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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 target audience of the journal includes specialists and medical professionals in general surgery and breast diseases.

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

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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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Current Opinion: Current Opinion provides readers with a commentary of either recently published articles in the European Journal of Breast Health or some other hot topic selected articles. Authors are selected and invited by the journal for such commentaries. This type of article contains three main sections

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.

Tables
Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are 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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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

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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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Contents

Review

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Clinical Evaluation of Breast in Childhood

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ABSTRACT

Childhood breast masses are mostly benign conditions starting from the newborn period continuing on to adolescence yet can cause high anxiety in the child and the family as well. As a complaint or physical finding, usually palpable mass, pain or discharge from the nipple is apparent in patients. All the clinicians interested in pediatric field should have full knowledge of immature and developing breasts so to proper diagnose and avoid overtreatment with unnecessary diagnostic or surgical procedures. Though malignancy or life-threatening disease has a very low probability during childhood, all child patients should be evaluated and followed up carefully. Especially training and then encouraging young people to periodically start self-assessment of the breasts after their 19th birthday while warning the ones who have had therapeutic chest radiation previously to begin self-assessment 8 years after the procedure or at 25 years of age whichever comes last, will be an appropriate intervention.

Keywords: Breast, breast disease, childhood, newborn, children, adolescent

Cite this article as: Karaayvaz S. Clinical Evaluation of Breast in Childhood. Eur J Breast Health 2019; 15(3): 137-140.

Introduction

Development of breast begins during 5th week of gestation and completes the growth under estrogen effect. Pubertal breast development (thelarche) physiologically occurs at 8-13 years in girls under increased estrogen effect which is triggered by the hypothalamus and pituitary gland on the ovaries (1-3). In every stage of childhood, breast examination should be an indispensable part of physical examination either in girls or boys and should be included in the annual examination of all children and adolescents.

The American College of Obstetricians and Gynecologists recommends that all the adolescents should be educated and encouraged to carry out self-assessment of their breasts after their 19th birthday and for the patients who have had therapeutic chest radiation previously, to start 8 years after the procedure or at 25 years of age which comes last (4).

Neonatal Period

In some newborns, breasts could be observed overtly or palpably occurring under maternal estrogen effect. The nipple is seen shortly after birth in normal conditions, but it is usually depressed. Sometimes nipple discharge which mimics milk (witch's milk) can be observed in both sexes due to increasing prolactin levels of lactation (1, 2). The condition is diagnosed clinically and frequently resolves spontaneously. Although mastitis and breast abscess are rare in newborns, some traditional approaches (some creams, mixtures or to rub down) can exacerbate the condition and in these cases the use of antibiotics and a close follow up would be necessary (1, 2).

In Children

Lipomastia

Breast enlargement may be seen due to increased adipose tissue in overweight/obese children in both sexes (Lipomastia) (3). It is a clinical entity and differential diagnosis is made mostly by physical examination. There is no glandular tissue under the areola and the view is overt when the patient is sitting. Sometimes it is difficult to make differential diagnosis with gynecomastia where an ultrasonography would be needed (5).

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Hemangiomas/lymphangiomas
In some cases, breast enlargement in prepubertal children may also be caused by hemangiomas or lymphangiomas (1). Although the diagnosis is clinically easily made in some cases there need to be advanced approaches such as ultrasonography and/or magnetic resonance imaging.

Amastia/hypomastia
Congenital forms may be isolated and genetical however some of the cases are associated with clinical entities such as ectodermal dysplasia, Poland syndrome, Crohn disease, some endocrinological disease's (1, 2, 6). Amastia/hypomastia are very rare conditions and mostly placed unilaterally. If there exists any extraordinary physical findings or complaints from the patient next to breast diversion, further investigation is needed.

Acquired forms are seen in traumas, radiotherapy, burns, some surgical procedures, and inappropriate biopsies of the