study, menopausal status was not significantly different between ILC and IDC (1). In a study, the rate of postmenopausal patients was significantly lower in IDLC than in

ILC, while no significant difference was found between IDLC and IDC (19). In a study comparing ILC, IDC and IDLC, there was no significant difference between the histological groups in terms of menopausal status (20).

In our study, both mean tumor size and the rate of T3 tumors were highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. In some studies comparing ILC and IDC, no significant difference was found between the two histological types in terms of tumor size (9, 14, 15, 17, 18, 21, 22); in other studies, tumor size was significantly larger in ILC compared with IDC (1, 8, 10-13, 23); in one study the rate of T1 tumors was significantly lower in ILC compared with IDC (16). In a study comparing IDLC with IDC and ILC, the rate of T3 tumors was significantly higher in IDLC than in IDC, while no significant difference was found between IDLC and ILC (24); in another study, mean tumor size was largest in IDLC, smallest in IDC, with significant difference in histological group comparisons (there were no pairwise comparisons) (20); in another study no significant difference was found in IDLC compared with ILC and IDC in terms of tumor size (19). In our series, the rate of MFMC tumors was highest in IDLC, lowest in ILC, with significant difference found in comparisons of IDLC vs ILC and IDLC vs IDC and no significant difference found for ILC vs IDC. In some studies comparing ILC and IDC, the rate of MFMC tumors was found to be significantly higher in ILC compared with IDC (12, 13, 17, 18). In one study, no significant difference was found between the two histological types in terms of MFMC tumor rate (15). In a study investigating IDLC, ILC and IDC, MFMC tumor rate was found to be significantly higher in ILC (20).

In our series, within the subset of patients with vascular invasion, perineural invasion, ER and PR status evaluations, vascular invasion positivity rate was highest in IDC, lowest in ILC, with significant difference in comparison of ILC vs IDC. In studies comparing ILC and IDC, vascular invasion was significantly lower in ILC vs IDC (1, 9, 23). In our series, the rates of perineural invasion and ER positivity were highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC for both. Similarly, PR positivity rate was highest in IDLC, lowest in IDC, with significant difference detected in comparisons of IDLC vs ILC and IDLC vs IDC. In some studies comparing ILC and IDC, ER and PR positivity were found at significantly higher rates in ILC than in IDC (8, 10-13, 16, 18, 21-23) while some studies found no significant difference between these two histological types in terms of ER status (9,15). In one of the studies comparing IDLC with IDC and ILC, ER positivity rate was significantly higher in IDLC than in IDC, with no significant difference between IDLC and ILC, and PR positivity rate was significantly higher in IDLC than in IDC and ILC (24); in another study, no difference was found between the three histological types in terms of ER and PR positivity (20); in a different study, ER and PR positivity was significantly higher in IDLC and ILC compared with IDC (25).

In our series, the rate of axillary lymph node positivity was highest in IDLC, lowest in ILC, with pairwise comparisons of IDLC vs ILC and IDLC vs IDC significant, while ILC vs IDC was not significant. In some studies comparing ILC and IDC, axillary lymph node positivity rate was not significantly different between ILC and IDC (1, 8-10, 15, 16, 18, 21-23). In other studies, it was significantly lower in ILC compared with IDC (14, 17); in some other studies it was significantly higher in ILC compared with IDC (11, 13). In one study comparing IDLC with IDC and ILC, axillary lymph node positivity

rate was significantly higher in IDLC than in IDC, with no significant difference between IDLC and ILC (24); in another study, there was no significant difference between the three histological types in terms of axillary lymph node positivity (20).

In our study, there was no significant difference between the patient groups according to histological type in terms of surgical treatment, mastectomy and breast-conserving surgery. Among studies comparing ILC and IDC, some had no difference in mastectomy and breast-conserving surgery rates (15, 16, 18, 22); while some found significantly more mastectomy performed in patients with ILC than breast-conserving surgery (1, 8, 10-12), more frequent application of mastectomy in ILC patients may be related to more frequent presence or higher likelihood of multicentric tumors in this histological type. In a study comparing IDLC with IDC and ILC, surgical treatment was not significantly different between the histological groups (20).

In our study, rates of metastasis to various locations did not vary significantly between the histological types, except for bone metastasis. Rate of bone metastasis was highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. In a study comparing these three histological types, no significant difference was found regarding the metastatic sites (20). Among studies comparing metastatic sites of ILC and IDC, some found no difference between the two histological types (16, 18, 21), while some found significantly higher rates of bone metastasis in ILC (1, 12); some studies found significantly more frequent lung metastases in IDC (1, 10, 12, 22, 26), while one study found it to be significantly higher in ILC (27). Some studies reported the rare occurrence of peritoneum-retroperitoneum metastases, as also seen in our series, and more frequently in ILC than in IDC (26, 27).

In this series, there was no significant difference between the three histological type groups in terms of metachronous contralateral breast cancer occurrence. Some studies found higher rates of metachronous contralateral breast cancer in ILC compared with IDC (10, 14, 16, 28), while others found no significant difference between the two histological types (1, 17, 21, 29, 30).

In our study, LRFS was not statistically significant among the patient groups with three histological types in univariate and multivariate analyses. In univariate analysis, DMFS rate was highest in IDC, lowest in IDLC, with the difference close to the level of significance for IDLC vs ILC and significant for IDLC vs IDC; however, there was no significant difference among the histological groups in multivariate analysis. In various studies comparing survival in ILC and IDC, no significant survival difference was found between the two groups (9, 10, 12, 14-18, 21-23, 26, 31, 32); in some studies, survival was found to be significantly better in ILC compared with IDC (8, 11). In two studies comparing IDLC with ILC and IDC, survival was not significantly different between the groups (19, 20); in another study, IDLC had significantly worse survival compared with IDC, while no significant survival difference was found between IDLC and ILC (24).

In our study two important prognostic factors according to TNM classification, namely tumor size and axillary lymph node status, were not significantly different between ILC and IDC, while IDLC had significantly larger tumor size and higher rates of axillary lymph node positivity than IDC; compared with ILC, IDLC had significantly

higher lymph node positivity rate, but no significant difference in terms of tumor size. Although these results suggest that IDLC may have a worse prognosis than IDC and ILC, in multivariate analysis LRFS and DMFS were not significantly different among the histological type groups. In our series, rates of metastasis to various locations did not vary significantly between the histological types, except for bone metastasis. Rate of bone metastasis was highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. Since the risk of developing metachronous contralateral breast carcinoma was similar in all three histological type groups, it is reasonable to use a similar approach for all histological types in the evaluation of contralateral breast in post-treatment follow-up of these patients. Retrospective nature of our study is a limitation. Future evaluations of prognostic characteristics of histological types should involve prospective controlled studies and include current, new prognostic characteristics in addition to the clinicopathological characteristics that were available within the period of the present study.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Health Sciences Istanbul Okmeydanı Training and Research Hospital (04.24.2019/1236).

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

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Phyllodes Tumor of the Breast: A Clinicopathological Evaluation of 55 Cases

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ABSTRACT

Objective: Phyllodes tumors are biphasic tumors consisting of epithelial and stromal components that account for less than 1% of all breast tumors. According to the World Health Organization (WHO) phyllodes tumors are classified into three categories as benign, borderline and malignant. It has been reported that these tumors are usually benign and both the stromal component and the epithelial component may progress to malignancy. In this descriptive study, it was aimed to present the cases of phyllodes tumor and to evaluate the clinicopathological features of these tumors in the light of the literature.

Materials and Methods: In our study, 55 cases of phyllodes tumor diagnosed between 2005-2018 in the Department of Medical Pathology were retrospectively studied. A total of 55 cases were included in the study.

Results: All cases were female with a mean age of 39.7±15.2 years. Fifty-seven tumors diagnosed in 55 cases were classed as benign in 20 cases (35.1%), borderline in 14 cases (24.6%) and malignant phyllodes tumors in 23 cases (40.3%). Ductal carcinoma in situ (solid and cribriform type) were detected in one case with malignant phyllodes tumor, whereas invasive ductal carcinoma was detected in one case. Bilateral ductal carcinoma in situ was present in the patient with invasive ductal carcinoma.

Conclusion: These tumors which rapidly grow into large masses can be clinically and pathologically confused with benign lesions, macroscopic and microscopic evaluation of concomitant in situ-invasive carcinomas should be considered. Phyllodes tumors have an important role in breast surgery and pathology.

Keywords: Fibroepithelial lesion, phyllodes tumor, breast

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Introduction

Phyllodes tumor of the breast is a rare biphasic tumor accounting for less than 1% of all primary breast tumors (1). This tumor was first described in 1774 as a giant type of fibroadenoma and was first named as “cystosarcoma phyllodes” by Johannes Muller in 1838. World Health Organization (WHO) adapted similar terminology in 1982 and uses the term “phyllodes tumor” in the classification (2, 3).

World Health Organization classifies phyllodes tumors in three groups as benign, borderline and malignant, based on histopathological features such as tumor margins, stromal cellularity, stromal cell atypia, mitotic activity, stromal overgrowth and the presence of malignant heterologous elements (4). The incidence of benign phyllodes tumor is 35-64%, whereas the incidence of malignant phyllodes tumor as 25% (5).

The development of lobular carcinoma in situ, ductal carcinoma in situ, invasive lobular carcinoma, invasive ductal carcinoma, infiltrative carcinoma and squamous cell carcinoma have been reported in patients with phyllodes tumor (6-8).

In this descriptive study, it was aimed to present cases of phyllodes tumors and evaluate clinicopathological features of these tumors in light of the literature.

Material and Methods

55 cases of phyllodes tumor diagnosed between 2005-2018 in the Department of Surgical Pathology were retrospectively analyzed. Hematoxylin-eosin and immunohistochemically stained slides were re-evaluated.

The inclusion criteria in the study were cases diagnosed as phyllodes tumor, cases with available clinical data and suitability of blocks and slides for re-evaluation. Cases without an available clinical data, with insufficient tissue and slide quality for evaluation and cases without available blocks and slides were excluded from the study.

Phyllodes tumors are classified into three groups as benign, borderline and malignant phyllodes tumors according to WHO classification based on histopathological features such as stromal cellularity, stromal cell atypia, tumor margins, mitotic activity, stromal overgrowth and the presence of malignant heterologous elements. Tumors with well-circumscribed, mildly increased stromal cellularity, with or without minimal atypia, a mitotic activity generally <5 per 10 high-power fields, no marked stromal overgrowth and no heterologous elements are classified as benign phyllodes tumor. Tumors with focal infiltrative borders, moderate stromal cellularity, mild or moderate atypia, mitotic activity between 5-9 per 10 high-power fields, marked focal stromal overgrowth and no malignant heterologous elements are classified as borderline phyllodes tumor. Tumors with infiltrative borders, marked stromal cellularity and atypical stromal cells, high mitotic count (≥ 10 per 10 high-power fields), stromal overgrowth and heterologous elements are evaluated as malignant phyllodes tumor.

The immunohistochemically stained slides were re-evaluated using Ki-67 (RM SL6 Monoclonal Clone, 1/250 dilution Cell Marque) antibody in Leica Bond-Max Automatic Immunohistochemistry Staining Device (Leica Microsystems, Berlin, Germany) on the sections taken from the formalin-fixed paraffin-embedded blocks at a thickness of

4 micrometers. Ki-67 proliferative index was counted with Olympus CX31 binocular microscope in 1000 cells in areas where the proliferative activity is the highest.

Demographic information such as gender, age, tumor localization and tumor size; clinical information such as clinical presentation, radiological imaging, choice of treatment, follow-up period, recurrence and metastasis were obtained from the patient files in the electronic hospital database.

The conformity of continuous variables to normal distribution was analyzed using Shapiro-Wilk test. Variables were expressed as median (minimum: maximum) and mean $\pm$ standard deviation values. The Mann-Whitney U or Kruskal-Wallis tests were used to compare the continuous variables among the study groups according to the test of normality. When Kruskal-Wallis test was found to be significant, paired comparisons between groups were performed using the Dunn-Bonferroni approach. For statistical analysis, SPSS Statistical software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used and $p < 0.05$ was considered statistically significant.

The study was approved by the Uludağ University Clinical Research Ethics Committee with the decision no. 2018-1/28 on 25 September 2018. Informed consent was not received due to the retrospective nature of the study.

Results

A total of 55 cases diagnosed with phyllodes tumors between 2005-2018 were detected. The general characteristics of patients is summarized in Table-1. All cases were female with a mean age of 39.8 ± 15.3 years (Age range: 15-75).

Fifty-seven tumors diagnosed in 55 cases were classified as benign in 20 cases (35.1%), borderline in 14 cases (24.6%) and malignant phyllodes tumor in 23 cases (40.3%). Tumors were located in the right breast in 33 cases (61.1%), left breast in 19 cases (35.2%) and bilateral in 2 cases (3.7%). One of the cases was consulted from an external center, tumor localization was not specified and no clinical information

Table 1. Clinicopathological findings of cases (n=55)

Variable	No. of cases	
Gender	Female	55
	Male	0
Age	≤ 30	18
	31-49	23
	> 50	14
Tumor site	Left	19
	Right	33
	Bilateral	2
Initial diagnosis	Fibroadenoma	26
	Malignancy	17
	Phyllodes Tumor	10
Diagnosis	Benign	20
	Borderline	14
	Malignant	23
Initial treatment	Excision	
	Mastectomy and sentinel lymph node dissection	41
	Mastectomy	7
Follow-up (months)		4
		34
(Range: 2-142)		



Figure 1. The patient admitted to the clinic with complaints of a palpable breast mass with borderline phyllodes tumor

was available. One other case had two foci in the same breast while all the other cases had a single focus of tumor.

24 tumors were located in the upper outer quadrant, 4 in the lower outer quadrant, 7 in the lower inner quadrant, 9 in the upper inner quadrant, 5 in the subareolar region and 1 case had extensive tumor occupying all quadrants. The tumor localization of 7 cases could not be determined.

The mean diameter of benign phyllodes tumors was 3 cm (Range: 0.9-9), borderline phyllodes tumors diameter was 4.5 cm (Range: 1.2-12) and malignant phyllodes tumor was 3.7 cm (Range: 1.5-12). The tumor diameter in a total of 6 cases (1 benign, 3 borderline and 2 malignant) could not be detected.

Ki-67 proliferative index was counted as 52/1000 cells in benign phyllodes tumor, 110/1000 cells in borderline phyllodes tumor and 200/1000 cells in malignant phyllodes tumor.

Forty-four patients were admitted to the clinic with complaints of a palpable breast mass (Figure 1), 5 with pain and 1 with discharge. One of the cases had an incidental tumor and information of clinical presentation was not available in 6 cases.

Ultrasonographic examination of 51 patients revealed a well-defined and hypoechoic solid mass lesion. Eight patients with available mammographic images had macrolobulated well-circumscribed lesions. Dynamic contrast-enhanced magnetic resonance imaging was performed in 17 patients. Fast, heterogenous contrast-enhanced lesion was observed in the early stage of dynamic imaging after the contrast agent was given (Figure 2).

The physical examination and radiological findings suggested the diagnosis of fibroadenoma in 26 cases, malignancy in 17 cases and phyllodes tumor in 10 cases. The clinical data of 7 cases were not available.

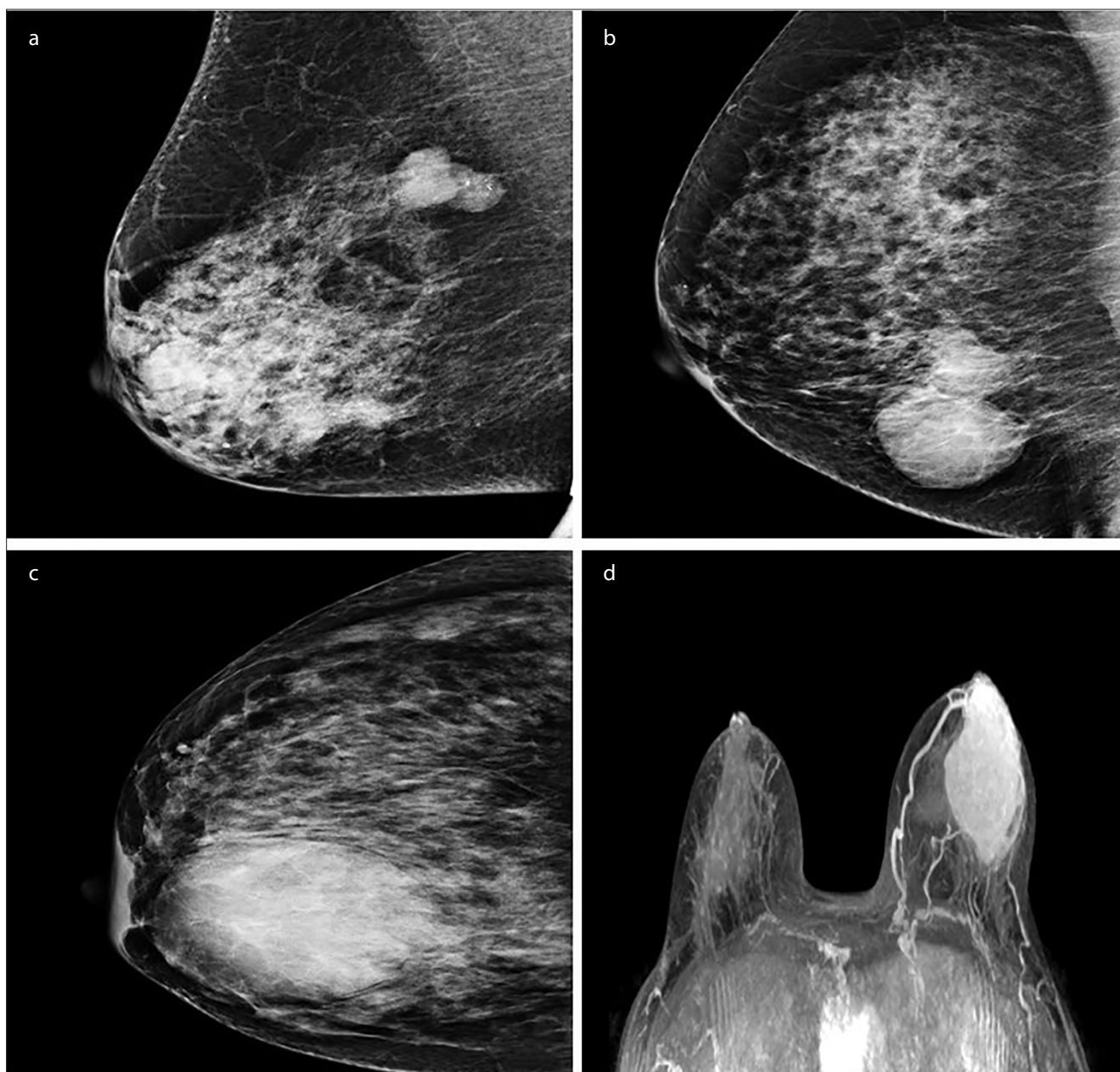


Figure 2. a-d. Benign phyllodes tumor mammography imaging (a). Borderline phyllodes tumor mammography imaging (b). Malignant phyllodes tumor mammography imaging (c). Malignant phyllodes tumor magnetic resonance imaging (d)

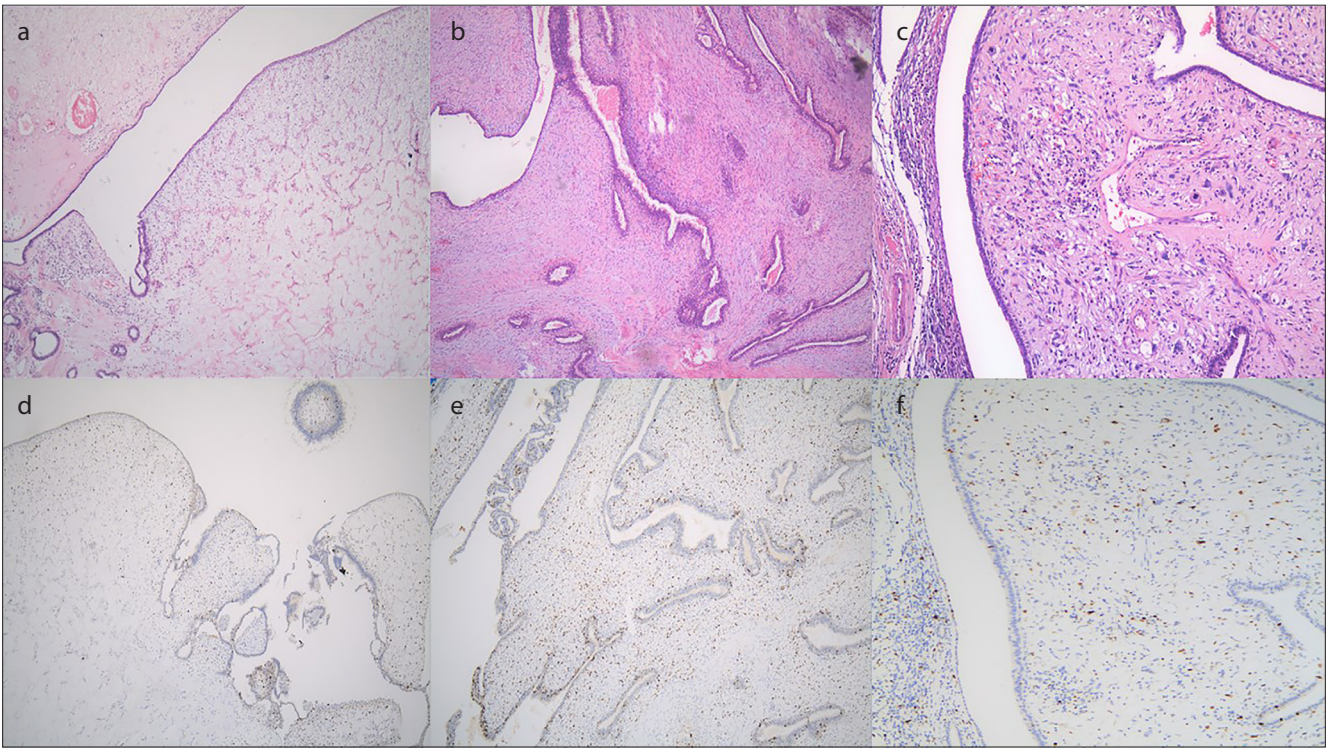


Figure 3. a-f. Benign Phyllodes Tumor: Typical leaf-like pattern, slight increase in cellularity of the stromal component and low ki-67 proliferative index (H&E, immunohistochemistry stain x40) (a, b). Borderline Phyllodes Tumor: Mildly increased cellularity and high ki-67 proliferative index (H&E, immunohistochemistry stain x40) (c, d). Malign Phyllodes Tumor: Stromal overgrowth, marked cellular atypia and brisk mitotic activity and ki-67 proliferative index (H&E, immunohistochemistry stain x100) (e, f)

Of the 39 patients who underwent core biopsy, 30 were diagnosed with fibroepithelial lesion, 8 with phyllodes tumor and 1 with fibrocystic changes. Core biopsy results of 16 patients were not available.

Surgical excision was planned in patients with the diagnosis of fibroepithelial lesion on core biopsy, patients who had clinical and radiological findings suggestive of malignancy, patients with fast growing lesions and with increased mitotic activity and high ki-67 proliferative index. Patients who were scheduled for radical mastectomy with a tumor of 5 cm diameters or more (considering the technical failure of sentinel lymph node dissection in case of detection of malignancy postoperatively) and who had a recurrent tumor with chest wall and axilla involvement, underwent surgical excision with sentinel lymph node dissection.

Forty-one patients were treated with wide local excision (lumpectomy), 7 underwent mastectomy and sentinel lymph node dissection, and 4 underwent mastectomy only. The surgical procedure of three cases were not available.

Gross examination of all the resection materials showed a solid multinodular mass with relatively smooth margins, greyish cut surface. Some of them had areas of cystic degeneration.

Histopathological examination revealed tumors composed of epithelial and myoepithelial cell layers with an intracanalicular growth pattern, branching cleft-like spaces and a stroma with increased cellularity around the cleft-like spaces (Figure 3). Benign phyllodes tumors were well-circumscribed. Cytological atypia or heterologous elements were not observed. Average mitosis was counted as 2.7 in 10 consecutive high-power fields. In malignant phyllodes tumors nuclear pleomorphism, prominent nucleoli and cytological atypia was observed. Lesions showed infiltrative borders and stroma was highly cellular. Aver-

age mitosis was counted as 13.2 in 10 consecutive high-power fields. Ductal carcinoma in situ (solid and cribriform type) was detected in one case of malignant phyllodes tumor and invasive ductal carcinoma was detected in another. Bilateral ductal carcinoma in situ (solid, micropapillary, mucinous type) was present in the case with invasive ductal carcinoma. In addition, in another case of malignant phyllodes tumor, invasive ductal carcinoma was detected concomitantly in the contralateral breast. Histopathological examination of sentinel lymph node biopsy showed no evidence of metastasis.

Five patients (8.9%) developed recurrence after the treatment. Three of the recurrent cases were initially diagnosed as borderline and 2 as malignant phyllodes tumor. One of the cases with borderline phyllodes tumor recurred as malignant phyllodes tumor after 33 months of initial diagnosis. In 4 out of 5 cases, the initial diagnosis was made in an external center and surgical margin information could not be obtained. In 1 case, the surgical margins of the resection material were positive and extended resection material revealed tumor at a distance of 0.2 cm in the closest surgical margin. Lung metastases were detected in 2 cases of malignant phyllodes tumor and one of them recurred two times. The patient who had lung metastasis 27 months after the first diagnosis, was given 5 cycles of chemotherapy and died after 36 months of initial diagnosis. The other case was a patient who had lung metastasis 2 months postoperatively. The patient started receiving chemotherapy but died after 1 month.

Adjuvant chemotherapy (doxorubicin, cyclophosphamide) or hormone therapy (tamoxifen, letrozole) along with radiotherapy (Mean dose: 30 Gray) was given to 1 case of borderline and 5 cases of malignant phyllodes tumor. Chemotherapy or hormone therapy was given to 2 cases of borderline and 4 cases of malignant phyllodes tumor, and radiotherapy alone was given to 7 cases of malignant phyllodes tumor.

The mean follow-up period of 55 cases was 34 months (Range: 2-142). Follow-up data was not available for eight cases.

Discussion and Conclusion

Phyllodes tumor is a biphasic tumor consisting of mesenchymal and epithelial elements, constituting less than 1% of all breast tumors with an incidence of 2.1/1000000 (1, 9). They are usually diagnosed in females in 4th or 5th decades of life and are very rare in men with few cases reported in the literature (5, 10). In our series, all of the cases were female and the mean age of diagnosis was 39.8 ± 15.3 years.

Although hyperestrogenism and breast trauma are thought to play a role in the development of phyllodes tumor, its etiology has not been yet fully elucidated (11). Cases of phyllodes tumor in pregnancy have been reported (12). In our series, 2 cases were diagnosed during pregnancy. Recurrence was observed in one of these cases following surgery.

Patients usually present with complaints of a breast mass. Complaint of a rapidly growing painless mass is a significant finding for phyllodes tumor (13). Tumors are usually unifocal. The most commonly involved site is upper outer quadrant. Multifocality and bilaterality have been reported in the literature (14, 15). In our series, the most commonly involved site was also the upper outer quadrant consistent with the literature. Two of the cases were bilateral and 1 was multifocal.

Phyllodes tumors does not have a pathognomonic radiological finding that distinguishes fibroadenoma from benign, borderline, and malignant phyllodes tumor. In recent studies, findings on contrast-enhanced MRI including tumor size over 3 cm, poorly demarcated and microlobulated architecture, heterogeneous appearance in echogenicity, hypervascularity and presence of internal cystic spaces have been reported to support phyllodes tumor in the differential diagnosis of two tumors with similar mammographical findings (16). In dynamic gadolinium-enhanced MRI, fast contrast-bearing tumors in dynamic imaging, well-circumscribed and high signal density in fat-saturated T2-weighted images with internal septation support benign phyllodes tumor (17).

Grossly, phyllodes tumors appear as well-defined, firm and multinodular masses. The cut surface is grayish white and has a homogeneous appearance. Myxoid areas, cystic spaces, areas of hemorrhage and necrosis can be seen (18). In a study including 145 benign, 33 borderline and 15 malignant phyllodes tumors Kim et al. (19) found the mean tumor diameter to be 4 cm. The mean tumor diameter was reported as 3.7 cm in patients with benign phyllodes tumor, whereas 4.2 cm in borderline phyllodes tumor and 6.2 cm in malignant phyllodes tumor. In our series, the mean tumor diameter was 3.2 cm in benign phyllodes tumors, 5.06 cm in borderline phyllodes tumors and 4.6 cm in malignant phyllodes tumors.

Phyllodes tumor is histopathologically characterized by leaf-like phyllodes structures lined by double layered epithelium, an internal epithelium with a myoepithelium outside, that has cleft-like cystic spaces with hypercellular stroma and intracanalicular growth pattern. Pseudoangiomatous stromal hyperplasia, cartilaginous, osseous, lipomatous metaplasia or stromal giant cells can be seen. Squamous and apocrine metaplasia of the epithelium is uncommon. Rarely ductal and lobular carcinoma in situ and invasive carcinoma may develop from the epithelium of phyllodes tumor (20). Rodrigues et al. (9) reported a total of 11 cases with malignant epithelial transformation in a series of 183 cases. 6 of the cases developed ductal carcinoma in situ, 4 cases lobular carcinoma in situ, and 1 case developed invasive ductal

carcinoma. In our series, ductal carcinoma in situ was detected in one case of malignant phyllodes tumor, whereas invasive ductal carcinoma was detected in another case. Bilateral ductal carcinoma in situ (solid, micropapillary, mucinous) was also present in the patient with invasive ductal carcinoma.

Phyllodes tumors are classified as benign, borderline and malignant according to WHO classification (21). Tan et al. (22) reported 72.7% benign, 18.4% borderline and 8.9% malignant phyllodes tumor in their series consisting of 605 cases. In our series, 34.5% benign, 24.1% borderline and 39.7% malignant phyllodes tumor were detected. We determined that the rate of malignant phyllodes tumor is not compatible with the data available in the literature because our center is the only tertiary health institution in its region.

The differential diagnosis of phyllodes tumor includes cellular fibroadenoma, spindle cell carcinoma, primary and metastatic breast sarcomas. Fibroadenoma should not be interpreted as phyllodes tumor based on only the histopathological findings of increased cellularity and mitotic activity which are more frequently detected especially in the pediatric group (23). Phyllodes tumor is difficult to differentiate in core biopsy materials and should be reported as 'fibroepithelial lesion with increased stromal cellularity' and the excision of the mass should be recommended (24). In the fibroepithelial lesion series consisting of 54 patients aged between 10 and 18 years conducted by Ross et al., juvenile fibroadenoma was detected in 23 cases. In cases of juvenile fibroadenoma, 1-7 mitosis was observed and increased stromal cellularity were present in 61% (25).

Primary or metastatic breast sarcomas are extremely rare but should be considered in the differential diagnosis of phyllodes tumors. When a sarcomatous tumor is encountered in the breast, the tumor should be examined with plenty sections and the presence of a benign epithelial component should be investigated (4).

In the treatment of phyllodes tumors, surgical excision is the main treatment and a wide local excision of the tumor with adequate margins of at least 1 cm is necessary. Radiotherapy, chemotherapy and hormone therapy are controversial in the treatment of phyllodes tumors (26-28). In their series, Chaney et al. (29) recommended adjuvant radiotherapy in malignant phyllodes tumor cases which had high risk of local recurrence. Surgical margin positivity, presence of tumor less than 0.5 cm of the surgical margin, detection of recurrent tumor or tumor diameter over 10 cm were considered high risk for local recurrence. There appears to be no consensus regarding the dosage that should be used in treatment.

Although there is no routine chemotherapy protocol for treatment of phyllodes tumors, it is suggested that these tumors should be treated like a sarcoma rather than a carcinoma when giving treatment. Especially patients with malignant phyllodes tumors larger than 5 cm and with high risk of recurrence are candidate for chemotherapy. Doxorubicin and dacarbazine were used as single agents but it is reported that treatment response is better in combined treatments with cisplatin or iphosphamide (30, 31).

Studies suggest that axillary lymph node sampling is not necessary in cases of phyllodes tumors. In their series consisting 48 cases of malignant phyllodes tumors, Kapiris et al. (32) did not detect metastasis in 21 axillary lymph node samples. In a series of 106 phyllodes tumor cases Ben Hassouna et al. (33) identified one patient with lymph node metastasis out of 20 cases that had undergone axillary lymph node

biopsy. In our series, no metastasis was found in 7 patients who underwent axillary lymph node dissection.

In patients with phyllodes tumor, varying rates of recurrence can be observed during follow-up. Recurrence of benign, borderline and malignant phyllodes tumors have been reported as 17%, 25% and 27%, respectively (22). The epithelial expression of E-cadherin which affects the Wnt signaling pathway in phyllodes tumors, is thought to be correlated with recurrence rates (26). Recurrent malignant phyllodes tumors might have a more aggressive biological behavior than the initial tumor. Borderline and malignant phyllodes tumors might also metastasize to distant organs. It has been reported that the tumor usually spreads by hematogenous route and metastasis is found most frequently in lungs and bone but can be detected in any localization. Histopathologically, stromal component is frequently found rather than the epithelial component in a focus of metastatic phyllodes tumor (34, 35). In 2012, Tan et al. (36) reported 12 cases with distant metastases in their series of 605 cases. All the cases with liver, lung, pleural, soft tissue and vertebrae metastases were diagnosed as malignant phyllodes tumor and no metastasis was detected in borderline and benign phyllodes tumors. The role of surgery and radiotherapy in the treatment of metastatic disease is controversial and reports are found that chemotherapy might be useful (37). In our series, 5 cases developed recurrence and lung metastasis was observed in 2 cases.

In conclusion, phyllodes tumors are rare tumors showing epithelial and mesenchymal components. The grading of phyllodes tumors is crucial due to diverse potential for recurrence and metastasis. The treatment of choice for phyllodes tumors is surgical excision. The role of radiotherapy and chemotherapy in preventing possible recurrences and metastases is controversial and clinical and radiological follow-up of the patients is recommended.

Ethics Committee Approval: Ethics committee approval was received for this study from the Uludağ University Clinical Research Ethics Committee.

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

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Prevalence of Molecular Subtypes of Breast Cancer: A Single Institutional Experience of 2062 Patients

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ABSTRACT

Objective: The aim of the study was to analyze the prevalence of molecular subtypes of all breast cancer patients treated at tertiary cancer centre in West India in 12 years.

Materials and Methods: A retrospective observational study carried out in Tertiary Cancer Care Centre in Western India. Electronic medical records of all breast cancer patients were retrieved from the hospital database between March 2007 to March 2019. Patient's characteristic, histological features and molecular subtypes were collected and analyzed.

Results: A total of 2062 women fulfilled the criteria for this study and were analyzed. The median age of study population was 51 years (range 22–100 years). Among these, 1357 (65.8%) were of ≤55 years and 705 (34.2%) were over 55 years. The overall incidence of Hormonal Receptor-positive patients (either estrogen-receptor (ER) or progesterone-receptor (PR) or both) was 1162 (56.4%). The Mean tumor size was 3.8cm (range 0-18cm). The most common histology was IDC (96%). Axillary nodes were positive in 62.5%. Luminal type A was positive in 762 (37%) patients while Luminal type B was present in 157 (7.6%) patients. Basal-like subtype was observed in 537 (26%) patients while HER2 rich subtype was seen in 229 (11.1%). The incidence of Luminal A subtype increased with age. The highest observed among patients (72%) aged 70 years or more. Incidence of Basal like subtype was highest in patients less than 30 years (52%).

Conclusion: Luminal-like disease is the most common molecular subtype in India. Identification of Basal like breast cancer, a highly aggressive, biologically and clinically distinct subtype different than its non-basal variant, is important for treatment planning and target therapy.

Keywords: Retrospective observational study, molecular classification, breast cancer, immunohistochemistry, tertiary cancer centre

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Introduction

Breast cancer is a global health issue among women. As per the recent GLOBOCAN 2012 data, the age-standardized incidence rate (ASR) for invasive breast cancer (females) in Asia was 29.1 per 100,000 women-years which is approximately 30% of Western population (North America has an ASR of 91.6 while Europe has an ASR of 71.1 per 100,000 women-years) (1). However, the incidence of breast cancer has increased significantly in Asian countries as compared to Western countries. Breast cancer accounts for the most frequently diagnosed cancer in Asian women. Although the incidence of breast cancer remains high in developed countries, there has been a shift in global distribution of breast cancer cases among women in South America, Africa, and Asia (2).

Pathology plays a key role in understanding complex disease such as cancer. However, in our country, there is paucity in data on key epidemiological findings (3). Are there any variances in breast cancers in India and Western literature? The answer is evidently yes. The proportion of breast cancer subtypes is different in the Indian continent.

Some of the established prognostic and predictive factors for breast cancer include tumor size, nodal involvement, histologic type, and histologic grade. Expression status by immunohistochemistry (IHC) such as estrogen receptor (ER), or progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2) are key prognostic factors (4). However, these traditional classifications do not reflect the diversity of breast cancer. For example, women with HER2-negative or ER-negative tumors do not response to HER2-targeted or

endocrine therapy, women with HER2-positive or ER-positive tend to show capricious responses to such targeted treatment (4). Thus, there is a need to better classify breast cancer types in order to predict outcomes in such patients.

In the past 18 years, there has been varying changes in the overall classification of breast cancer. Microarray-based gene expression profiling has helped in determining breast cancer from its histopathologic type to the molecular subtype. Today, ER-positive and ER-negative breast cancer subtypes are considered as different diseases (4). The Cancer Genome Atlas (TCGA) Network has helped established a refined subtypes of breast cancer through extensive profiling of protein levels, microRNA, and DNA (5). The molecular subtypes include “luminal A,” “luminal B,” “HER2-enriched,” and “basal-like” each of which have changed the paradigm of breast cancer treatment. The subtypes based on mRNA gene expression alone are similar to the intrinsic subtype (6). Each subtype has been associated with varying incidence, prognosis, preferential metastatic organs, response to treatment, recurrence or disease-free survival outcomes (6, 7).

Uncontrolled proliferation is a unique feature of cancer. The most common measurement of proliferation involves immunohistochemical assessment of Ki-67 antigen (8). Ki-67 has played a key role as a proliferation as it is present in all proliferating cells. Ki-67 is one of the 21 selected genes included in the Oncotype DX™ assay that has helped in predicting the extent of chemotherapy benefits and risk of recurrence among women with node negative and ER+ breast cancer. Ki-67 can have potential use in determining relative prognosis, resistance to endocrine therapy or chemotherapy, and estimation of

residual risk in patients on standard therapy. It has also been used as a dynamic biomarker of treatment efficacy among patients who receive neoadjuvant therapy, specifically those who received neoadjuvant endocrine therapy (9). The St. Gallen Consensus has for years led to the development of treatment personalized towards clinical and biological subsets of breast cancer. The consensus could also be used to make informed adjuvant treatment decisions (10).

The prevalence of molecular subtypes of breast cancer have not been studied extensively in developing countries. The objective of this study is to estimate the status of different molecular subtypes of breast cancer in a tertiary cancer centre. In addition to the molecular subtypes, clinicopathological factors such as age, tumor size, and lymph node involvement have been compared.

Materials and methods

Patient population

A total of 2062 histopathologically confirmed cases of breast cancer were selected. Key factors such as age, gender, laterality, treatment-related factors, type of surgery, tumor size, histological subtype, nodal status, and molecular subtype were taken into consideration. Patient records were evaluated over a period of twelve years (March 2007 to March 2019). Age-wise distribution of molecular subtypes was also taken into consideration. Manavata Clinical Research Institute Ethics Committee approval (ACDMW-00003) was obtained prior to the commencement of the study. Informed consent from all patients were obtained.

Data collection

All records were collected from the hospital electronic medical records. The histopathological and immunohistochemical (IHC) examination was performed in accordance with the College of American Pathologists/American Society of Clinical Oncology (CAP/ASCO) guidelines.

ER and PR scoring for all cases was done using Allred scoring. ER and PR were considered positive for cases, which scored 3+ or more on Allred score. HER2 scoring was done according to the ASCO/CAP guidelines. We classified breast cancer cases in 4 subtypes based on hormonal receptor and Her2 status. This were luminal A (ER+ and/or PR+/HER2-), luminal B (ER+ and/or PR+/HER2+), HER2-enriched (ER- and PR-/HER2+) and Basal like (ER- and PR-/HER2-). Those patients who had Her2 2+ expression (Equivocal) were not included in molecular subtype analysis.

Statistical Package for the Social Sciences version 22 (IBM Corp.; Armonk, NY, USA) was used for data analysis. We used descriptive analysis to present our results.

Results

The patient's age ranged from 22 to 100 years with a median age of 50.02 years. The 41-50 age group represented most of the patients (31.3%) followed by the 51-60 age group (27.6%), 31-40 age group (16.9%), 61-70 age group (15.4%), above 70 years (5.8%), and less than 30 years (3.1%) (Table 1). In context to gender, 99.1% (2043) comprised of females while 0.9% (19) comprised of males (Figure 1). In context to laterality, 51.2% (1056) had left-sided breast cancer, 47.4% (978) had right-sided breast cancer, followed by those with bilateral breast cancer, 17 (0.8%) (Figure 2).

In context to intent of treatment, majority of our patients, i.e. 90% (1860) received radical treatment followed by 10% (202) who received

Table 1. Age-wise distribution of breast cancer patients

Age group	Number	%
< 30	63	3.1
31-40	348	16.9
41-50	645	31.3
51-60	569	27.6
61-70	317	15.4
>70	120	5.8

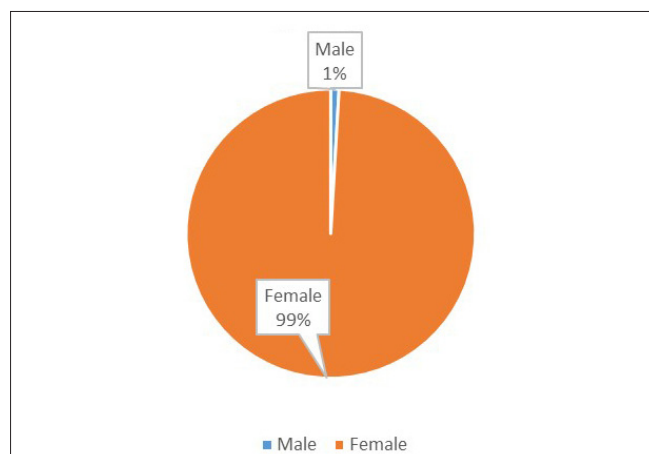


Figure 1. Gender distribution of breast cancer at our centre

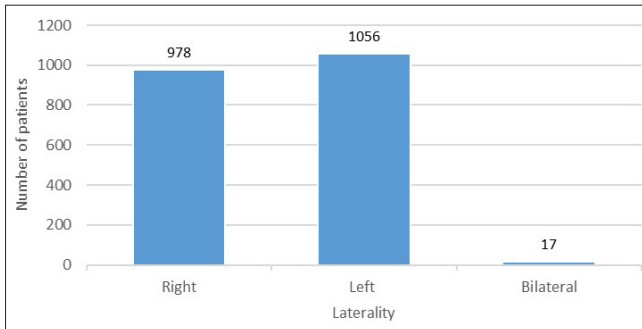


Figure 2. Distribution of cases as per laterality

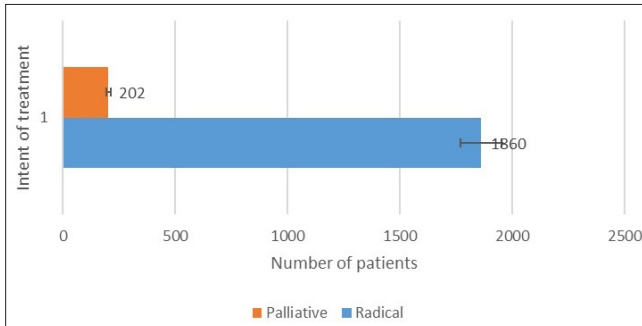


Figure 3. Distribution of cases as per intent of treatment

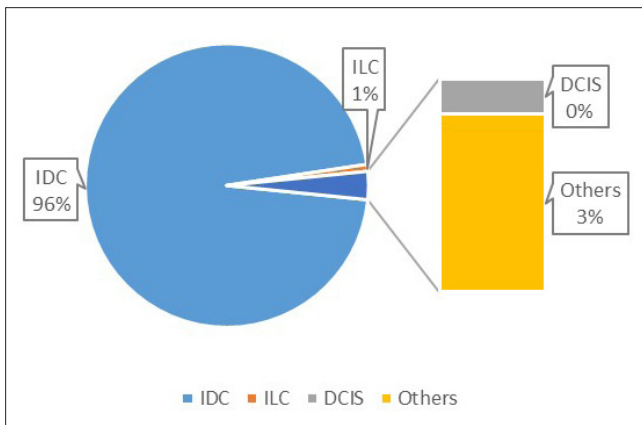


Figure 4. Distribution of cases based on histological type

palliative treatment. At our hospital, 53% (972) patients underwent modified radical mastectomy (MRM) while 47% (869) underwent breast conservation treatment (Figure 3).

The mean median tumour size was 3.0 cm. The tumour size ranged between 0 to 18 cm. At our centre, patients with breast cancer present with varying histological subtypes. While 96% (1980) of the patients had invasive ductal carcinoma, 0.8% (16) had invasive lobular carcinoma and 0.5% (11) had ductal carcinoma in situ, 2.7% (55) had other histological subtypes (Figure 4). In the context of nodal involvement, 62.5% (1289) were found to have nodal involvement while 37.5% (773) had no nodal involvement (Table 2). The overall incidence of Hormonal Receptor-positive patients (either ER or PR or both) was 56.4% (1162).

Among the molecular subtypes, Luminal A was the most common one (37%) followed by basal-like (26%), HER2 rich (11.1%), and luminal B (7.6%). We also had patients with unclassified subtypes (18.3%) due to the equivocal status of HER2 receptor (Figure 5).

Table 2. Number of patients based on nodal involvement

Age group	Number	%
Positive	1289	62.5
Negative	773	37.5

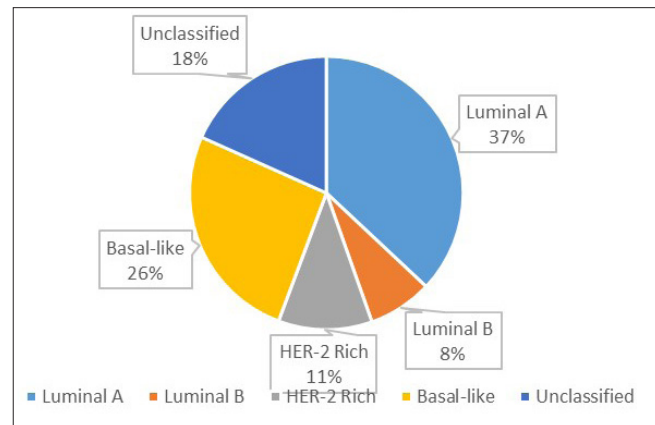


Figure 5. Distribution of cases as per molecular subtypes

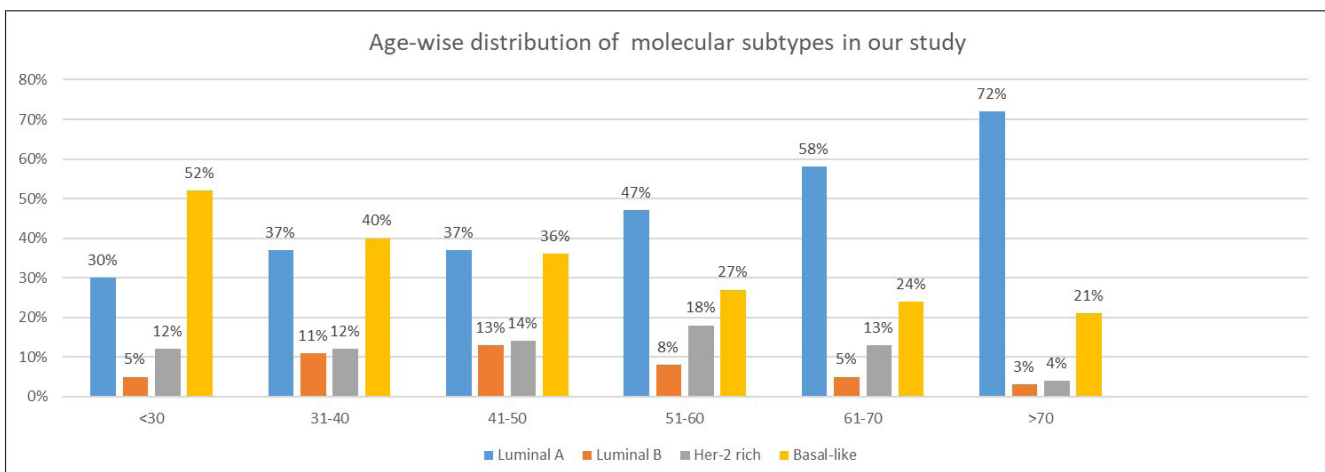


Figure 6. Age-wise distribution of molecular subtypes in our study

Table 3. Incidence of various subtypes based on international studies

Study	Luminal A	Luminal B	HER2 enriched	Basal-like	Total no of patients
British Columbia Cancer Agency [16,17]	71%	6%	7%	15%	3348
Mayo Clinic Breast Cancer study [18]	86%	9%	2%	4%	256
Vancouver General Hospital study [19]	78%	4%	6%	12%	246
University of British Columbia [20].	42%	15%	17%	26%	365
Carolina breast cancer study [21].	51.4%	15.5%	6.6%	26.4%	496
Dawood et al. [22].	65.8%	14.3%	4.9%	15%	1945
Mane et al. [11]	43.8%	14.8%	16.1%	25.3%	521
Tubtimhin et al. [23]	31.6%	15.6%	9.9%	11.3%	523
Elidrissi Errahhali et al. [24]	61.1%	16.1%	8.6%	14.2%	2260
Our study	37%	8%	11%	26%	2062

Discussion and Conclusion

Breast cancer remains one of the leading causes of death among women globally. It is a heterogeneous and complex disease attributed to clinical, pathological, and biological factors that vary from one population to another. Identifying these prognostic factors is key for the successful management of breast cancer patients. However, molecular classification of breast cancer has emerged as a vital tool for optimal patient management. Thus, to gain insights into breast cancer and molecular subtypes among Indian women, we analyzed 2062 breast cancer patients from our hospital database. Thus, to the best of our knowledge, this paper represents one of the largest studies in India on breast cancer using a large series of patients.

The study population in our study comprised of 2062 patients ranging between 22-100 years with a mean age of 51.18 years. Our findings are similar to those reported by Mane et al. (11) In our case, 37% of patients were luminal A, 8% were luminal B, 11% were HER2 rich, and 26% were basal-like. In the case of Mane et al. (11) 43.8% were luminal A, 14.8% were luminal B, 16.1% were Basal-like, and 16.1% were HER2 rich.

The age-specific incidence rates of breast cancer vary among Western and Asian population. In Asian population, breast cancer is characterized at an early age as contrast to advancing age among Western women. The age-specific incidence decreases or plateaus after 50 years in Asian women (12-15).

In our case, luminal A (37%) was the most predominant histopathological subtype observed followed by basal-like, HER2 rich, luminal B, and other unclassified subtypes. As per international studies, the incidence of luminal A has remained predominant followed by luminal B, HER2, and basal-like (Table 3) (16-24). We also observed that the incidence of Luminal Type A subtype increases with age. The incidence rate of the luminal A subtype peaked among patients aged >70 years (72%) (Figure 6). In Our study, the incidence of luminal B cancers was much more evenly distributed, with almost similar rates among patients aged 50–59, 60–69 and >70 years respectively. In our case, basal-like histopathological subtype was found to be predominant. The rate of triple negative or basal-like subtype in our case is more or less similar to other national and international studies (16-24).

The age-wise distribution based on molecular subtypes have been described in Figure 6. The mean tumor size in our study was 3.8 cm while 1430 (69%) of patients had a tumor size of more than 2 cm. Kumar et al. (25) from India also found similar results. They reported mean tumor size 3.4 cm and 85.8% of their cases had a tumor size more than 2 cm. However, Zhu et al. (26) reported mean size of 2.1 cm. The higher mean tumor size in our study and in India may be due to late presentation during the progression of the disease because of the existing social circumstances in this subcontinent. Another important cause may be the lack of mammographic screening program and cancer awareness.

As per the literature, HER2 rich molecular subtype is observed in about 15% to 20% of breast cancers (27). In our case, HER2 rich subtype was observed in 11.2% of patients. However, the number is less than expected as we did not include patients with equivocal (2+) Her2 receptor status. In our study, 181 (8.8%) patients had equivocal (2+) HER2 receptor expression. As per the recommendations of the American Society of Oncology and College of American Pathologist, Fluorescence in situ hybridization (FISH) could not be performed for HER2 equivocal cases. This is a major limitation as it could have helped in obtaining precise results of prevalence of molecular subtypes of this entity. In our study, the rate of HER2-enriched cancers peaked among those aged between 51–60 (Figure 6) and the distribution was most skewed toward the younger age groups.

Although we provide a comprehensive overview on the prevalence of several molecular subtypes in our institute, there are several limitations to our findings. We have not considered Ki-67, cytokeratin 5/6, and epidermal growth factor receptor-1 (EGFR-1) factors. We have not taken into consideration about menopausal status, stage, histological grade, vascular emboli status, post-and mastectomy radiation details.

Our study found that 4th & 5th decades are the most affected age groups by breast carcinoma in this region. The mean size of the tumors and axillary lymph node involvement were found to be high in this study. In conclusion, luminal A was predominant followed by basal-like, HER2 rich, and luminal B. Identification of Basal like breast cancer, a highly aggressive, biologically and clinically distinct subtype different than its non-basal variant, is important for treatment planning and target therapy.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Manavata Clinical Research Institute.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.P., R.P., V.P., S.G., R.N.; Design - P.P., R.P., V.P., S.G., R.P., R.N.; Supervision - P.P., S.G., R.N.; Materials - P.P., R.P., V.P., S.G., R.P., R.N.; Data Collection and/or Processing - P.P., R.P., V.P., S.G., R.P.; Analysis and/or Interpretation - P.P., R.P., S.G.; Literature Search - P.P., R.P., V.P.; Writing Manuscript - L.F., Y.V.R.; Critical Review - R.N.

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

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Androgen Receptor Expression in Adenoid Cystic Carcinoma of Breast: A Subset of Seven Cases

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ABSTRACT

Objective: Adenoid cystic carcinoma (ACC) of the breast is an uncommon salivary type of breast carcinoma. It is a triple negative breast carcinoma with a basal-like phenotype that behaves in an indolent manner. Herein, we aimed to document clinicopathologic findings and hormone receptor status of ACC in the breast diagnosed in our institution during an eleven-year period.

Materials and Methods: Medical data of cases diagnosed as adenoid cystic carcinoma in the breast between January 2006 and December 2016 were retrospectively reviewed from hospital data base. Paraffin blocks of seven cases were retrieved from the archive of Pathology Department and androgen receptor (AR) immunohistochemistry was applied to each case.

Results: All of the cases diagnosed as ACC were females with a mean age 56.2. Solid growth pattern was present in two cases. P63 was constantly expressed in the whole group, and at least one additional myoepithelial marker (calponin, caldesmon, etc.) was co-expressed in tumors. While weak estrogen receptor expression was detected only in one patient, AR was strikingly expressed in majority (85.7%) of the tumors.

Conclusion: To our knowledge, our series is the first to report such high levels of AR expression. This new finding, in turn, suggests considering hormonal therapy as an option in the management of ACC of the breast.

Keywords: Breast, adenoid cystic carcinoma, hormone therapy

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Introduction

Adenoid cystic carcinoma (ACC) of the breast is an uncommon salivary type of breast carcinoma which represents less than 0.1% of all breast malignancies. ACC of the breast is typically a triple negative carcinoma with rare axillary involvement, not in more than 5% of all cases (1). Similar to other breast malignancies, it is mostly seen in women in their 60s and 70s. The most common symptom is a palpable mass. Grossly, the tumor is a firm mass with a cystic cut surface, ranging in diameter from 1 to 3 cm. Histologically, it is composed of two types of cells: ductal epithelial cells lining true glandular luminal and basal/myoepithelial type cells surrounding eosinophilic cylinders composed of basement membrane like material (2). Similar to the ACC of the salivary gland, proportion of solid growth is the determinant of tumor grade: tumors with either cribriform or tubulo-trabecular pattern lacking solid areas are classified as grade I, tumors with ≤30% of solid growth as grade II, and tumors with >30% solid growth as grade III (3). It is generally negative for estrogen and progesterone receptors (ER and PR, respectively) as well as HER2/neu (c-erbB2). The c-Kit (CD117) positivity is a distinguishing characteristic for luminal epithelial cells. However, androgen receptor (AR) status of this rare tumor has not been well documented. Akin to its salivary gland counterparts, ACCs of the breast are characterized by the t(6;9) (q22-23; p23-24) chromosomal translocation, which generates fusion transcripts involving the oncogene MYB and the transcription factor gene NFIB (3, 4). Due to its rare incidence, the diagnosis and treatment protocol of this tumor is challenging (1-3, 5). Herein, we present a 10-year institutional feedback on ACC.

Materials and Methods

The medical records of seven patients diagnosed with ACC of the breast between January 2006 and December 2016 were retrospectively retrieved from our local data base and reviewed in relation to the age at diagnosis, presenting complaints, operation modality, tumor size and loca-

tion, histopathologic features such as tumor grade and immunophenotype, axillary status, postoperative treatment choices [chemotherapy (CT) and radiation therapy (RT)], median follow-up period with outcome (i.e. overall survival and disease-free survival). AR immunohistochemically (IHC) was applied to one representative block in all cases. All IHC assays were performed by Leica BOND-III Fully Automated IHC&ISH Staining System (Leica Biosystems, Weltzar, Germany) The primary AR antibody (Clone EP 120, Cell Marque Sigma Aldrich Company, Darmstadt, Germany) was then applied at 1:150 dilution and incubated for 1 h.

Ethics committee approval was received for this study from the ethics committee of İzmir Katip Celebi University School of Medicine (2019-GOKAE-1166). Written informed consent was obtained from patients who participated in this study.

Results

We found seven cases with ACC of the breast in an eleven year period. Out of seven 4 were consultation cases. The median age of the patients was 58, with a mean of 56.2. All patients presented with a palpable mass in the breast, except one with breast pain. None of the patients had a significant family history. Two of 7 patients (28.6%) developed recurrences following their primary treatment; recurrences occurred four years and sixteen years after the first diagnosis, in cases#1 and

#7, respectively. Left breast involvement was noted in six cases. Out of the seven patients, three underwent modified radical mastectomy (MRM), two breast-conserving surgery (BCS) with axillary dissection, one BCS with negative sentinel lymph node sampling and the last one, BCS only. Mean tumor size was 4.08 cm (Table 1). Majority of the tumors showed tubular-trabecular and cribriform growth patterns. In addition, glandular and pseudo-glandular structures were noted. Solid pattern of ACC was noted in two cases (cases#3 and #5) (Figure 1). The glands were formed by cells with round to oval nuclei and eosinophilic cytoplasm. Luminal PAS positive neutral mucin was present. Pseudo-cystic spaces were surrounded by cells with oval nuclei and scant cytoplasm. Eosinophilic basal membrane-like material was noted intermingling with glandular areas (Figure 2). Existence of solid component implies worse prognosis, however grading of ACC is still controversial (6). Only a single (14.3%) case of our series had a solid component (<30%, grade 2).

Six cases had neither ER nor PR hormone receptor expression, one showed (case #2) focal and weak ER positivity (5%). None of the cases showed HER2 positivity. Six tumors demonstrated cytoplasmic CD-117 expression (Figure 3). Of the applied myoepithelial markers such as calponin, caldesmon and smooth muscle actin, at least one was positive in each case. While CD10 was negative, p63 was steadily expressed in all cases. Positive expression in basal keratins such as keratin5/6 or

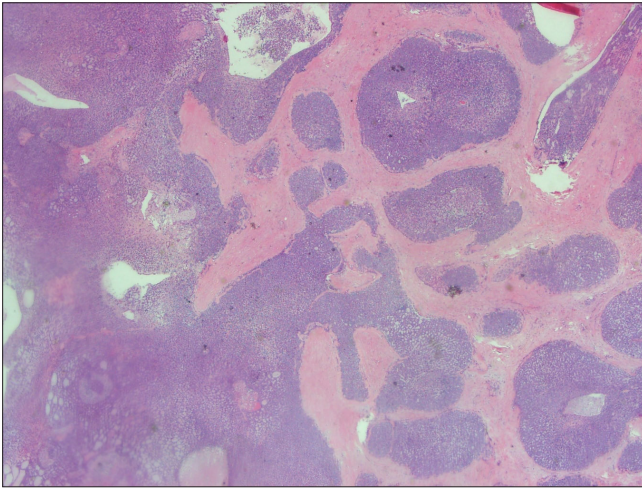


Figure 1. Solid growth pattern in ACC

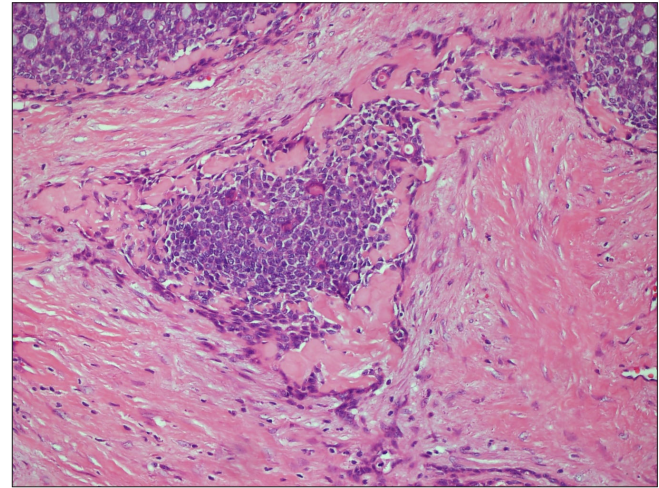


Figure 2. Basal membrane- like matrix surrounding tumoral nests

Table 1. Demographic features with treatment modalities and follow-up period of the cases

Case no	Age	Side/Operation	Axillary status	Treatment	Follow-up (mts)
1*†	58	L/MRM	RLH	CT+RT	96
2	58	L/BCS+AD	RLH	CT+HT	120
3‡	44	L/BCS+AD	RLH	CT+HT	86
4‡	57	L/BCS	Unknown	RT	84
5‡	50	R/BCS+SLN	RLH	CT	81
6	68	L/MRM	RLH	CT+RT	45
7**	59	L/MRM	RLH	CT+RT	204

BCS: Breast conserving surgery; AD: Axillary dissection; SLN: Sentinel lymph node; MRM: Modified radical mastectomy; mts: Months; CT: Chemotherapy; RT: Radiation therapy; HT: Hormone therapy *Recurrence

†Exitus

‡Consultation case

Table 2. Immunohistochemical results of the tumors

Case no	Size (cm)	Grade	ER/PR	c-erbB2	AR	Ki67	BKs	CD117	P63	MEs
1	7.5	1	N/N	N	30% 1 (+)	%20	P	P	P	N
2	3	1	P/N	N	10% 3 (+)	15%	P	P	P	N
3	5	2	N/N	N	2% 1 (+)	%20	P	P	P	N
4	3	1	N/N	N	20% 2 (+)	10%	P	P	P	N
5	3	2	N/N	N	N	40%	P	P	P	N
6	3	1	N/N	N	1% 1 (+)	15%	P	P	P	P
7	?	1	N/N	N	10% 2 (+)	15%	P	P	P	P

ER: Estrogen receptor; PR: Progesterone receptor; N: Negative; P: Positive; AR: Androgen Receptor; BKs: Basal keratins; MEs: Calponin; caldesmon; smooth muscle actin

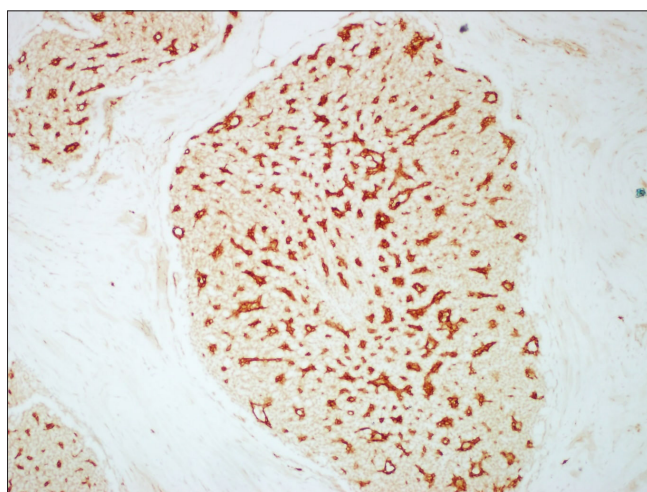


Figure 3. CD117 expression of the tumor cells

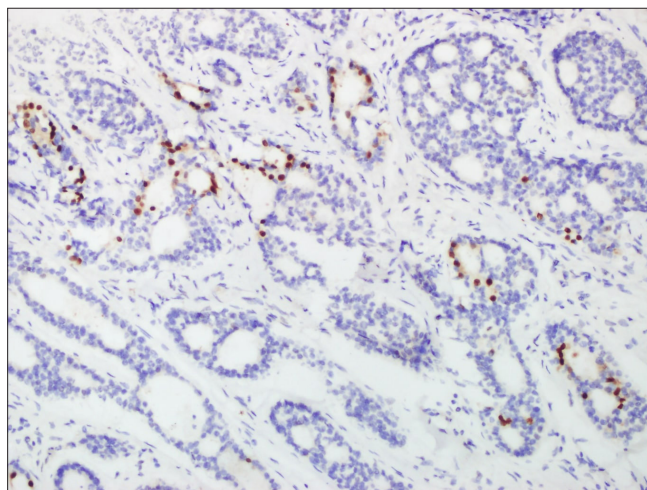


Figure 4. Nuclear AR positivity

keratin 14 was also conspicuous. Immunohistochemical test results have been shown in Table 2. AR positivity were noted in six cases (Figure 4). Percentage of AR IHC staining ranged from 1 to 30%, while staining intensity was ranked as weak (1+), moderate (2+) and strong (3+).

All cases of the series received either CT or RT, or both. Case #7 who had not undergone any post-operative treatment i.e. CT/RT follow-

ing the MRM, received both CT and RT after recurrence. Maximum follow-up period was 204 months with a mean of 102.2 months. All cases are alive, except for case #1 who died of an unknown cause eight years after the first diagnosis (Table 1).

Discussion and Conclusion

Adenoid cystic carcinoma of the breast is mostly seen in adult women with a mean age of 59-63, as in our series (3, 7, 8).

Although, the majority of tumors were localized in the left breast in our series, there is no significant side predilection (2, 9). ACC of the breast is widely treated by BCS (3, 4, 7, 10). In the current study two cases were treated by BCS with axillary dissection, one case by BCS with sentinel lymph node sampling while one case was treated by BCS only. There were three axillary dissections performed in our series; one of them being sentinel lymph node sampling with a negative result. Since ACC is not a tumor with a tendency to metastasize to the lymph nodes, axillary dissection is not advised (7). The size of ACC varies from 0.5 to 12 cm with a mean of 1.8 to 3.5 cm in published series. Herein, the mean diameter was 3 cm in concordance with the literature (2, 3, 7, 8, 11-14). Histologically the tumor consists of epithelial and myoepithelial cells arranged in various architectural conformations such as classic tubular, trabecular, cribriform or solid. There were two cases containing solid components in our series. Recurrence was observed in case #1 only.

Based on immunohistochemical studies, ACCs are essentially hormone receptor (ER and PR) and HER2 negative tumors, which tend to express one or more basal/myoepithelial cell markers (CK5/6 and CK14) (7, 8, 11, 15). In our series, PR and c-erbB2 expressions were completely absent, while only a single weak ER positivity was observed, similar to the report of Viranic et al. (16). Applied basal markers such as keratin 5/6 and keratin 14 were strongly expressed in all tumors, and at least one myoepithelial differentiation marker expression was also present in our series. P63 nuclear positivity and CD117 expression was expectedly seen in all cases (2, 3, 6-8, 13, 15).

The differential diagnosis of the carcinoma includes cribriform ductal carcinoma in situ, invasive cribriform carcinoma, which are both the positive expression ER and PR while ACC is ER and PR negative. The basement membrane-like material found in the lumens of ACC does not exist in both in situ and invasive cribriform carcinoma. The invasive cribriform carcinoma lacks myoepithelial cells related to its

invasive characteristics. Collagenous spherulosis is a benign breast tumor and should be considered in the differential diagnosis. The collagenous spherulosis has acidophilic spherules rich in collagen, which have positive Periodic Acid-Schiff (PAS) staining and accompany usual type epithelial hyperplasia.

Androgen receptor status in ACC of the breast is restricted with case reports in the English literature (17, 18). In our series AR-IHC application resulted in 85.7% positivity (6 cases). The only AR negative case demonstrated a predominantly solid growth pattern (case #5). Solid component was more prominent in one of the cases with weak AR positivity (case #3). To our knowledge, the current study is the first report in a subset of a series with positive AR immunohistochemical results in contrary to the published papers. Since ACC of breast is usually considered in triple-negative category, hormonal therapy is not an indication in patient management. Based on our findings, we suggest AR positive patients to be considered for hormone therapy in the future. Undoubtedly, this idea needs to be confirmed by consecutive supportive studies. Unlike other triple-negative breast cancers that are associated with poor prognosis, ACC has an overall excellent prognosis. This rather intriguing situation might be explained by the presence of myoepithelial differentiation as in salivary glands (19).

Molecular studies have showed a translocation in t(6;9) involving oncogene MYB and NFIB in ACC of breast similar to its counterpart in the salivary glands. MYB-NFIB fusion may be considered for new therapeutic strategies. However, relevant molecular studies could not be performed in the current series due to institutional limitations.

In conclusion, ACC is an uncommon salivary type tumor of the breast. It is mostly negative for steroid hormones i.e. ER, PR and c-erbB2 however in the current study 85.7% of the tumors showed AR positivity. Patients with ACC in breast may also benefit from targeted hormone therapy. Moreover, CD117 positivity should be regarded not only for diagnostic purposes, but also for targeted therapy modalities of ACC.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İzmir Katip Celebi University School of Medicine (2019-GOKAE-1166).

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Examination of Sexual Quality of Life and Dyadic Adjustment among Women with Mastectomy

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ABSTRACT

Objective: To investigate the effect of mastectomy on sexual quality of life and dyadic adjustment among women with breast cancer.

Materials and Methods: This study was carried out in an analytical and retrospective way by comparing women with mastectomy and the control group who had similarities to this group and did not have breast cancer. The study included 88 women who underwent mastectomy surgery at least 1 year and at most 5 years ago and 88 women who did not undergo mastectomy with matching ages and levels of education. The data were collected using the "Individual Characteristics Form", "Sexual Quality of Life-Female", and the "Dyadic Adjustment Scale" for women with and without mastectomy.

Results: In both groups sexual quality of life and dyadic adjustment were positively correlated. Sexual quality of life and dyadic adjustment of women with mastectomy were significantly lower compared to the control group. It was found that sexual quality of life improved as the education level of women with mastectomy increased. Also, sexual quality of life and dyadic adjustment were significantly higher in women with mastectomy whose income was equal to or greater than their expenditures compared to those with income lower than expenditures.

Conclusion: Sexual quality of life and dyadic adjustment of women with mastectomy are low than women without mastectomy. Nurses should to assess the risk of low dyadic adjustment and sexual quality of life, educate and consultant women on how they can maintain healthy sexual relationships and dyadic adjustment with their spouse after mastectomy.

Keywords: Breast cancer, mastectomy, sexual quality of life, dyadic adjustment

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Introduction

Breast cancer is the type of cancer most frequently seen among women both in the world and in Turkey (1) and its prevalence is increasing every year (2). The incidence of breast cancer in Turkey was 39 per hundred thousand in 2010 (2), increased to 43.8 per hundred thousand in 2015 (3). Although the number of women surviving from breast cancer increases with early detection and treatment options (4) cancer detection remains a disease that may affect psychosocial functionality even years after the end of medical treatment and threaten life (5).

Although breast conserving surgery is the most preferred surgical method for early-stage breast cancer in Turkey, modified radical mastectomy is common performed with various reasons such as the size or position of the tumour among others (6). Mastectomy which causes a permanent change in the appearance of women (7), may bring about fear, uncertainty, depression, and anxiety (5) as well as problems as to body image, sexual functioning, and close relationships for both of the spouse (5, 7, 8). Therefore, mastectomy has been not only described as a woman's illness but as a partner illness because of it causes serious threats for both woman and their partners (9).

The breast is perceived in Turkey and many other cultures as the principal symbol of femininity and sexuality. Mastectomy threatens the attractiveness and sexual desirability as well as the identity of woman (9). This contributes to the altered of body image, reduction of self-esteem, the lack of desire for sexual activity, low libido, and depression (10). Negative body image has strong effects on psychosocial adjustment and social functioning. On the other hand, iatrogenic menopause (low libido, vaginal lubrication, dyspareunia, and loss of sensitivity in breasts that were sensitive before) can impair sexuality considerably (5). Also, psychosocial problems such as depression and anxiety also contribute to sexual problems (11). Moreover, in our society in which sexuality is a taboo, the belief that women who

are fighting breast cancer will no longer interested in sexuality might prevent women from communicating on this matter, causing further sexual problems to be experienced (12).

Sexuality is the way an individual expresses their sexual assets (9) and it is an important determinant of the quality of relationship between couples (13). Sexual problems are common in women with breast cancer (8), which may negatively affect the satisfaction of the relationship between the couples (7, 8, 14). On the other hand, the quality of the relationship between couples in women with breast cancer is also a strong determinant of sexual functioning (15). Poor communication between the couples about low self-esteem and altered body image after mastectomy may leads to unresolved marriage conflicts and even divorces (9). In addition, loss of role in home or work due to illness, interruption of relationships and becoming dependent or fears about life may cause deterioration in close relationships and marriages (10, 16, 17). Research findings indicate couples a range of communication, intimacy and sexuality concerns which greatly impacted their interactions with each other (17).

In Turkey, although there are studies focusing on body images (7, 14) and sexual problems (11, 18) of women with mastectomy, in a limited number of studies have examined sexual functionality and couples' adjustment (19). Because mastectomy is considered as a couples' illness (9), there is need for further studies in order to understand the sexual quality of life and dyadic adjustment following mastectomy and to intervene to couples in coping with cancer. This study examined the couple adjustment and the quality of sexual life of women with mastectomy compared to women who did not undergo mastectomy.

Materials and Methods

This analytical and retrospective study was carried out in the breast polyclinic of a training hospital in Istanbul between June 2016 and January 2017. The inclusion criteria were being aged between 18 and 65, having a diagnosis and treatment at least 1 year and at most 5 years ago, not being in menopause, being in complete remission (the status of being in remission was determined according to the file information and physicians' statements), not having cancer treatment except for tamoxifen (Tamoxifen; CP Pharmaceuticals Ltd., Wrexham, England), not having breast reconstruction, being married or living with a partner, not having a treatment history due to other types of cancers, not having a medical or mental disorder disrupting the functionality of the husband and/or women, and volunteering to participate to study. Women who received systemic treatment such as chemotherapy were not included in the study.

The sample consisted of 88 women with mastectomy who met the inclusion criteria (mastectomy group) and 88 women without a diagnosis of breast cancer who were matched with the mastectomy group on the basis of age and level of education (control group). The records of women who had mastectomy in the last five years in the surgical service of the institution where the study was conducted were examined. A total of 169 women with mastectomy were determined who met the study inclusion criteria. We excluded six patients for they were deceased, five patients for they did not agree to participate, 11 patients for they could not be reached, and 59 patients for they did not meet the study inclusion criteria. Consequently, 88 women with mastectomy whose followed in the breast polyclinic were included in the study. The control group consisted of 88 women without a diagnosis of breast cancer who applied to the breast polyclinic, who were matched with the mastectomy group on the basis of age and level of education, and

who agreed to participate. In this group, 12 women rejected to participate and were not included in the study as they gave up filling in data collection forms five women.

In this study excluded age and menopause, which are known to affect breast cancer, and treatments used in breast cancer that have systemic effects due to the effects of mastectomy on sexual quality of life and couple adjustment. Women with mastectomy were compared to women in the control group that did not have breast cancer in order to minimize the differences that might arise in the variables of sexual quality of life and couple adjustment before and after the surgery.

Measures

The data were collected using the "Individual Characteristics Form", the "Sexual Quality of Life-Female (SQOL-F)", and the "Dyadic Adjustment Scale" for the mastectomy and control groups.

Individual Characteristics Form: This form consisted of common questions for women in both the mastectomy and control groups (age, level of education, marital status, employment status, income status, number of children) and questions related to medical treatment such as the time of breast cancer diagnosis, the time of surgery, the duration since the surgery, whether tamoxifen treatment was implemented, and whether chemotherapy and radiotherapy were implemented until 1 year ago.

Sexual Quality of Life-Female (SQOL-F): The sexual quality of life of women was measured using the Turkish version (20) of the SQOL-F, which was developed by Symonds et al. (21) in 2005. The sexual quality of life of women for the past 4 weeks was investigated using this scale, which can be used as a valid and reliable measurement tool for women aged 18-65. For the scale, consisting of 18 items, the scores of the items 1, 5, 9, 13, and 18 were reversed before calculating the scale items, which were scored between 1 and 6. The total score to be obtained from the scale was converted to 100. The formula [(raw score of the scale - 18) x 100/90] was used for this conversion. High scores indicate a good sexual quality of life (20). Cronbach's alpha value of the Turkish version of the scale was 0.83 (20). In this study, Cronbach's alpha value of the scale was 0.81."

Dyadic Adjustment Scale (DAS): The dyadic adjustment of the women was measured using the Turkish version (22) of the DAS, developed in 1976 by Spainer (23). The DAS, which was developed in order to measure the properties of dyadic relationships perceived by couples, consists of 32 items and 4 subscales. These are dyadic satisfaction, dyadic cohesion, dyadic consensus, and affectional expression. Of 32 questions that form the scale, 30 are Likert-type questions with 5 to 7 options. These questions have options varying from "always" to "never" and scores between 0 and 6. The other 2 questions, on the other hand, can be answered by "yes" or "no" and are scored as 0 or 1. The range of scale scores is between 0 and 151. High total scores indicate that the relationship of the individual or dyadic adjustment is good (22). The Cronbach's Alpha value of the scale, in study which was adapted to Turkish by Fırsıloğlu (22), was 0.92. In this study, Cronbach's Alpha value of the scale was 0.82.

The women in the mastectomy and control groups who met the study inclusion were first informed about the study. In order to achieve consistency in data collection, all the scales (including the items) were read out loud to the participants by a single researcher in face-to-face interviews. The participants completed all the scales, which took approximately 10-15 min.

Permission was obtained from the Marmara University Ethical Committee (28.03.2016/3) and the administration of the institution in which the study was carried out (13.04.2016/1600095081) prior to the study. Also, consent was taken from the authors of the Turkish versions of the SQOL-F and DAS. All the participants gave their written informed consent to participate in the study. The principles of the Helsinki Declaration were followed during the study.

Statistical Analysis

The Statistical Package for Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA) for Windows Evaluation Version was used for data analysis (Contract Number: GS-35F-5899H). The suitability of the data for normal distribution was analyzed with Shapiro Wilks test. The individual characteristics of the groups were calculated using descrip-

tive statistics (ratio, mean, standard deviation, median, minimum-maximum). The chi-square test was used for the compared of the individual characteristics of groups. The t-test for normal distribution data and Mann Whitney U test for non-normal distribution data was used in compare the mean scores obtained from the scales. The association between scale scores was tested Pearson's correlation analysis for normal distribution data and Spearman correlation analysis for non-normal distribution data. The statistical alpha significance level was accepted as $p < 0.05$.

Results

The mean age was 46.8 ± 5.5 (range, 33-55) for women with mastectomy and 45.7 ± 6.2 (range, 35-55) for women in the control group.

Table 1. Individual characteristics of the groups (n=176)

	Mastectomy group (n=88) n (%) or Mean (SD)	Control group (n=88) n (%) or Mean (SD)	p
Age (year) (min.-max.)	46.8±5.5 (33-55)	45.7±6.2 (35-55)	0.234
Age groups			
30-39	11 (12.5)	18 (20.5)	
40-49	44 (50)	36 (40.9)	
≥50	33 (37.5)	34 (38.6)	0.286
Education level			
≤Primary education	58 (65.9)	69 (78.4)	
≥Secondary education	30 (34.1)	19 (21.6)	0.543
Employment status			
Working	9 (10.2)	10 (11.4)	
Not working	79 (89.8)	78 (88.6)	0.100
Income status			
Less than revenue	42 (47.7)	36 (40.9)	
Equivalent to income and more	46 (52.3)	52 (59.1)	0.677
Child presence			
No	2 (2.3)	3 (3.4)	
Yes	86 (97.7)	85 (96.6)	0.684

Table 2. Comparison of the mean scores of the groups from sexual quality of life and dyadic adjustment scales (n=176)

	Mastectomy group (n=88)		Control group (n=88)		p
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
SQLQ total score	43.3±29.4	37.7 (0-100)	80.1±21.4	87.7 (5.5-100)	<0.001
DAS total score	98.5±28.8	102 (13-148)	123.8±22.6	129 (53-151)	<0.001
Satisfaction	34.1±9.7	36.5 (0-48)	41.4±6.6	43 (15-50)	<0.001
Cohesion	13.2±6.1	12.5 (0-24)	18.7±4.6	20 (6-24)	<0.001
Consensus	44.2±13.5	47.5 (3-65)	54.3±11.6	57 (20-65)	<0.001
Affectional expression	6.9±3.4	7 (0-12)	9.3±2.7	10 (0-12)	<0.001

SQLQ: Sexual Quality of Life Questionnaire; DAS: Dyadic Adjustment Scale

Also, 55.7% of women with mastectomy and 68.2% of women in the control group were primary school graduates and all of them were married. The individual characteristics of women in both groups were presented in Table 1. No statistically significant difference was found between the groups in terms of individual characteristics ($p>0.05$).

When the clinical characteristics of women with mastectomy were examined, it was found detection of cancer approximately 32.4 ± 20.8 months ago and they underwent operation approximately 30.7 ± 20.9 months ago. Of these women, 89.8% ($n=79$) received chemotherapy (75%) and radiotherapy (69.3%) apart from surgical treatment and 38.6% ($n=34$) used tamoxifen.

Table 3. Association between the scores from the sexual quality of life and dyadic adjustment scales in the groups (N=176)

	Mastectomy group (n=88)					Control group (n=88)				
	SQL	DA	S	CH	CN	SQL	DA	S	CH	CN
Dyadic Adjustment (DA)	0.457 [†]					0.500 [†]				
Satisfaction (S)	0.267*	0.867 [†]				0.414 [†]	0.837 [†]			
Cohesion (CH)	0.383 [†]	0.813 [†]	0.620 [†]			0.388 [†]	0.799 [†]	0.544 [†]		
Consensus (CN)	0.476 [†]	0.928 [†]	0.681 [†]	0.658 [†]		0.433 [†]	0.959 [†]	0.698 [†]	0.717 [†]	
Affectional expression (AE)	0.538 [†]	0.861 [†]	0.681 [†]	0.717 [†]	0.771 [†]	0.625 [†]	0.798 [†]	0.596 [†]	0.542 [†]	0.758 [†]

SQL: Sexual Quality of Life; DA: Dyadic Adjustment; S: Satisfaction; CH: Cohesion; CN: Consensus; AE: Affectional expression

*Correlation is significant at the 0.05 level (2-tailed). †Correlation is significant at the 0.01 level (2-tailed)

Table 4. Scores of women with mastectomy from sexual quality of life and dyadic adjustment scales according to their individual and clinical characteristics (n=88)

Individual and clinical characteristics	n	Sexual quality of life		Dyadic adjustment	
		Mean±SD	p	Mean ± SD	p
Age groups					
<50 age	55	44.37±30.63	0.935	97.90±31.30	0.861
≥50 age	33	43.42±27.97		99.18±25.74	
Education level					
<Primary education	58	36.54±28.10	0.002	98.17±26.74	0.718
≥Secondary education	30	56.5±28.02		99.40±33.35	
Employment status					
Working	9	61.60±37.70	0.092	107.00±30.65	0.298
Not working	79	41.28±27.96		97.63±28.83	
Income status					
Less than revenue	42	33.35±26.05	0.003	88.90±30.55	0.004
Equivalent to income and more	46	52.50±29.74		107.43±26.61	
Number of children					
≤2	57	46.60±28.59	0.096	97.40±29.80	0.268
≥3	29	37.08±29.64		99.75±28.02	
Time after diagnosis of cancer					
≤2 year	43	47.51±29.40	0.203	99.16±27.55	0.770
≥3 year	45	39.40±29.35		98.04±30.58	
Time after surgery					
≤2 year	49	46.36±29.40	0.301	99.08±26.25	0.626
≥3 year	39	39.59±29.56		97.97±32.42	
Tamoxifen use					
Use	34	40.35±28.98	0.466	98.26±29.69	0.830
Disuse	54	45.26±29.92		98.79±28.80	

The comparison of the scores of the participants from sexual quality of life and dyadic adjustment scales were presented in Table 2. The total mean scores for both sexual quality of life and dyadic adjustment were significantly lower among women with mastectomy than in the control group ($p < 0.001$). Dyadic adjustment subscale mean scores also were significantly lower among women with mastectomy than women without mastectomy ($p < 0.001$).

The association between the scores obtained from the scales was investigated for each group and the results were given in Table 3. It was found that there was a positive correlation between sexual quality of life and couple adjustment in both groups.

When the scores that women with mastectomy obtained from the SQOL-F and DAS were compared according to their individual and clinical characteristics, no statistically significant difference was observed except for the level of education and income status ($p < 0.05$) (Table 4). In the assessment performed according to the level of education, women with an educational level of secondary school and above had higher scores for sexual quality of life than women with an educational level of primary school and below (56.5 ± 28.02 against 36.54 ± 28.10 , respectively) ($p = 0.002$). When compared to those whose income was lower than their expenditures, the women whose income was equal to or greater than their expenditures had significantly higher scores of both sexual quality of life (33.35 ± 26.05 against 52.50 ± 29.74 , respectively) and dyadic adjustment (88.90 ± 30.55 against 107.43 ± 26.61 , respectively) ($p = 0.003$ and $p = 0.004$, respectively).

Discussion and Conclusion

The aim of the present study was to determine whether mastectomy affected sexual quality of life and dyadic adjustment and to investigate the effects of individual characteristics of women with mastectomy on sexual quality of life and couple adjustment. Therefore, this study excluded age, menopause, and systemic treatments such as chemotherapy, which could affect sexual functionality apart from mastectomy. Furthermore, the study did not have a prospective design and the sexual quality of life and dyadic adjustment of the women at the time of the implementation were assessed. The study included women without a breast cancer diagnosis matched in age and level of education in order to have information as to these parameters before mastectomy and to determine changes that might have emerged after the surgery.

The study findings showed that mastectomy negatively affected sexual quality of life and dyadic adjustment. In the literature, although there are other studies that support present study findings but there are studies that do not support them. In studies focusing on sexual functions in women with breast cancer, it was reported that sexual functions of women with mastectomy were considerably affected compared to healthy women and they experienced problems such as dislike of sexual intercourse, decline in sexual desire, and difficulties in sexual arousal (8, 19). Burwell et al. (8) found that though sexual problems declined in time after mastectomy, they continued 1 year after the surgery. Similar results are reported in studies focusing on dyadic adjustment in women with mastectomy. Uçar et al. (7) and Al-Ghazal et al. (24) determined that mastectomy affected couples' adjustment negatively compared to healthy women. Fobair et al. (10) found that women aged below 40 experienced more problems related to body image and increased couple maladjustment.

In the present study, sexual quality of life and couple adjustment were assessed separately in each group. A positive correlation was deter-

mined between sexual quality of life and couple adjustment in both groups, implying that individuals with a high sexual quality of life had a higher couple adjustment or vice versa. This finding is similar with the literature which shows dyadic adjustment affects sexual functionality and sexual functionality affects dyadic adjustment (13, 15). In a study which was carried out to investigate the effects of the surgery type in breast cancer on body image, sexual functions, self-esteem, and dyadic adjustment reported that mastectomy disrupted body image and disrupted body image caused decline in sexual satisfaction and dyadic adjustment (19). Moreover, the authors of the present study emphasized the surgery type alone did not affect dyadic adjustment and the effect of dyadic adjustment and sexual adjustment on each other was more significant. These results indicate that it is important to assess sexual relationships and/or relational satisfaction and dyadic adjustment as well as physical and emotional requirements related to medical treatment while planning the care towards women with mastectomy and to address these during interventions towards couples in coping with cancer.

Another point investigated in the study was the effect of individual characteristics of women with mastectomy on sexual quality of life and dyadic adjustment. The study findings showed that the education level of women with mastectomy influenced sexual quality of life. Women with mastectomy with an educational level of secondary school and above had higher sexual quality of life than women with an educational level of primary school and below. Similarly, Aygin et al. (18) found that women with breast cancer with a low educational level experienced more sexual dysfunctions, Sertöz et al. (19) that sexual functionality increased as the level of education rose, and Huguhe et al. (25) that the level of education affected sexual life and university graduates had better sexual lives than primary school graduates. This might be because health perceptions of individuals get better as the level of education increases and these individuals do not stick to family/social value judgments in sexual matters and sexual myths.

Furthermore, similar to other studies (7, 26), the findings of this study showed that both sexual quality of life and dyadic adjustment were significantly better in women with mastectomy whose income was equal to or greater than their expenditures compared to those with income lower than expenditures. This might be because having a regular job and planning life according to a certain wage leads to having fewer worries about life and coping with the process of illness and treatment easier in financial terms. On the other hand, there are other studies reporting the income level do not affect sexual functions (27).

The literature reports varying results for the relationship between age and dyadic adjustment among women with mastectomy. Uçar et al. (7) reported that women with mastectomy aged 50 and above had lower dyadic adjustment, while Engel et al. (28) stated young women with mastectomy had better dyadic adjustment. Avis et al. (29) reported women with mastectomy aged over 50 had better dyadic adjustment. The findings of the present study showed that age did not have any effects on dyadic adjustment and sexual quality of life. There is a need for comprehensive studies investigating the effect of age on dyadic adjustment and sexual quality of life in women with mastectomy.

There are certain studies in the literature indicating that the number of children affects sexual dysfunction (12, 30). This may be due to the fact that a woman who has had multiple births gets physically exhausted and cannot spend sufficient time for herself, time spent for the husband decreases, and also because of the drawbacks of having

breast cancer. However, the findings of this study showed the number of children did not affect sexual quality of life and dyadic adjustment.

The findings of the present study are consistent with the literature results showing that the duration after the diagnosis of cancer and surgery in women with mastectomy did not affect sexual quality of life and dyadic adjustment (7, 14, 25). This may be associated with the fact that women with mastectomy included in the study received the diagnosis of cancer approximately 32 months ago and had surgery about 30 months ago, and in time they came to terms with the illness and returned to their daily lives. Additionally, the present study revealed that the use of tamoxifen did not affect sexual quality of life and dyadic adjustment, which is similar to the findings of previous studies (7, 11, 14). On the other hand, some studies report hormone therapy affects sexual functionality (31).

In conclusion, the findings of the study showed that sexual quality of life was directly associated with dyadic adjustment and that women with mastectomy had lower sexual quality of life and dyadic adjustment compared to women without mastectomy. Also, it was seen that sexual quality of life improved as the education and income level of women with mastectomy increased. It is important that nurses assess the psychosocial requirements of women with mastectomy with a holistic approach and implement nursing interventions towards providing information giving emotional and social support about this issue. Certain coping mechanisms towards couples might be helpful in increasing the mechanisms to cope with mastectomy and maintaining a close relationship. Nurses should to assess the risk of low dyadic adjustment and sexual quality of life and educate women on how they can maintain healthy sexual relationships with their spouse and to direct couples to such interventions as marriage counseling or dyadic counseling after the surgical procedure. Furthermore, extensive studies on the issue are recommended.

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Rheumatological Findings in Patients with Breast Cancer

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ABSTRACT

Objective: Breast Cancer (BC) is the most frequently diagnosed malignancy worldwide. Not only may BC be associated with rheumatic symptoms and diseases, but also the drugs used in the treatment of this disease, including aromatase inhibitors (AIs), may lead to musculoskeletal system symptoms. In this study, we aimed to investigate the spectrum of rheumatic symptoms and diseases developing in patients with BC having no previous diagnosis of any inflammatory rheumatic disease.

Materials and Methods: Patients with a history of BC referring to Rheumatology Outpatient Clinics with complaints of musculoskeletal system symptoms at two centers between 2008 and 2018 were screened retrospectively. Patients with a previous diagnosis of any inflammatory rheumatic diseases before the occurrence of BC were excluded. Demographic data, onset and duration of BC, as well as onset and duration of rheumatic symptoms/diseases were recorded. Relevant laboratory tests, including autoantibodies, available imaging findings and the treatments received were also registered.

Results: Mean age of 128 BC patients at the time of admission was found to be 54.76±8.21 years. Mean durations of disease for BC and rheumatic disorders were 85.705±15.507 and 60.84±19.20 months, respectively. Out of 128 BC patients, nearly one third (n: 41; 32.03%), developed an inflammatory rheumatic disease, and rheumatoid arthritis was the most frequent pathology. Nonspecific arthralgia and myalgia were more frequent in patients receiving AIs than those receiving tamoxifen, despite lack of significant difference (p=0.421, p=0.411).

Conclusion: Given that nearly one third of the patients developed an inflammatory rheumatic disease, it should be remembered that locomotor symptoms in patients with BC may be caused not only by bone metastasis or paraneoplastic effects, but they may also suggest the presence of associated rheumatic diseases.

Keywords: Breast cancer, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome

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Introduction

The risk of malignancy association is high in certain rheumatic diseases including dermatomyositis, polymyositis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjögren Syndrome (pSS) and Systemic Sclerosis (SSc) (1, 2). On the other hand, nonspecific rheumatic symptoms such as arthralgia, arthritis, myalgia and skin lesions, or typical inflammatory rheumatic diseases may occur in patients with malignancy. The malignancies causing rheumatic symptoms most frequently are leukemias and lymphomas. The relevant symptoms may develop due to metastasis involving bones, muscles and joints, or as a paraneoplastic syndrome, or the adverse effect of chemotherapeutic drugs (1, 3). Clinical presentations such as arthritis, Coombs positive hemolytic anemia, skin rash and weight loss that are frequently seen in patients with lymphoma, may be due to associated SLE, adult-onset Still's disease or a systemic vasculitis. Some rheumatic symptoms might be the first manifestation of an occult malignancy (23%), and tumor resection may lead to a regression in rheumatic symptoms (4). It has been shown that Aromatase Inhibitors (AIs) used in breast cancer (BC) therapy increases the risk of rheumatic diseases, especially RA (5).

The most common malignancy diagnosed worldwide is BC; more than one million cases are diagnosed with BC every year. It is the most frequent cause of cancer in women and the second most frequent cause of cancer deaths in women in United States (US) (6). In this study, we aimed to investigate locomotor system symptoms and the distribution of rheumatic diseases in patients with BC.

Materials and Methods

The data of 148 patients with BC referring to Rheumatology Outpatient Clinics due to musculoskeletal symptoms at two different centers (İzmir Katip Çelebi University Atatürk Teaching and Research Hospital and Muğla Sıtkı Koçman University Teaching and Research Hospital) between January 2008 and October 2018 were retrospectively evaluated. Twenty patients with a previous diagnosis of a certain rheumatic disease and/or with demonstrated bone metastasis were excluded. The remaining 128 patients with BC without bone metastasis or a previous diagnosis of any inflammatory rheumatic disease were included. The demographic data, onset and duration of BC,

as well as presence, onset and duration of rheumatologic symptoms (Sicca syndrome, photosensitivity, alopecia, Raynaud's phenomenon, arthralgia, arthritis, sclerodactyly, ocular manifestations, muscle weakness, muscle pain, inflammatory back pain, sausage finger, aphthous ulcers, genital ulcers and specific skin lesions) were recorded. Relevant laboratory tests, including erythrocyte sedimentation rate, C-reactive protein, complete blood count, hepatic and renal function tests, hepatitis markers, calcium, thyroid function tests and autoantibodies (antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-dsDNA and anti-extractable nuclear antigen antibodies) were noted. Available imaging findings and the treatments they received, including surgery, radiotherapy, chemotherapy and hormone therapy (particularly anastrozole and letrozole), were also recorded.

Table 1. Frequency of rheumatic symptoms in patients with breast cancer

Symptoms	Number (%)
Arthralgia	77 (60.1)
Monoarthritis	5 (3.90)
Oligoarthritis	7 (5.46)
Polyarthritis	22 (17.1)
Raynaud's Syndrome	7 (5.46)
Photosensitivity	2 (1.56)
Cutaneous vasculitis	2 (1.56)
Inflammatory back pain	4 (3.125)
Oral ulcerations	8 (6.25)
Genital ulcerations	4 (3.125)
Sicca symptoms	22 (17.1)
Myalgia	60 (46.8)
Dactylitis	2 (1.56)
Sclerodactyly	4 (3.125)
Anterior Uveitis	4 (3.125)

Table 2. Frequency of patients with autoantibody positivity and hypocomplementemia

	Number (%)
Rheumatoid Factor	12 (9.375)
Anti-Nuclear Antibody	21 (16.4)
Anti-Scl70	2 (1.56)
Anti-Sm	1 (0.78)
Anti-SSA/La	5 (3.90)
Anti-SSB/Ro	4 (3.125)
Anti-CCP	5 (3.90)
Anti-dsDNA	3 (2.34)
Anti-centromer	2 (1.56)
Low C4	1 (0.78)
Low C3	1 (0.78)

Among 128 patients with BC, those fulfilling the classification criteria of various rheumatic diseases including RA (7), pSS (8), SLE (9), SSs (10), ankylosing spondylitis (AS) (11), non-radiographic axial spondyloarthritis (nrAxSpA) (12), psoriatic arthritis (PsA) (13), Behçet's syndrome (BS) (14) and gout (15) were carefully noted.

This retrospective study was approved by the ethical board of Muğla Sıtkı Koçman University (158/180175).

Statistical Analysis

All the statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS Inc.; Chicago, IL, US). Descriptive analysis was used for the demographic and clinical characteristics. Statistical analysis of the difference between the groups with normal distribution was performed using chi-square test for qualitative data. $P < 0.05$ was considered to be statistically significant.

Results

At the time of referral, mean age of 128 patients with BC was found to be 54.76 ± 8.21 years. Mean disease durations of BC and rheumatic disorders were 85.705 ± 15.507 and 60.84 ± 19.20 months, respectively. The symptoms and findings suggestive of a rheumatic problem were given in Table 1, while laboratory abnormalities including autoantibody positivity were given in Table 2. Of the patients, 18% had bilateral mastectomy and 22% unilateral mastectomy operations, while 38% had a previous history of radiotherapy. At the time of admission to rheumatology outpatient clinics, 71 patients had been using AIs and 48 patients had been receiving tamoxifen. Nonspecific arthralgia

Table 3. Distribution of inflammatory rheumatic diseases observed in BC patients

Disease	Number (%)
Rheumatoid Arthritis	10 (7.81)
Primary Sjogren's Syndrome	7 (5.46)
Psoriatic Arthritis	6 (4.68)
Systemic Sclerosis	4 (3.125)
Gout Disease	4 (3.125)
Behçet's Syndrome	4 (3.125)
Systemic Lupus Erythematosus	3 (2.34)
Ankylosing Spondylitis	2 (1.56)
Non-radiographic axial spondyloarthritis	1 (0.78)

Table 4. The histopathological types of breast cancer in all patients developing a rheumatic disease

Disease	Invasive Ductal Cancer	Malign Epithelial Tumor	Invasive lobular Cancer
Rheumatoid arthritis (n:10)	4	4	2
Primary Sjogren's Syndrome (n:7)	2	5	-
Psoriatic Arthritis (n:6)	3	-	3
Systemic Sclerosis (n:4)	4	-	
Gout Disease (n:4)	2	1	1
Behçet's syndrome (n:4)	3	-	1
Systemic Lupus Erythematosus (n:3)	1	1	1
Ankylosing Spondylitis (n:2)	1	1	
Non-radiographic axial spondyloarthritis (n:1)	1	-	-

Table 5. Details of breast cancer management in patients developing rheumatoid arthritis

Age at the time of breast cancer diagnosis (years)	Chemotherapy	Radiotherapy	Operation	Tamoxifen
43	+	+	+	+
48	+	+	+	+
38	-	-	-	+
48	+	+	+	+
46	+	-	-	+
44	+	-	+	+
42	+	-	-	+
32	-	-	-	+
49	+	+	+	+
45	+	-	-	+

and myalgia were more frequent in patients receiving AIs than those receiving tamoxifen, despite lack of significant difference ($p=0.421$, $p=0.411$). Various inflammatory rheumatic diseases were diagnosed in 41 (32.03%) of the patients included in the study (Table 3). RA was the most frequent associated inflammatory rheumatic disease (n: 10; 7.81%), followed by pSS (n: 7; 5.46%) and PsA (n: 6; 4.68%). Besides, osteoporotic compression fractures were detected as the cause of vertebral pain in 3 (2.34%) patients. Three patients with vertebral fractures received AI therapy. The histopathological types of BC in all patients developing a rheumatic disease were given in Table-4. The features of those 10 patients developing RA, including their ages and details of BC management they received, were given in (Table-5). All of these patients were in pre-menopausal or peri-menopausal state with the ages ranging from 32 to 49 years (mean age $\pm$ SD: 43.5 $\pm$ 5.21years). Interestingly, all of them had a history of tamoxifen treatment.

Discussion and Conclusion

This study is notable for investigating the locomotor system symptoms and findings, as well as rheumatic diseases in BC patients with no previous diagnosis of any inflammatory rheumatic disease. Out of 128 BC patients, nearly one third (n: 41; 32.03%) developed an inflammatory rheumatic disease after the diagnosis of BC. RA was the most

frequent associated inflammatory rheumatic disease, followed by pSS, PsA, SSc, gout, Behçet's Syndrome, SLE, AS and nrAxSpA, with a decreased frequency. In consistent with literature data, we also found that nonspecific arthralgia and myalgia were more frequent in patients receiving AIs than those receiving tamoxifen, despite lack of significant difference. However, unlike Caprioli et al. (5), who reported the influence of AIs on the occurrence of RA in women with BC, we could not confirm this observation. Interestingly, all of those 10 patients developing RA had received tamoxifen treatment rather than AIs.

Tamoxifen and AIs are efficacious hormonal therapies in BC patients with hormone receptor positivity. Tamoxifen is a selective estrogen receptor modulator, while AIs suppress plasma estrogen level manifestly by preventing the conversion of androgens into estrogen by inhibiting or inactivating aromatase enzyme (16, 17). In general, tamoxifen is preferred for pre-menopausal patients, while AIs are used in post-menopausal patients. Given that occurrence of RA is more common in post-menopausal patients, there may be a bias with respect to association of AIs use and RA development in women with BC (5). Other than RA, musculoskeletal system complaints, such as arthralgia and morning stiffness, can be observed in patients using AIs. In a randomized controlled study, 21.3% of the patients receiving tamoxifen and 27.8% of the patients receiving AIs were reported to have musculo-

skeletal system symptoms (18). Crew et al. (19) observed arthralgia and morning stiffness in 47% and 44% of the patients using AIs, respectively. Likewise, Presant et al. (20) reported arthralgia and/or bone pain in 61% of the patients using AIs, causing cessation of AIs in 20% of these patients. In the study of Henry et al. (21), AI treatment had to be discontinued in 10% of the patients.

Given that, in a recent nationwide study, prevalence of RA in Turkey has been reported as 0.89% for females, the frequency of patients developing RA (7.81%) fulfilling ACR 2010 criteria (7) in our series of 128 patients with BC seems to be rather high. If we make the comparison according to age groups, prevalence of RA in the Turkish female age groups of 45-54 years, and 55-64 years, which are close to mean ages of BC patients included in this study, were 0.77% and 0.88%, respectively. The increased frequency of occurrence of inflammatory rheumatic diseases, especially RA may be explained possibly by presence of common genetic pathways contributing both to malignancy and autoimmunity tendency. Besides, therapeutic agents used for management of BC may also contribute. On the other hand, patients might have skeletal symptoms due to neuropathy (caused by chemotherapy) and paraneoplastic syndromes, leading to confusion. The histopathology and stage of BC may also affect the symptoms and clinical picture (22).

As also mentioned in the previous paragraphs, AIs are at the top of the list, among therapeutic agents used for the management of BC and associated with occurrence of RA. In a previous study performed by Caprioli et al. (5) and including 10,493 patients with BC, RA risk was found to be higher in those receiving AIs, compared to those receiving tamoxifen. Why we could not confirm this association and why all of our patients developing RA had received tamoxifen treatment rather than AIs, are difficult to explain. We certainly cannot claim a causal relationship between tamoxifen use and RA development. On the other hand, we also found nonspecific locomotor symptoms to be more frequent in patients receiving AIs in our study. It may be speculated that, some of these patients treated with AIs may also develop RA in the future, if they would be followed up long enough.

With respect to other rheumatic disease, in a study of Laroche et al. (23), eight out of 24 (33%) patients with BC receiving AIs were diagnosed with SS. Guidelli et al. (24) presented three cases diagnosed as SS within the first year of AIs use, based upon autoantibody positivity and minor salivary gland biopsy findings. In our study, 7(5.46%) patients had SS diagnosis by 2016 ACR/EULAR criteria (8) and there were more patients diagnosed with SS in the tamoxifen group (3.90%) with respect to AI group (1.56%).

The pathogenesis of induction of musculoskeletal symptoms and possibly the occurrence of rheumatic diseases following treatment with AIs is not known. Interestingly, Shim et al. (25) showed the development of severe autoimmune exocrinopathy in Aromatase Knockout (ArKO) mice. Based upon this observation, it may be speculated that deficiency or inhibition of aromatase enzyme resulting in estrogen deficiency might play a role in the occurrence of rheumatic diseases in patients with BC. However, since estrogen contributes to autoimmunity itself, it needs explanation how the deficiency of estrogen facilitates the occurrence of autoimmune diseases in patients with BC. Alternatively, possible common genetic tendency may explain the later occurrence of systemic autoimmune diseases in patients with BC.

In patients with BC receiving AIs, musculoskeletal complaints due to osteoporotic bone fractures may also be observed. In contrast to tamoxifen, AIs can cause bone mineral loss by reducing endogenous estrogen levels. Perez et al. (26) studied the effects of letrozole which is an AI on bone mineral density (BMD), and observed a manifest decrease in the pelvic and vertebral BMD values of their patients after 24 months of letrozole treatment. Similarly, Muslimani et al. (27) found a higher risk of osteoporosis in their patients receiving AIs. Three patients included in our study also experienced vertebral fractures and associated pain with L2-L4 BMD T scores less than 2.5. Only one of these three patients had received AIs.

In literature, most of the studies about the association of rheumatic and malignant diseases concentrate on the development of malignant diseases in patients with rheumatic diseases. In other words, an increased risk of developing various malignancies have been reported in many systemic inflammatory rheumatic diseases including RA, SLE, SSc (28), SS (29) and AS (30). However, in the present study, the primary diagnosis is BC, and later occurrence of rheumatic diseases is discussed, which may be considered as the other side of the coin.

The main limitation of the present study is the possible failure to notice vague symptoms of the rheumatic diseases before the diagnosis of BC. Given that the appearance of autoantibodies precedes the occurrence of clinical symptoms in many systemic autoimmune diseases, the patients might have omitted vague symptoms of the rheumatic disease before the diagnosis of BC. Hence, the patient history might have misled the physicians. On the other hand, chemotherapy of BC including corticosteroids and immunosuppressive agents, generally improves the symptoms of rheumatic diseases as well. Therefore, the initial symptoms of rheumatic diseases may be realized when BC improves resulting in cessation of chemotherapy.

In conclusion, we found that nearly one third of the patients with BC developed an inflammatory rheumatic disease, mostly RA. This may implicate that not only malignant diseases may occur during the course of systemic rheumatic diseases, but also the reverse might happen in patients with BC. It should also be remembered that locomotor symptoms in patients with BC may be caused not only by bone metastasis or paraneoplastic effects, but they may also suggest the presence of associated rheumatic diseases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Muğla Sıtkı Koçman University (158/180175).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

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The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis

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ABSTRACT

Objective: The aim of this study was to investigate the relationship between the inflammatory parameters including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and the prognosis of idiopathic granulomatous mastitis (IGM).

Materials and methods: In this retrospective study, a total of 41 patients with IGM who had no malignant disease or inflammatory pathologies were included between January 2010 and December 2017. The patients were divided into two groups according to presence or absence of recurrence. Subsequently, the relationship between patient characteristics, pre- and postoperative NLR and PLR levels and disease recurrence were evaluated.

Results: With a mean follow-up period of 28.4 months, 19.5% of patients were found to have recurrent IGM. Age, body mass index, patient characteristics such as oral contraceptive use, smoking status, and family history, surgical treatment and postoperative NLR, preoperative PLR, and postoperative PLR were not statistically significant between groups. However, only preoperative NLR was significantly associated with a recurrent IGM ($p=0.024$). Preoperative NLR predicted recurrence with a sensitivity of 62.5% and specificity of 84.8%.

Conclusion: These results demonstrated that a high level of NLR was predictive of poor outcome in patients with IGM.

Keywords: Granulomatous mastitis, neutrophils, platelets, ratios

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Introduction

Idiopathic granulomatous mastitis (IGM) is a rare chronic inflammatory disease of breast. It is a difficult entity for both clinicians and patients due to its diagnosis, prognosis, and related complications (1, 2). Although IGM is a histopathologically benign disease, its complications such as fistulas and recurrences make the disease behave like a malignant entity (3, 4). Its etiology remains unknown; however, some associate it with tuberculosis, sarcoidosis, mycotic or parasitic infections, local irritants, and autoimmune process (2, 4). There are case series in the literature from all over the world, mostly being reported in the Eastern countries, although there is no epidemiological evidence (3, 5, 6). Additionally, there is a still controversy in the diagnosis due to its clinical and radiological similarity to the malignant breast tumors (1, 2, 4, 6).

Idiopathic granulomatous mastitis can be diagnosed through biopsy, including fine-needle aspiration, core or excisional biopsy; and excisional biopsy is commonly reported superior to identify the presence or absence of malignancy (1, 3). Although there is no established marker for the recurrence of IGM, the most common factor and the main etiology is the failure in excision margins. The main treatment modality is surgery, and drug therapies have been still investigated including anti-inflammatory agents, corticosteroids, and antibiotics to treat the primary disease and prevent recurrences (1-3, 5). Recurrence may be observed at the rate of 5% to 50% despite wide surgical excision of IGM (7). Although IGM is a chronic and recurrent disease, there is an obvious lack of knowledge regarding its recurrence.

In the present study, we aimed to investigate the relationship between the inflammatory parameters including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and the prognosis of IGM.

Materials and Methods

In this retrospective study, a total of 50 patients' medical records were collected from two centers in Ankara, Turkey between January 2010 and December 2017. Nine patients were excluded from the study due to concomitant malignancy, inflammatory pathologies such as infections, fat necrosis, and foreign body reactions, or insufficient data (Figure 1). The study was carried out in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent was not required because of the retrospective nature of the study.

All of the patients underwent a clinical breast examination and an ultrasound examination of the affected breast; mammographic examination was performed as needed. Definitive diagnosis was obtained by fine-needle aspiration biopsy, core needle biopsy, or surgical excision. The pathological criteria for the diagnosis of IGM were presence of non-caseous granulomatous inflammation on breast lobule. All patients underwent a surgical excision of the lesion, based on the physical examination and ultrasound findings.

The main outcome of this study was recurrence of IGM. All patients were divided into two groups according to presence or absence of disease. Data on demographic features, patient characteristics, pertinent family history of IGM, diagnosis strategies, pre- and postoperative NLR and PLR levels, and clinical outcomes was garnered from the hospital database. Information about height and weight based on the patients' own statement in the preoperative period were also obtained from the database. The return of inflammatory signs, skin changes, and symptoms after a remission was accepted as recurrence. While preoperative parameters were measured before the surgical procedure, postoperative parameters were measured just before discharge.

Blood sample analysis

Platelet, lymphocyte, and neutrophil counts were measured as part of the automated complete blood cell count using a Coulter LH 750 hematology analyzer (Beckman Coulter, Fullerton, CA, USA). The measurements were performed using the similar technique in both centers. In addition, there was no change in the measurement process and the devices used during the study period. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and PLR was calculated by dividing the absolute platelets by the absolute lymphocytes.

Statistical Analysis

Data were expressed as mean $\pm$ standard deviation for continuous variables and frequency for categorical variables. The Shapiro-Wilk test was used to ensure the normality of the data. Numerical data were analyzed using Student's *t*-test for normally distributed variables or Mann-Whitney U test for non-normally distributed continuous variables. Two-tailed chi-square or Fisher's exact tests were used where appropriate to compare categorical variables. Receiver-operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of the preoperative NLR to predict recurrent disease. *p* value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences version 16.0 for Windows (SPSS Inc.; Chicago, IL, USA).

Results

The study included 41 female patients. The age ranged from 20 to 55 years (mean, 35.0 ± 7.3 years). The mean follow-up was 28.4 ± 10.1 months. 12.2% of patients were unmarried; the others were (87.8%) married. The vast majority of the patients (85.4%) gave a history of breastfeeding for 6 months or more. All patients, except two, were premenopausal. The mean BMI was 30.9 ± 5.4 kg/m². Of the 41 patients, 7 (17.1%) had a history of oral contraceptive use, 12 (29.3%) had a history of cigarette smoking. Only 4.9% of the cases were bilateral. The demographics and clinical characteristics of enrolled patients are detailed in Table 1.

The recurrence rate of IGM was 19.5% at one-year follow-up. Age ($p=0.594$), follow-up ($p=0.306$), BMI ($p=0.672$), and patient characteristics such as marital status ($p=0.596$), breastfeeding ($p=0.331$), oral contraceptive use ($p=0.416$), smoking habits ($p=0.158$), family history ($p=0.596$), or localization of the disease ($p=0.356$) were not statistically significant between patients with recurrence and those with no recurrence. Regarding inflammatory parameters, postoperative NLR, preoperative PLR, and postoperative PLR were not also found to be statistically significant between groups. However, patients with recurrence of IGM had significantly higher preoperative NLR (7.1 ± 4.5 vs. 3.3 ± 1.4) compared to others ($p=0.024$) (Table 2).

The ROC curves of preoperative NLR were found to be associated with IGM recurrence. The area under curve (AUC) for the preoperative NLR was 0.76 (95% CI 0.55–0.97; $p=0.024$). Using a cut-off

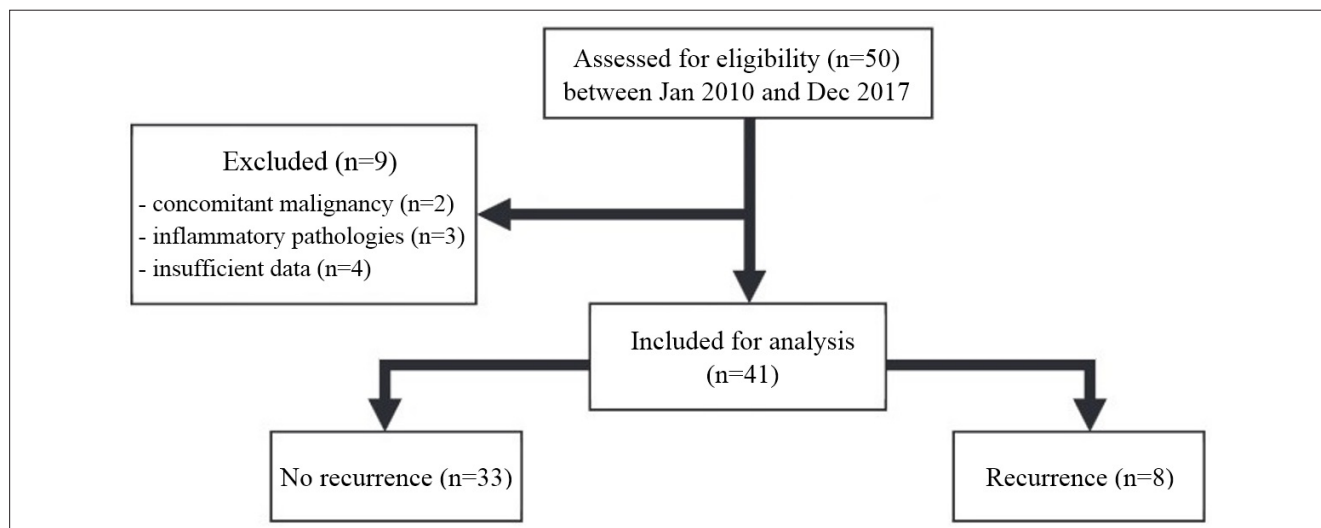


Table 1. The demographic and clinical characteristics of the study population (n=41)

Variables	
Age (years)	35.0±7.3
Follow-up (month)	28.4±10.1
BMI (kg/m ²)	30.9±5.4
Marital status, n (%)	
Unmarried	4 (12.2%)
Married	37 (87.8%)
Breastfeeding status, n (%)	
No	6 (14.6%)
Yes	35 (85.4%)
Menopausal status, n (%)	
Premenopausal	39 (95.1%)
Postmenopausal	2 (4.9%)
Oral contraceptive use, n (%)	7 (17.1%)
Cigarette smoking habits, n (%)	12 (29.3%)
Family history of IGM, n (%)	4 (9.8%)
Localization of the disease, n (%)	
Unilateral	39 (95.1%)
Bilateral	2 (4.9%)
Pathological diagnosis, n (%)	
Fine-needle aspiration biopsy	5 (12.2%)
Core needle biopsy	25 (61.0%)
Surgical excision	11 (26.8%)
Recurrence, n (%)	8 (19.5%)

IGM: idiopathic granulomatous mastitis; BMI: body mass index

value of 5.02, the preoperative NLR predicted recurrence with a sensitivity of 62.5% and specificity of 84.8%. When the study population was divided into 2 groups using a cut-off value of 5.02, the odds ratio (OR) of patients with an NLR greater than 5.02 was calculated as 9.3 (95% CI 1.67–52.06; $p=0.013$) (Figure 2).

Discussion and Conclusion

Idiopathic granulomatous mastitis is a histopathologically benign disease, although it is associated with recurrences and complications such as fistulation, ulceration, and delayed wound healing (1-3). It is a clinically chronic inflammatory disease of the breast of unclear etiology (2-7). Granulomatous mastitis is referred as 'idiopathic' when no etiologic explanation can be found after an appropriate and complete diagnostic evaluation. Therefore, other possible causes of granulomatous lesions, such as infections, systemic disorders, foreign body reaction, and fat necrosis must be excluded (1, 5). To-date, there is no consensus or guideline on the ideal treatment approach for patients with IGM. Several different treatment modalities are used for IGM, including antibiotic therapy, systemic or topical steroids, anti-inflammatory agents, surgical excision, and mastectomy (2, 4-8). Recurrence rates vary according to the treatment strategy, patient specific factors, and duration

Table 2. Comparison of the findings in patients with non-recurrent and recurrent IGM

Parameters	No recurrence (n=33)	Recurrence (n=8)	p
Age (years)	34.6±7.4	36.7±7.6	0.594
Follow-up (month)	27.8±10.3	30.8±9.5	0.306
BMI (kg/m ²)	30.7±5.5	31.7±5.7	0.672
Patient characteristics			
Married	30 (90.9%)	7 (87.5%)	0.596
Breastfeeding	29 (87.9%)	6 (75.0%)	0.331
Oral contraceptive use	5 (15.2%)	2 (25%)	0.416
Smoking	8 (24.2%)	4 (50.0%)	0.158
Positive family history	3 (9.1%)	1 (12.5%)	0.596
Bilateral IGM	1 (3.0%)	1 (12.5%)	0.356
Preoperative NLR	3.3±1.4	7.1±4.5	0.024
Postoperative NLR	3.3±3.7	2.8±0.8	0.778
Preoperative PLR	160.0±58.7	174.2±41.1	0.642
Postoperative PLR	156.1±46.4	149.7±30.3	0.628

BMI: body mass index; IGM: idiopathic granulomatous mastitis; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

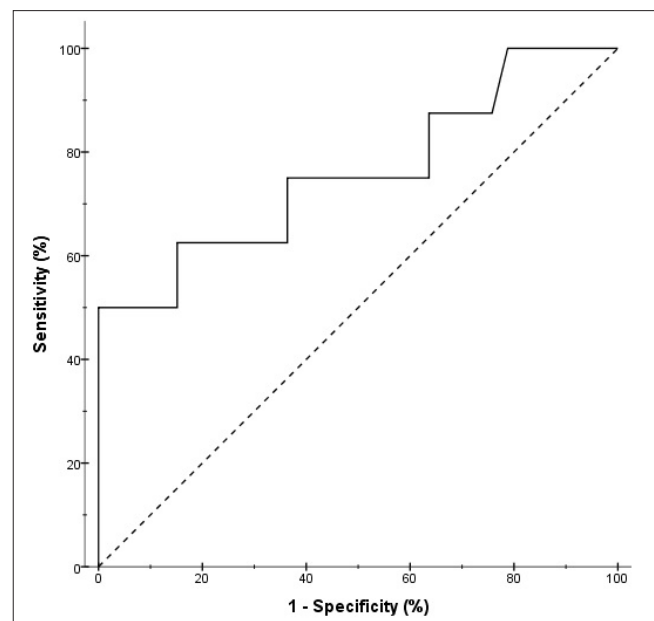


Figure 2. The receiver-operating characteristic (ROC) curve analysis of preoperative neutrophil to lymphocyte ratio for recurrence prediction

of follow-up. It is reported up to 50% despite wide surgical excision and even complete resolution (5-8).

In present study, 41 patients with IGM were evaluated with a mean follow-up time of 28.4 months. The follow-up periods were almost same in both groups. The mean age of the patients was 35 years, and only two patients were postmenopausal, which is consistent with the previous findings (4-7). Our recurrence rate of 19.5% is also comparable to the reported rates (5-7). We think that this low recurrence rate

is probably due to the fact that all patients were treated with the surgical removal of the lesions. A systemic review and meta-analysis by Lei et al. (8) revealed that complete remission rate of oral steroids (71.8%) was much lower than that of surgical managements (90.6%) and oral steroids plus surgical managements (94.5%). It was also reported that the recovery period of steroids was much longer when compared to surgical excision (8).

Idiopathic granulomatous mastitis is an inflammatory disease with high rates of recurrence which usually makes it difficult to follow and evaluate the results of surgical treatment. Various clinical, patients-related, and treatment-related factors may influence the prognosis of IGM. In a recent study by Yilmaz et al. (9), the mean number of births, duration of lactation, BMI, presence of fistulas, presence of abscess formation, and luminal inflammation were found to be significantly different between patients with recurrence and those with no recurrence. In addition, they developed a scoring system to predict IGM recurrence risk using clinical, radiological, and pathological factors. However, to date, there is no established marker for IGM to predict recurrence. This study compared the pre- and postoperative NLR and PLR levels of patients with and without recurrence. Moreover, several patient characteristics were compared between the groups. Age, BMI, breastfeeding, oral contraceptive use, smoking habits, family history, or localization of the disease were not found to be statistically significant between patients with recurrence and those with no recurrence; unlike other studies, which found an association between BMI (9), breastfeeding (6), or smoking (4, 6) and IGM recurrence. Regarding inflammatory parameters, the mean preoperative serum NLR level was significantly higher in patients with recurrence than in those without recurrence.

Neutrophil-to-lymphocyte ratio and PLR are found to be associated with inflammatory response and disease activity in a variety of autoimmune diseases and have been considered as the indicators of representing the severity of inflammation (10). Today, these parameters are being increasingly used as a prognostic marker for predicting prognosis of several diseases, and cancers (10-12). In a study, Pan et al. (10) demonstrated that NLR and PLR had positive correlation with disease activity in patients with Takayasu's arteritis. In a systematic review and meta-analysis, Zheng et al. (13) concluded that an increased pretreatment NLR or PLR significantly associated with poor outcomes for patients with hepatocellular carcinoma. Another systematic review and meta-analysis by Ethier et al. (14) revealed that high NLR was associated with an adverse overall survival and disease-free survival in patients with breast cancer. In the present study, increased preoperative NLR (cut-off value of 5.02) predicted IGM recurrence. Therefore, this simple marker can be used for the follow-up of the patients and be evaluated as a recurrence predictor. However, a similar association was not found for pre- or postoperative PLR levels.

A number of important limitations need to be considered. First, this study has a relatively low number of cases in both groups. In addition, there is no standard definition of recurrence or remission of IGM (8); thus, different definitions may lead to strikingly different conclusion. Considering that some authors suggest that IGM is an autoimmune process (2, 7), the relatively short follow-up period may be another limitation. Also, it was not evaluated whether the IGM lesions were unifocal or multifocal and the size of the lesions. Lastly, there are inherent selection biases that confound any retrospective cohort. Despite these limitations, it is the first study that focused on the prognostic values of NLR and PLR levels measured pre- and postoperatively in patients IGM treated with the surgical removal of the lesions.

Clinicians commonly use complete blood count in their daily practice particularly in inflammatory conditions and following the treatment responses. The use of NLR seems simple, cost-effective, and promising indicator of the prognosis and recurrence of IGM, which is a challenging disease for both clinicians and patients. However, PLR is not associated with the outcomes for patients with IGM.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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Post-Traumatic Growth in the Early Survival Phase: From Turkish Breast Cancer Survivors' Perspective

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ABSTRACT

Objective: The purpose of this descriptive phenomenological study was to explore the nature of post-traumatic growth (PTG) in Turkish breast cancer survivors in the post-treatment first two years.

Materials and Methods: Semi-structured in-depth interviews were conducted with 13 breast cancer survivors. Data were collected between August 2015 and January 2016 in the medical oncology outpatient clinic of a university hospital in Turkey.

Results: Two main themes were identified. They are as follows: making sense of the cancer (questioning life and death and religious meaning) and positive restoring (changes in values and increased coping skills).

Conclusion: Health care professionals should be aware of these positive changes in the post-treatment period in accordance with aspects of PTG and they should be designed programs directed towards facilitating and enhancing post-traumatic growth in the breast cancer survivors.

Keywords: Breast cancer, survivors, post-traumatic growth, qualitative study

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Introduction

The number of breast cancer survivors is increasing with advances in diagnostic techniques and treatment of breast cancer (1, 2). Despite this increase, breast cancer is a traumatic experience including serious biopsychosocial and existential changes (3). Although researchers have traditionally been interested in these negative changes following breast cancer, focusing only on negative effects of traumatic experiences causes failure to understand post-traumatic reactions (4). In fact, traumatic life events like breast cancer can result in positive changes called post-traumatic growth (PTG) (5, 6). Health care professionals knowing the nature of PTG after breast cancer can provide better guidance for breast cancer survivors in recognition of positive aspects of their lives facilitate positive interpretations of their disease experiences and strengthen them in terms of coping with negative effects of the cancer.

Post-traumatic growth is individuals' experiencing of meaningful positive changes arising from their struggles with major life difficulties. They experience a positive change in self-perception, interpersonal relationships and life philosophy (spiritual and existential changes) (6). The term "growth" means that these individuals have exceeded their prior adjustment abilities, psychological functioning or life awareness (6, 7). Although research in psycho-oncology focuses on negative outcomes of breast cancer, there has been a rise in the number of studies examining PTG in the breast cancer journey. However, there is limited information about post-treatment PTG in breast cancer survivors. Most of the relevant research has focused on predictors, prevalence and domains of PTG (5). In addition, the Post-traumatic Growth Inventory (PTGI) has been extensively used in adult cancer populations including breast cancer (7). PTGI includes five domains: personal strength, new possibilities, relating to others, appreciation for life, and spiritual change (8). Frequently described domains of PTG for breast cancer survivors are increased personal strength, enhanced appreciation of life and deeper relationships with others (9, 10). However, the quantitative methodology may cause difficulty in understanding and gaining a deep insight into life experiences of the survivors about each of five PTG domains and the ways through which growth and related variables mediate positive changes. Qualitative methodology can provide a rich understanding of PTG following breast cancer (11).

Only a few qualitative studies have specifically been directed towards explaining the nature of the PTG in the post-treatment period (12–14). One of these studies focused on positive changes in Japanese breast cancer survivors in different survival phases (post-surgical 1.2 to 26.5 years). The study showed that the survivors had awareness of death and life, strengthened trust in their families and friends, increased appreciation of life, awareness of self, empathy for others, hope for the future, willingness to help others and lifestyle changes (14). Fallah et al. (13) in their study on PTG in Iranian breast cancer survivors revealed the themes closeness to God, making meaning to suffering, and spiritual development, self-confidence, resiliency, improvement in problem solving and positive thinking skills, appreciation of life and thanks to God. In a qualitative study on Indian breast cancer survivors, closer, emphatic and warmer relationships, prioritizing oneself, feeling mentally stronger, positive changes in perspectives toward life, and richer spiritual dimension of life were described (12).

The present study is the first one carried out to describe the phenomenon of PTG in Turkish breast cancer survivors. Socio-cultural factors are environmental factors affecting PTG (15). In Turkish culture, cancer has negative connotations. Breast cancer patients identify cancer with death and suffering and its prognosis with uncertainty (16). One other factor likely to affect PTG can be related to social support. It plays an important role in Turkish culture. Some researchers have also noted that presence of social support can make great contributions to development of PTG (17, 18). The aim of this study was to explore the nature of PTG in Turkish breast cancer survivors. Results of the study are expected to provide guidance in development of effective interventions facilitating PTG and to provide insight into addressing PTG as a source of support for survivors' early adaptation to the post-treatment.

Materials and Methods

Design

In this study, a descriptive phenomenological approach was used. This approach helps to gain insight into the meaning of PTG in breast cancer survivors' life/world (19). We used the Consolidated Criteria for Reporting Qualitative Research (COREQ) to guide the reporting of this study (20).

Participants

The study was conducted on breast cancer survivors followed in a Medical Oncology outpatient clinic of a university hospital in Turkey. To recruit a diverse sample, variability in age, employment status and clinical parameters was achieved. Inclusion criteria were age of

over 18 years, completion of hospital-based treatment lasting minimum six months and maximum two years before the study and not having metastasis. First, patient records were examined in terms of the inclusion criteria and a list of potential participants was created. Each potential participant was contacted on the phone and was explained the aim of the study. Three survivors refused to participate in the study. Those agreeing to participate in the study were scheduled for interviews. The study sample consisted of 13 breast cancer survivors.

Data collection

Data were collected through semi-structured interviews by the first author, having knowledge and experience about the qualitative method. Before each interview, informed consent was obtained from the participant. The participants were individually interviewed in a one-to-one and face-to-face basis in a quiet, comfortable room in their home. The interviews were conducted in accordance with a semi-structured interview schedule including open-ended questions (Table 1). It was created by the researchers in light of the literature to help the participants describe their experiences in PTG. Each interview lasted between 30 and 47 min and was audiotape-recorded. The interviews were recorded with the same voice recorder and each participant was interviewed once. They continued until a saturation point at which no new information was obtained. Although data saturation was reached at the eleventh interview, the researcher conducted two more interviews.

Data analysis

All the interviews were verbatim transcribed by the first author. Data analysis was made independently by two researchers experienced in qualitative research. In a descriptive phenomenological study, only the data gathered are analyzed and the analysis is made only to describe the phenomenon without interpreting or explaining it and to shed light on the essence of the phenomenon (21). The analysis was inspired by Colaizzi's descriptive phenomenological data analysis method. It proceeded as follows: Each transcript was read and re-read until it could be divided into significant statements. These statements were coded, and a list of codes was created. Similarities and differences between the codes were determined and meanings were formulated from these statements. The formulated meanings were assigned into categories. Each category was named in accordance with its content. Then themes were defined, and the researchers agreed on the themes. The structure of the phenomenon was described. Finally, the participants' approval about the results of the research was obtained (22).

Trustworthiness

Trustworthiness approaches; credibility, transferability, dependability and confirmability were based in the research process (23). Credibility and transferability were achieved by using a semi-structured interview schedule and obtaining expert opinions about questions. The researchers tried to get a deep understanding of information obtained at the interviews. The participants with various backgrounds were included into the study so that differences related to positive life changes could be revealed. The research team consisted of two female researchers and they were trained in qualitative research. The interviews were conducted by the first author who educated and experienced about qualitative studies. To achieve dependability and confirmability, data analysis was made independently by two researchers. The consent of the participants regarding themes was obtained.

Table 1 Semi-Structured Interview Schedule

Breast cancer is an experience that affects a woman's life in many aspects. After this experience, women experience not only negative but also positive changes. Could you please tell me...

What positive life changes associated with breast cancer you have had?

What these changes are like?

In what areas of your life have you experienced these positive changes?

This study was approved by the ethical review boards at the Dokuz Eylül University. Only the women volunteering to participate in the study were included. Informed consent was obtained from all the participants before the interviews.

Results

The study sample comprised 13 breast cancer survivors with a mean age of 48.76 years. Of 13 women, five were high school graduates, 11 were married and 10 were unemployed. They had completed their hospital-based treatment of 13.30 months on average, prior to participation in the study (Table 2).

The findings showed that the women had a positive restoring process in the post-treatment period and made sense of cancer promoting PTG. Thus, two themes emerged: making sense of cancer and positive restoring (Figure 1).

Theme 1. Making Sense of Cancer

The women mentioned their interpretations of cancer while explaining their positive experiences. They defined breast cancer as a traumatic experience. They reported to question the meaning of cancer in their lives upon facing breast cancer. This theme involved the subthemes questioning life and death and religious meaning.

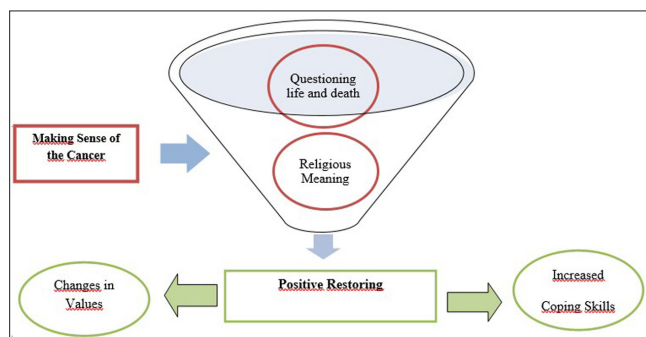


Figure 1. Schematic presentation of themes and sub-themes

Questioning life and death

The women mostly identified breast cancer with death. Diagnosis of cancer forced them to question life and death. They reported that they were aware of the reality of death and that this awareness had a contribution of increasing the value of life. "First, one thinks about life and death. Normally, no one thinks that death is something concrete and may happen to everyone. However, it is real. In view of this reality, one realizes that life is short." (Participant IX).

Religious meaning

Some women reported that they interpreted cancer based on their religious beliefs. They said their experience with cancer strengthened them and they attributed this to their religious interpretations of cancer. These women assumed that cancer was God's warning to a person in order to reorganize their life. For these women, God had a purpose in giving this disease, and for them, trying to understand this purpose was associated with growth. "God (Allah) warned me not to get upset about anything and to prioritize my own needs" (Participant II).

Some of the women said that they perceived the disease as a test given by God to check whether they are patient. They believed that, in this process, God was with them, and that they would be rewarded by God if they showed patience (such as healing from cancer). "I thought this disease was a test given by God. I stayed patient and grew stronger" (Participant XI).

Theme 2. Positive Restoring

The post-treatment period was a restoring process. The women reported to have positive life experiences during this restoring process. This theme involved the subthemes changes in values and increased coping skills.

Changes in values

Breast cancer caused the women to question their values. They described changes in the value of life, self-value and relationships after this questioning. The women reported that they recognized the value of life and felt more committed to life after breast cancer. "I used to live

Table 2. Sociodemographic Characteristics of the Survivors (n: 13)

Participant	Age (Years)	Education	Marital Status	Number of Children	Employment	Stage	Months since post-treatment
I	41	Primary School	Married	2	Not Employed	I	22
II	53	High School	Single	2	Not Employed	II	10
III	46	Primary School	Married	1	Not Employed	II	18
IV	40	High School	Married	1	Not Employed	II	11
V	48	Primary School	Married	2	Not Employed	II	9
VI	45	University	Married	0	Not Employed	I	14
VII	61	High School	Married	1	Not Employed	III	7
VIII	50	University	Married	1	Not Employed	II	17
IX	52	University	Married	1	Employed	II	20
X	70	University	Married	1	Not Employed	III	16
XI	39	High School	Married	0	Employed	II	9
XII	34	High School	Single	0	Employed	III	8
XIII	55	Primary School	Married	2	Not Employed	II	12

without being aware of beauty of life, but now I can say life is beautiful despite all difficulties. It is great to survive. I have found out it while struggling against the disease; I suffered from serious side-effects of chemotherapy" (Participant XII).

With the increased value of life, priorities of the women also changed. Being healthy became the main priority for the women. "Now I feel different from the past. I care about nothing except my health. I have discovered that nothing is more important than health" (Participant IV). Becoming aware of the value of life brought about seizing the day. "I understand how valuable every day is and consider a day as beautiful if it is spent with a loved one. I understand that nothing is important in life; neither money nor status is important" (Participant VIII). The women aware of the value of life noted that they did not postpone anything. "I've realized that life is short, and I must enjoy everything. I used to put off realizing my plans, but now I don't miss anything enjoyable" (Participant IV). The women also reported changes in self-value after breast cancer. They prioritized their own needs: "First, I meet my needs and then needs of others. I try doing things for myself. I used to take account of others' criticisms, but now they are unimportant for me" (Participant III).

Considered as a traumatic experience, having breast cancer caused changes in values attributed to relationships. The women realized that their families were very precious for them: "I've found out that life is not very important, but my family and loved ones are important (Participant XIII)." The women also questioned their relationships with others. "I've determined the degree of my relationship with each of my friends. Now I know how close my friends and my relatives are" (Participant XII). After this questioning, the women put an end to some of their relationships, but the value of their other relationships increased. "I became aware of my values such as respect. Now I've limited my relationships with friends who do not respect me. I've become aware of the value of my friends who gave both financial and social support during diagnosis and treatment of the disease. It appears that the real gain in life is to have real friends" (Participant III).

In addition to awareness of the value of their friends, the women described growth in the value of their relationships with their spouses. Some women mentioned that their bond with their spouses was strengthened. "I believe that I've become more committed to my husband. In fact, my husband is the only one who has always been with me" (Participant VIII). Moreover, the women were found to have more empathy concerning their relationships with others after breast cancer. Especially the women needing support from other women experiencing the same condition reported that they were willing to help women facing breast cancer. "I feel the need to help because of my experiences. Actually, I wanted to talk to somebody having had the same experiences" (Participant VIII).

Increased coping skills

The women described increased coping skills after their struggle against breast cancer. First, they revealed changes in meaning they attached to their problems. "I used to be obsessed with everything, but now I don't care about anything" (Participant V). Next, the women described a positive point of view and a positive reappraisal of stressors. "I try to think that everything, i.e. whatever I experience, will have a positive outcome. I believe that they have favorable outcomes. I think positive thinking will bring about positive effects" (Participant VII).

Furthermore, some women noted that they can be more tolerant. "I still give importance to problems, but I am able to be more tolerant. I think I can have a different attitude to the issue" (Participant IX).

While the women had difficulty in expressing their negative feelings initially, they easily talked about their feelings after the disease, which could be considered as an important progress. "I didn't use to tell Serpil, a friend, that I felt uneasy with her. She used to visit me and cause stress. However, now I've told her that she disturbs me" (Participant X). Some women also commented that they sought social support for management of stress. "I used to be reserved, but now I don't. I feel more comfortable. I used to disapprove of telling my husband about a quarrel between me and someone else, but now I can tell about such things comfortably" (Participant IV).

Some women noted that they could reject things after breast cancer: "I didn't use to say no, but now I can. I simply refuse to do anything which causes me to feel stressed out or I don't want to do" (Participant XI).

With the changes in their priorities, the women have had time on their hobbies, which they postponed in the past. "Now I have hobbies, which I did not use to spend time on. I used to clean home as soon as I came home ... however, now, I do not clean home. Instead, I have taken a course to learn how to play the lute" (Participant XI).

Discussion and Conclusion

The findings of this study provide a specific insight into the nature of PTG in breast cancer survivors in the first post-treatment two years. In addition, the present study contributed to Turkish breast cancer survivors' understanding the phenomenon of PTG.

The findings of the study showed that breast cancer was a traumatic experience, but that attempts to make sense of cancer during this experience promoted PTG in the early survival phase. Traumatic events result in cognitive processing and deeply influence basic beliefs of individuals about the world and their place and function in the world (24). During this process, searching for meaning is an important part of experiences with cancer. Patients question causal attributions of cancer and the meaning of cancer in their lives (25). In this study, the women mostly identified cancer with death while making sense of this disease. In traditional Turkish culture, cancer is considered as a lethal disease. Facing a life-threatening disease leads patients to become aware of death and their mortality. Individuals realize that routines, habits and priorities lose their importance in the face of death and they can gain new understandings of their lives (26). Health care professionals should provide patients with an opportunity to express their opinions about cancer and guide them to share their feelings, thoughts and experiences to promote a cognitive restructuring process. Health care professionals' empathy for the patients' seeking a meaning of life and disease can provide support.

Another way of making sense of traumatic events is the use of religious beliefs. Religious beliefs provide a framework for understanding, managing and coping with traumas and are an important component of growth (15, 27). Concerning this aspect of making sense of cancer, the survivors in this study commented that cancer was a test and a warning sent by God in their lives. According to Muslim culture, diseases are tests given by God and individuals have to question the meaning of these tests and be patient about difficulties caused by diseases. Patience can give patients hope for the future. In addition, it makes great contributions to personal development. This supports acceptability of life crises and positive changes (27). Health care professionals should realize that patients' such statements as "cancer is a kind of a test given by God" are a part of their interpretation process of the disease and they

should support the patients' efforts to remain patient, and struggle shaped by this interpretation so that they help patients to find meaning in life while living with the disease.

The women mentioned positive restoring in the value of life, self-value and relationships. Similarly, results of qualitative studies showed survivors experience PTG in appreciation of life, personal strength, and deepened relationships with others (12, 13). Traumatic experiences lead individuals to perform an existential questioning. Responses obtained through this questioning result in changes in the meaning of life and goals (15). After a traumatic experience, individuals become more willing to live and lead a life they have selected instead of the one involving routines only (28). They also become aware of their vulnerability and mortality (15). Growing stronger after suffering helps to acquire a new perceived self and enhances appreciation an individual has for oneself (29). Also, the survivors in the current study noted that their available relationships and bonds with people became more valuable. Likewise, attention has been attracted towards increased depth of relationships after breast cancer in several studies (12, 14). Social support is an important source of coping in Turkish breast cancer patients in the cancer trajectory (16, 30). It is mostly provided by family members during diagnosis and treatment processes. Struggling against breast cancer, a traumatic experience, strengthens relationships (5). Traumatic experiences can lead individuals to become more honest while telling about their emotions and thoughts (15, 28). These experiences also help individuals become more aware of their own sensitivities, which encourages them to be more affectionate. In fact, the participants in the present study described willingness to help others. It is striking that the participants having had the need for help from others with the same experiences in the breast cancer journey were eager to provide such support. This finding reflects a deficiency in care for cancer patients in Turkey.

Another finding of this study was enhanced coping skills. Coping with difficulties led by a trauma means acquisition of new coping skills in life. In fact, with a traumatic event, people become aware of their own vulnerabilities and strengths, which results in development of their coping skills (29). The women in this study also commented that they were able to express their feelings better, reject things and have a positive attitude to life and new interests thanks to changes in their priorities and their increased self-value. Similarly, several studies draw attention to increased problem solving and positive thinking skills and developing new interests (12, 13, 31). Improvements like increased self-respect, being more assertive and tolerant, feeling more powerful and more confident help women with breast cancer to be able to cope with stress and conflicts (32). Health care professionals should question the nature of PTG in breast cancer survivors, help them recognize positive psychosocial changes in their lives and use these changes as a source of coping with negative effects of cancer.

The interviews were conducted on 13 breast cancer survivors in the extended phase. Although data saturation was considered to have been achieved, inclusion of survivors from different backgrounds could have improved the generalizability of the results.

The results of this study revealed that breast cancer survivors experience positive restoring in the first post-treatment two years. Making sense of cancer promotes PTG after breast cancer. Further studies focusing on each aspect of PTG separately and explaining the predictors of PTG may provide valuable insights for an effective survivorship care.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Dokuz Eylül University (2150-GOA, 2015/15-14)

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Ş.İ.; Design - F.Ş.İ.; Supervision - F.Ş.İ., B.Ü.; Resources - F.Ş.İ.; Materials - F.Ş.İ.; Data Collection and/or Processing - F.Ş.İ.; Analysis and/or Interpretation - F.Ş.İ., B.Ü.; Literature Search - F.Ş.İ., B.Ü.; Writing Manuscript - F.Ş.İ.; Critical Review - F.Ş.İ., B.Ü.

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Correlation Between Gamma-Glutamyl Transferase Activity and Glutathione Levels in Molecular Subgroups of Breast Cancer

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ABSTRACT

Objective: The gamma-glutamyl cycle catalyzed by gamma-glutamyl transferase (GGT) plays an important role in glutathione (GSH) homeostasis in the cell. In cells continuously exposed to the drug, the main phase of the enzymatic detoxification is the conjugation of the drug with GSH catalyzed by glutathione-S-transferase (GST). Conjugation of drugs with GSH is the first step in the development of chemotherapeutic drug resistance. In this study, we aimed to investigate the relationship between GGT and GSH in molecular subgroups of breast cancer patients.

Materials and Methods: Serum GGT activity and GSH levels for patients diagnosed with breast cancer (n=58) and healthy controls (n=8) were measured by a spectrophotometric method and a colorimetric kit, respectively.

Results: GGT activity was significantly higher in the total patient group and in the molecular subgroups than those in the control groups ($p<0.05$). Serum GSH levels were higher in the patient groups compared to controls without reaching statistical significance ($p>0.05$). GGT activity was positively correlated with GSH levels in the total patients and healthy controls ($p<0.001$ and $p<0.05$, respectively). There was also a positive correlation between GGT activity and GSH levels in Luminal A, HER2-positive (Human epidermal growth factor receptor 2), and Triple-negative groups ($p<0.05$).

Conclusion: This is the first study showing the relationship between GGT and GSH in molecular subgroups of breast cancer. An increase in GGT activity may affect intracellular GSH synthesis. Therefore, having a correlation between GGT and GSH in some molecular subgroups may affect the course of treatment in these patients.

Keywords: Gamma-glutamyltransferase, glutathione, molecular subgroups of breast cancer

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Introduction

Gamma-glutamyl transferase (GGT) (GGT, EC 2.3.2.2) is an enzyme known as (5-L-glutamyl)-peptide: amino acid 5-glutamyl transferase in systematic nomenclature. GGT is located on the outer surface of plasma membranes of cells which has ecto-enzyme activity. The enzyme is a dimeric glycoprotein composed of a heavy chain and a light subunit bound by a non-covalent bond, processed from a single chain precursor with an autocatalytic cleavage in prokaryotes and eukaryotes (1, 2). GGT is located in the plasma membrane of almost all cells, but mainly involved in epithelial tissues with secretory or absorbing functions (1). Although the enzyme is shown in many organs, the highest GGT activity is present in the kidney, then in the duodenum, small intestine and gallbladder, respectively (3). GGT is present in the biliary pole of hepatocytes and cholangiocytes in adult liver and thus secreted into bile. It is known that the main source of plasma GGT is the liver (1).

Glutathione (GSH) (GSH, L-glutamyl-L-cysteinylglycine) is a tripeptide which has a thiol group and it is present in 1-10 mM concentration in all mammalian tissues (4). It is the most abundant antioxidant molecule in cells and is involved in various critical cellular functions such as detoxification of xenobiotics and/or their metabolites, cell proliferation, apoptosis, and modulation of fibrogenesis (4). GSH is also an important determinant of sulfur assimilation, protection of cells against oxidative stress and storage and transport of nitric oxide and cysteine. The gamma-glutamyl cycle catalyzed by GGT uses GSH as a continuous source of cysteine for cells (5). GSH is synthesized in the cytosol and then transferred out of the cell. The extracellular GSH metabolism is initiated by GGT, which is the first enzyme of the GSH destruction pathway, and is then finished with membrane dipeptidases (6). The γ -glutamyl moiety released by the breakdown of GSH by

GGT is transferred to other amino acids and the resulting γ -glutamyl amino acid is reintroduced into the cell (6). This final compound is metabolized to form 5-oxoproline, which is then converted to glutamate which can be used in the formation of GSH again and amino acid (7). On the other hand, cysteinylglycine, which occurs after the removal of the gamma-glutamyl moiety of GSH, is also degraded by dipeptidases to form glycine and cysteine which will be transported back into the cell (7). Most of the cysteine taken by the cell is used to synthesize GSH again, and the remaining amount is introduced into newly synthesized proteins or is degraded into the sulphate and taurine (8).

One of the first studies on GGT activity was published in 1956 by Ball et al. (9). Despite a period of over 60 years, studies on GGT have not been concluded. Following the disclosure of the human genome, detection of the presence of other GGT genes with possibly overlapping activity has made the subject more complex but has aroused interest in it. GGT expression is often significantly increased in human cancers. It has been suggested that gamma-GGT can be used as an indicator of cancer risk, as well as its use as a marker of diabetes, cardiovascular and chronic kidney diseases (10). There are several hypotheses for the role of GGT in cancer. One of them is the increased GSH catabolism initiated by GGT. As described above, the extracellular degradation of GSH by GGT provides gamma-glutamyl amino acid and also cysteinylglycine, which is a highly

reactive metabolite (11). Cysteinylglycine allows the reduction of Fe^{3+} to Fe^{2+} , resulting in the production of reactive oxygen species. It, as a pro-oxidant, has been shown to induce low density lipoprotein (LDL) oxidation (12), lipid peroxidation as well as oxidative damage to DNA bases.

Living organisms are constantly exposed to xenobiotics or drugs. The main phase of enzymatic detoxification is the conjugation of activated xenobiotics/drugs with GSH catalyzed by GST (13). It has been reported that some compounds, once converted to glutathione-S-conjugates, enter the *mercapturic acid pathway* and generate highly reactive and toxic end products for the cell (14). The cytotoxicity of these GSH conjugates is mainly dependent on GST and GGT, which are enzymes that initiate the mercapturic acid synthesis pathway (15). High GST or GGT activity in cancer cells causes accumulation of GSH-drug conjugates and increases drug resistance (14).

The aims of this study are to investigate GGT activity and GSH levels in breast cancer and to evaluate the relationship between them in breast cancer according to the molecular subgroups.

Materials and Methods

Fifty-eight patients who applied to applied to the Istanbul University, Institute of Oncology, Clinical Oncology Department, Oncology Surgical Unit and and were diagnosed with breast cancer and had operation due to their illness, were included in the study. The patients were informed for participation in the study with approval prior to the operation date and informed consent forms from the patients were obtained. Serum samples were taken from 58 patients before the operation. Eight healthy women who applied to Surgical Oncology Unit for macromastia and for breast reduction surgery and no any breast cancer history in their family, between 18 to 70 years of age, without any known chronic illnesses (e.g. hypertension, diabetes mellitus, coronary artery disease, chronic liver disease, hepatitis, hyperlipidemia), any neoplastic and hormone related diseases, and history of regular alcohol consumption were included as the control group. Table 1 gives the main characteristics and clinic-pathological findings of the patients and the controls. Serum samples were stored at -80°C until use. The protocol for this research was approved by The Clinical Research Ethics Committee of Istanbul Faculty of Medicine.

Histopathological analysis and staging

All cases underwent standard histopathological evaluation, including macroscopic and microscopic analysis. Immunohistochemical staining for ER (estrogen receptor), PR (progesterone receptor), HER-2 and Ki-67 were performed on sections of formalin-fixed paraffin-embedded tissue from the primary tumours. Histopathological analyses were performed in the accredited laboratory of Department of Pathology of Istanbul Medical Faculty.

For persistence of ER and PR receptors were included all results with +, ++ or +++ on immunohistochemical examination. For persistence of HER-2 receptors were included all patients with +++ result on immunohistochemical analysis. In cases where ICT determined HER-2 neu positive status ++ patients underwent FISH analyses for defining the HER2-neu gene amplification status. Staging criteria for breast cancer were determined by using criteria from American Joint Committee (AJC) and TNM classification according to UICC (International Union for Cancer Control). According to the classification system for breast cancer subtypes, breast cancer is divided in Luminal A, Luminal B with HER2 negative, Luminal B with HER2 positive, HER2 enriched and basal-like (triple negative) (Table 2).

Table 1. Demographic characteristics and laboratory tests of the patient group

	Control (n=8)	Patient (n=58)
Age, average (SD)	36.3 (9.6)	53.1 (12.0)
Menopause Status		
Premenopausal, n (%)	6 (75)	33 (56.9)
Postmenopausal, n (%)	2 (25)	25 (43.1)
Cancer Stage, n (%)		
I	-	5 (8.6)
II	-	23 (39.7)
III	-	30 (51.7)
Tumor Location, n (%)		
Right	-	31 (53.5)
Left	-	26 (44.8)
Right + Left	-	1 (1.7)
Molecular Subtype, n (%)		
Luminal A	-	16 (27.6)
Luminal B / HER-2 (-)	-	8 (13.8)
Luminal B-HER-2 (+)	-	9 (15.5)
HER2 (+)	-	9 (15.5)
Triple negative	-	16 (27.6)
Laboratory tests		
Estrogen Receptor, mean (SD)	-	43.5 (43.3)
Progesterone Receptor, mean (SD)	-	21.5 (32.8)
Ki-67, mean (SD)	-	40.8 (26.2)
SD: standard deviation		

Measurement of serum GGT activity

To measure serum GGT activity, kinetic method based on the measurement of transpeptidase activity was used. This method, developed by Szasz (16), was modified in our study to measure with the microplate. GGT activity was measured at 0.05 mM 2-amino-2-methyl-1,3-propanediol (Sigma-Aldrich, Germany) buffer pH 8.6 in the presence of $MgCl_2 \cdot 6H_2O$ (Sigma-Aldrich, Germany), Gly-Gly (Sigma-Aldrich, Germany) and L-gamma-glutamyl-p-nitroanilide (PubChem, Bethesda, MD, USA) as GGT substrate. The reaction was monitored by follow-

ing the increase in absorbance at 405 nm linked to the release of p-nitroanilide (17). All data are expressed as mean (standard deviation, SS).

Total glutathione analysis

Total serum glutathione (tGSH) analysis was performed using a colorimetric kit (Glutathione (GSH) Assay Kit; Oxford Biomedical Research, MI, USA). In the 96-well microplate, both the standards and the samples were analyzed in accordance with the kit procedure. Measurements were carried out in absorbance (A) at 400 nm. All data are expressed as mean (standard deviation, SS).

Statistical analysis

The homogeneity of the data was evaluated with the Kolmogorov-Smirnov test. Since the data were not normally distributed, the results were compared using nonparametric tests. The Mann-Whitney U test was used to compare differences between patient and healthy controls. Spearman-correlation test was used to examine the relationship between the parameters for the non-normally distributed data. *P* values of less than 0.05 were regarded as statistically significant. Statistical analyzes were performed using the Statistical Package for Social Sciences for Windows software version 22 (IBM Corp.; Armonk, NY, USA).

Results

To determine whether the data from serum GGT enzyme activity and GSH analysis were distributed normally, a Kolmogorov-Smirnov test was used. According to test results, GGT enzyme activity and GSH data did not show a normal distribution ($p < 0.001$).

Serum GGT enzyme activity and GSH levels in the total patient group and breast cancer molecular subgroup average values are given in Table 3. GGT activity was statistically significantly higher in the total patient group and in the molecular subgroups than those in the control group ($p < 0.05$). Serum GSH levels were higher in the patient groups compared to controls, but not statistically significant ($p > 0.05$). When GGT activity and GSH levels were compared between molecular subgroups of breast cancer, no statistically significant difference was observed ($p > 0.05$).

When the relationship between GGT enzyme activity and GSH levels in total patient and control groups were examined, a statistically significant correlation was observed ($p < 0.001$ and $p < 0.05$, respectively) (Figure 1). In addition, Luminal A, HER2-positive, and Triple-negative patients showed a statistically significant correlation between GGT activity and GSH levels ($p < 0.05$). No statistically significant correlation was observed in Luminal B and Luminal B-HER2-positive patients ($p > 0.05$) (Table 4).

Table 2. Parameters Used in the Classification of Breast Cancer Patients

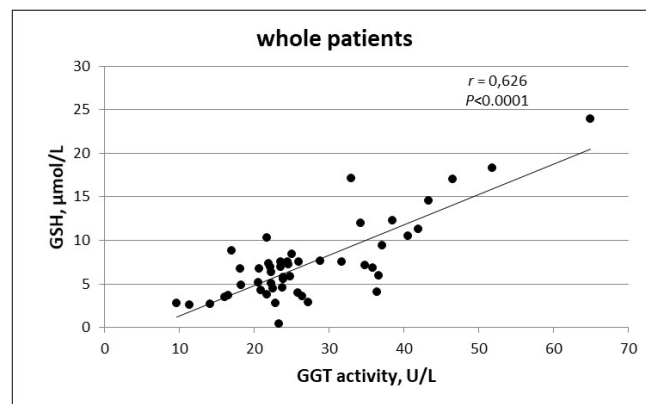
	Parameter
Luminal A	ER(+)/PR(+)/Ki-67<25%
Luminal B/HER-2 (-)	ER(+)/PR(+)/Ki-67≥25%
Luminal B/HER-2 (+)	ER(+)/PR(+)/HER-2(+)
HER2-positive	ER(-)/PR(-)/HER-2(+)
Triple-negative	ER(-)/PR(-)/HER-2(-)
ER: estrogen receptor; PR: progesterone receptor	

Table 3. Mean values and comparison of serum GGT enzyme activity and GSH levels of patient groups according to total and molecular subtypes

	n	Serum GGT Activity (U/L)	Serum GSH (μmol/L)
Controls	8	18.8 (4.4)	5.8 (1.4)
Total patients	58	26.2 (10.3)*	7.8 (5.5)
Luminal A	16	25.3 (8.1)**	6.3 (3.7)
Luminal B / HER-2 (-)	8	26.9 (9.8)**	10.1 (7.8)
Luminal B / HER2 (+)	9	25.1 (6.4)	7.6 (4.2)
HER2 (+)	9	32.9 (16.3)**	9.2 (7.1)
Triple (-)	16	27.0 (10.0)***	8.1 (6.3)
* $p < 0.01$ compared with the control group			
** $p < 0.05$ compared to the control group			
*** $p < 0.02$ compared to the control group			
GGT: gamma-glutamyl transferase; GSH: glutathione			

Table 4. The relationship between GGT activity and GSH levels in molecular sub-groups

	n	GGT – GSH r (p)
Luminal A	16	0.800 (0.003)
Luminal B/HER-2 negative	8	0.714 (0.071)
Luminal B-Her2-positive	9	0.100 (0.798)
Her2-positive	9	0.800 (0.010)
Triple-negative	16	0.552 (0.041)
GGT: gamma-glutamyl transferase; GSH: glutathione		

**Figure 1.** The relationship between GGT activity and GSH levels in controls and patients

Discussion and Conclusion

Various hypotheses have been suggested for the role of GGT in carcinogenesis, in the literature. One of them is the increased GSH catabolism initiated by increased GGT activity. Extracellular GSH degradation by GGT provides cysteine, a rate-limiting amino acid for GSH synthesis in the cell. Therefore, GGT plays an important role in GSH and cysteine homeostasis (18-21). GSH protects cells against carcinogens and regulates neoplastic transformation and viability of cells. Because of its reducing properties, GSH can inactivate some carcinogens, protect DNA against free radicals that are damaging, protect the integrity of different tissues, and prevent lipid peroxidation (22). On the other hand, cysteinylglycine, a product of the extracellular degradation of GSH by GGT, is a highly reactive carcinogenic metabolite. The second hypothesis for the role of GGT in cancer is its activity in the synthesis and metabolism of leukotrienes. It is believed that the relationship between chronic inflammation and cancer is due in part to the infiltration of the tumor microenvironment through inflammatory cells from which a number of proinflammatory mediators such as prostaglandin and leukotriene are released (23-24). In addition, GGT promotes free iron release from transferrin, which provides iron to malignant cells (25).

In our study, GGT activity was higher in the patients in all molecular-subgroups than those in the controls. Also, patients in the drug-resistant HER2-positive breast cancer group had slightly higher GGT activity than patients in the other sub-groups. Recently, in a study in which Shackshaft et al. (26) examined serum GGT activity in breast cancer subgroups, serum GGT activity was found to be slightly higher in breast cancer patients compared to the control group. They also found significant associations between serum GGT activity and development of ER+, ER- and PR+ breast cancers compared to controls and inverse associations between GGT levels and PR- breast cancers compared to PR+ (26). In a study by Staudigl et al. (27), no relationship was found between GGT enzyme activity and hormone receptor and HER2-status. Fentiman et al. (28) reported a positive correlation between increased GGT activity and breast cancer incidence in premenopausal women. On the other hand, Van Hemelrijck (29) explained that increased GGT levels were an independent risk-factor for breast cancer.

Expression of GGT involved in the mercapturic acid pathway has been reported to be induced in cancer cells, especially drug-resistant cancer cells (15). Since overproduction of GGT results in increased intracellular GSH synthesis, it plays an important role in the development of resistance to certain chemotherapeutics, such as alkylating agents (30). In our study, GSH levels were found to be higher in both total patient group and molecular subgroups in comparison with the control group without reaching statistical significance. However, there were significant positive correlations between GGT activity and GSH levels both in the whole patient group and in the Luminal A, Her2-positive, and triple-negative subgroups. This result supports the relationship between the increase in GGT activity and the increase in GSH levels. Although there are not many studies examining GGT and GSH in breast cancer at the same time, Mishra et al. (31) showed significant increases in GSH levels in breast cancer patients with/without metastasis when compared to healthy controls and increases in GGT levels in breast cancer patients with metastasis when compared to non-metastatic patients. However, they did not examine the correlation between the two

and therefore could not explain the relationship between high GSH levels and GGT.

In the breast cancer, the main treatment in hormone-positive patients is with tamoxifen or aromatase inhibitors (32). HER2-positive breast cancer cells respond to monoclonal antibodies and kinase inhibitors that block HER2 receptor, such as trastuzumab and lapatinib (33, 34). Since three receptors that are important for the development and proliferation of tumor cells in triple-negative breast cancer (TNBC) are not expressed (ER-, PR-, HER2-), standard hormone therapy and/or targeted treatment agents for these receptors cannot be used. Therefore, patients with TNBC are usually treated with chemotherapeutic agents that are cytotoxic. The efficacy of various chemotherapy agents such as anthracyclines, taxanes, ixabepilone, and platinum derivatives has been shown in different studies in the treatment of TNBC (35). However, different response rates are observed in patients. For example, while only 30% of patients with TNBC respond to chemotherapy, the remaining 70% of patients does not respond to chemotherapy or show resistance (36). Therefore, prevention of drug resistance in these patients is important for a positive treatment process. As suggested by our study's results and other studies, if increased GGT activity causes the accumulation of GSH-drug conjugates, we may consider that chemotherapeutic drug resistance may develop, and the treatment process may be affected in patients with high GGT activity and GSH levels. However, new studies are needed on the role of GGT activity and GSH in the development of drug resistance.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Istanbul Faculty of Medicine (23.03.2016).

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

Peer-review: Externally peer-reviewed.

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Pure Ductal Carcinoma in Situ in The Male Breast: A Rare Entity

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ABSTRACT

Pure ductal carcinoma in situ of male breast (DCIS) is extremely rare. Only a few cases have been reported until now. Its treatment is not well established. Prognosis is as good as in women. In this study, we reported 3 cases of pure ductal carcinoma in situ in the male breast. The mean age of DCIS patients was 58.3 years. The main symptom was a breast mass. The median size of the tumor was 25 mm. Two patients had an axillary lymph node. The left side was reached in 2 cases. All of the patients underwent mastectomy. The histopathological assessment showed papillary, cribriform, and comedocarcinoma in situ. There was no evidence of invasive carcinoma. In one case, the DCIS was associated with Paget's disease of the nipple. One patient received hormonotherapy. The time of follow-up ranged between 6 and 117 months. One patient developed an invasive recurrence.

Keywords: Male breast cancer, ductal carcinoma in situ, treatment

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Introduction

Pure Ductal carcinoma in situ (DCIS) of the man is extremely rare. The incidence is approximately 1% of all malignancies in men and 5% to 7% of male breast cancer (1). It is usually associated with invasive carcinoma. We reported three cases on DCIS in men. The aim of our study is to further emphasize the importance of this disease for men and to evaluate the management of this rare tumor.

Case Presentations

Case 1

A 58-year old man consulted for a left breast mass that has been evolving for 3 months. There was no remarkable personal history or family history of breast's disease. He had a remarkable history of smoking with 38 packages per year. On physical examination, we found a mobile, well-defined mass, measuring 20 mm × 20 mm without axillary lymph node. The right breast was unremarkable. Mammography and ultrasound showed a circumscribed nodule without calcifications in the left breast. This was considered as ACR 3 of the classification of the American College of Radiology (ACR) (Figure 1). We performed a core needle biopsy. The histological findings showed a DCIS. The patient underwent a mastectomy with sentinel node. Macroscopically, the tumor was greyish to white and measured 17 mm in its greater axis. The definitive histopathological assessments showed DCIS with papillary and cribriform patterns (Figure 2). The nuclear grade was intermediate, and there was no necrosis. Cells were polarized. The margins were free, with a clearance of 15 mm. No invasive cancer was present. The nuclear grade was I of Van Nuys. Van Nuys Prognostic Index score (VNPI) was 6 (Table 1). Sentinel lymph node sampling brought back three lymph nodes which were all negative. The immunohistochemical examination of estrogen (ER) and progesterone (PR) receptors were negative for both. The patient was noted to be doing well until now, and he is regularly followed up, with a total duration of follow-up of 10 years.

A written informed consent was obtained from the patient.

Case 2

An 85-year old man was referred for a retro-areolar mass of the left breast and nipple retraction for more than 6 months. He had a medical history of hypothyroidism and he didn't have a remarkable family history of breast disease. On physical examination, there was a mobile retro-areolar mass, measuring 25 mm × 20 mm in greater diameter with inflammatory skin changes (Figure 3). We also found an ipsilateral axillary lymph node. The mammogram and ultrasound revealed a suspicious retro-areolar masse which considered as ACR4. The core

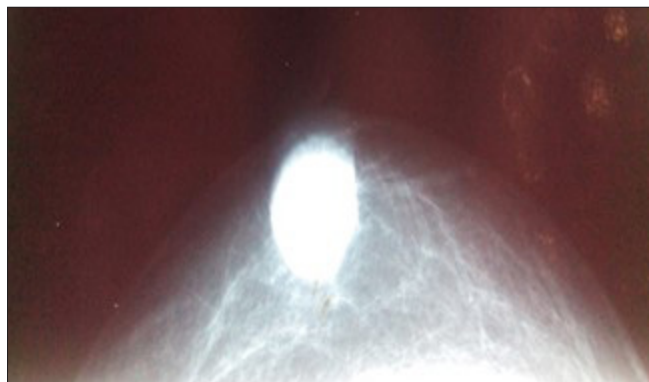


Figure 1. A retro-areolar, well-defined mass of the left breast

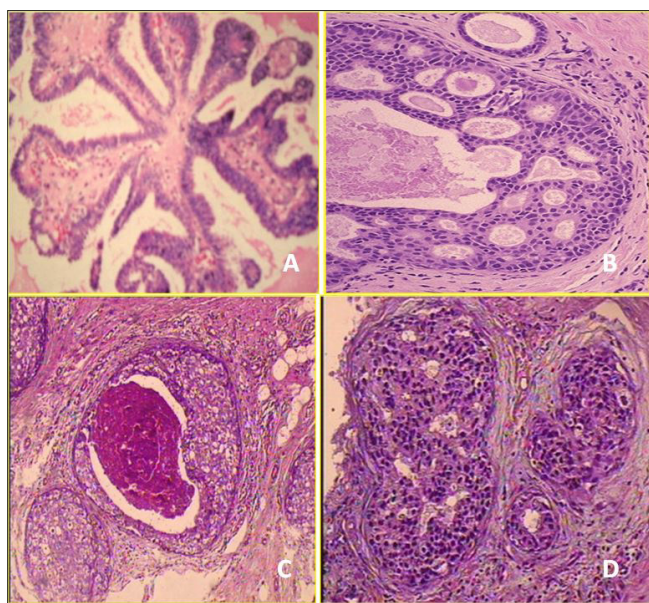


Figure 2. a-d. Papillary patterns of DCIS (a), cribriform patterns of DCIS (b), comedocarcinoma on DCIS (c), nuclear grade 2 of Van Nuys (d)

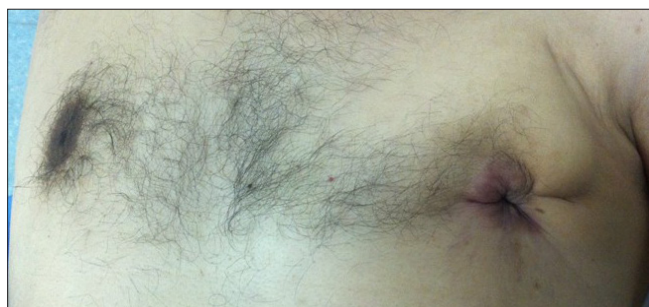


Figure 3. Clinical appearance of a retro-areolar lesion with nipple retraction and skin involvement

biopsy with histological assessment showed patterns of DCIS. A mastectomy with axillary lymph node dissection was performed. In histological findings, macroscopically the tumor measured 27 mm in its greatest diameter. The architectural patterns were cribriform and papillary, with Paget's disease of the nipple (Figure 2). We didn't identify necrosis. The nuclear grade was intermediate, and cells were polarized. The margins were free, with a clearance of 10 mm. The nuclear grade was I of Van Nuys. VNPI score was 5. All lymph nodes were negative. The ER and the PR were positive. Due to inflammatory skin signs in the first clinical presentation, the patient received Tamoxifen 20 mg per day for five years (TEVA Sante, MACORS, Paris, France). He is still being followed up without recurrence, with a total follow-up duration of 4 years.

A written informed consent was obtained from the patient.

Case 3

A 35-year-old man had a 3 weeks history of a painful lump in the peri-areolar region of the right breast. There was no remarkable personal history or family history of breast's disease. The patient was neither smoking nor alcoholic. On physical examination, we noted an elastic gynecomastia of the right breast without any palpable mass (Figure 4). There were no palpable lymph nodes. Mammography and ultrasound



Figure 4. Gynecomastia combining a tumor of the right breast

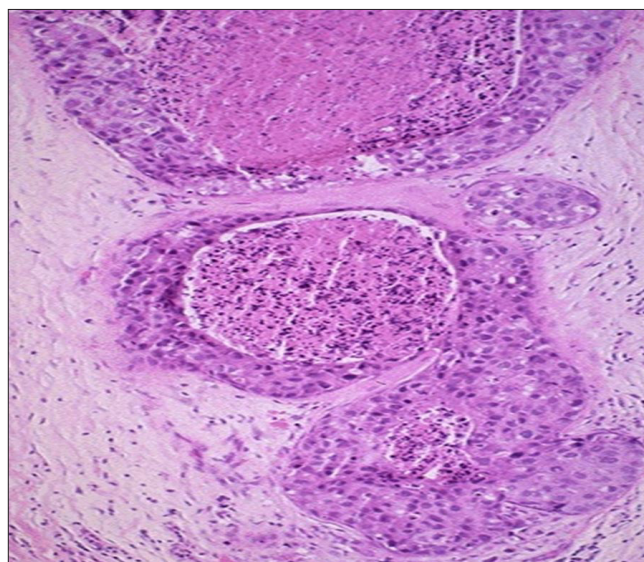


Figure 5. Microscopic section showing necrosis

Table 1. Scoring system according to the new Silverstein classification of VNPI

VNPI scoring system	1	2	3
Tumor size (diameter in mm)	less or equal to 15	16-40	greater or equal to 41
Margin width (in mm)	less or equal to 10	1-9	<1
Pathologic Classification	non-high grade, (nuclear grades 1 and 2) no necrosis	non-high grade, (nuclear grades 1 and 2) with necrosis	high grade (nuclear grade 3) with or without necrosis
Age (in years)	61 or older	40-60	39 or younger
Overall VNPI score	4-6	7-9	10-12
VNPI: Van Nuys Prognostic Index score; Mm: millimeters			

showed homogenous gynecomastia without nodules. A subcutaneous mastectomy was performed. Histological examination revealed a DCIS measured 10 mm in its greatest diameter, with papillary and comedo-carcinoma patterns, and the nuclear grade was intermediate (Figure 2). We identified the necrosis (Figure 5). Cells were rarely polarized. The ER and the PR were negative. The margins were free with a clearance of 5 mm. No invasive cancer was seen. The nuclear grade was II of Van Nuys. VNPI score was 8. The patient was immediately lost from view postoperatively. He consulted two years later for a retro-areolar mass. A core biopsy was done and the histological findings showed a recurrence of DCIS. A mastectomy with sentinel node was performed. The final histological exam showed a poorly limited mass that measured 30 mm in its greatest diameter. We noted the presence of necrosis. The ER and the PR were negative. The margins were free with a clearance of 10 mm. The sentinel lymph nodes were free of disease. The nuclear grade was II of Van Nuys. VNPI score was 8. The recurrence was confirmed, and we didn't recommend additional treatment for the patient. He was lost from view again. He consulted 6 months later for peri-cicatricial mass. The biopsy showed invasive ductal carcinoma. The chest X-ray, ultrasound of the abdomen, and bone scintigraphy were performed and there was no evidence of distant metastases. A large excision was done followed by radiotherapy. The patient is still followed up with no evidence of recurrence with a total duration of regular follow-up of 5 years.

A written informed consent was obtained from the patient.

Discussion and Conclusion

Male DCIS is a rare entity, the incidence of male DCIS is 7% of all male breast cancer (1). This low incidence is thought to be partly due to the lack of breast screening in male patients.

There is no clinical particularity of the DCIS in man. The median age of presentation is 65 years (range 25-94 years) but it is usually diagnosed at an advanced age (1, 2) as we reported in the second case. The most frequent clinical symptoms are subareolar mass in 58% followed by nipple discharge in 35% and rarely associated with gynecomastia in 19%, as we reported in the third case (2).

The radiological evaluation of the male breast is not standardized, the mammography is done first and is followed by ultrasound (1, 3).

The comparison with female breast shows that the calcifications are less frequently seen on the mammography as in our case series; we didn't find microcalcification (4). Ultrasonography of male DCIS typically reveals a cystic lesion (4).

Therefore, the DCIS of the male is expected to have a good prognosis with simple mastectomy only and no axillary sentinel node biopsy or chemotherapy is needed as in female patients. Meanwhile, some authors actually recommend the use of sentinel lymph node systematically (1, 4). Radiotherapy may be recommended for a male patient with DCIS treated by lumpectomy or patients with involved margins for reducing the local recurrence.

The European Organisation for Research and Treatment of Cancer (EORTC) cohort concluded to be DCIS is the most commonly observed precursor lesion in male breast cancer, which can explain the aggressive behavior that we reported in the third case (5).

Histological examination showed that the papillary lesion was the most frequently observed histological subtype at 74% and that the cribriform patterns were less common with a rate of 27%. The low-grade is the most frequent one (57%), and the intermediate grade is less common (43%) as we reported in our case series, where all the patients expressed a nuclear grade 2. On the contrary, high-grade DCIS is considered to be a very rare lesion in pure DCIS (6, 7). The grading system for DCIS is very varied; we used Van Nuys grading, which took into account nuclear features, and the presence or absence of necrosis.

Silverstein established the VNPI to attempt to identify the aggressiveness of DCIS in terms of local recurrence following breast-conserving surgeries (Table 1) (8). Initially, the index evaluated three factors frequently connected with the aggressiveness of DCIS. These included: total tumor size, classification of pathological 'nuclear grade' (including presence or lack of necrosis), and margin clearance. Later, Silverstein added patient age to the stratification scoring (9). He reviewed the record of 706 patients with pure DCIS, who were treated with breast preservation. In patients with VNPI scores of 4, 5 or 6, regardless of whether radiation therapy was used, there was no statistical difference in the 12-year local recurrence-free survival (p =not significant). However, patients with VNPI scores of 7, 8, or 9 received a statistically significant average of 12% to 15% local recurrence-free survival benefit when treated with radiation therapy (p =0.03) (9).

In our series, all the patients had a surgical resection consisting of mastectomy with sentinel lymph node in two cases and a lymph node dissection in one case due to the presence of ipsilateral palpable lymph node. We didn't indicate radiotherapy as an adjuvant treatment due to the free margins in the histological exam and the absence of invasive underlying carcinoma. However, as we reported in the third case, even with radical treatment and free margins, the patient had a local recurrence with invasive behavior. In this case, the patient was under 40 years old and we observed necrosis in the histological assessment. The

tumor measured 3 cm in its greatest diameter and the VNPI score was 8 according to the new score established by Silverstein (9). This statement leads to the consideration of radiotherapy for some patients even when mastectomy was done. Due to the rarity of this entity in men, further investigations have to be conducted to confirm this hypothesis.

The hormone receptor expression rate in DCIS remains undefined due to the rarity of this entity. In a recent cohort of EORTC, including 1483 patients, the authors found that ER, PR, and androgen receptors (AR) were mostly positive in invasive breast male cancer, and the tumor was frequently Luminal B-like/ human epidermal growth factor receptor 2 negative (HER2). In our series, we found positive ER and PR in only one patient (10).

Hormonotherapy is not often used; however, some previous studies demonstrated a benefit of the use of Tamoxifen (3, 6). In our series, only one patient had hormonotherapy and was aged 85, we can conclude that hormonotherapy in DCIS was efficient.

The prognosis is uncertain because of the small number of populations in the literature. We consider the third case unusual in the sense that a DCIS in a male patient presented with gynecomastia, which was radically treated, but the patient exhibited an invasive local recurrence. Meanwhile, the prognosis is usually excellent. Some studies showed worse prognosis for male DCIS than female (11). We recommend regular follow up with clinical examination and regular ultrasound and mammography.

In conclusion, there are few studies about DCIS in men, so there are no clear guidelines for its management. Breast cancer should be considered for any male patients presenting with mass breast, gynecomastia or nipple discharge, which would lead to earlier detection and better overall prognosis. We recommend a mastectomy with sentinel lymph node as treatment standard. We can administer hormonotherapy when the ER and PR are positive. The place of radiotherapy remains uncertain and further investigations are needed to select the right candidate for it. The prognosis is excellent, but we are still waiting for future studies to understand the biology of this disease.

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

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

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Erratum

In the article by İzci et al., entitled “Impact of Personality Traits, Anxiety, Depression and Hopelessness Levels on Quality of Life in the Patients with Breast Cancer” (Eur J Breast Health 2018; 14: 105-111. DOI: 10.5152/ejbh.2018.3724) that was published in the April 2018 issue of European Journal of Breast Health, the institution information of the 10th author was incorrect. Upon receipt of a written request from the authors, the correction was implemented.

The aforementioned manuscript can be accessed through the following link:

<https://doi.org/10.5152/ejbh.2018.3724>

Erratum

In the article by Ordu et al., entitled “Prognostic Significance of Adjuvant Chemotherapy Induced Amenorrhea in Luminal A and B Subtypes” (Eur J Breast Health 2018; 14: 173-179. DOI: 10.5152/ejbh.2018.3808) that was published in the July 2018 issue of European Journal of Breast Health, the institution information of the 15th author was incorrect. Upon receipt of a written request from the authors, the correction was implemented.

The aforementioned manuscript can be accessed through the following link:

<https://doi.org/10.5152/ejbh.2018.3808>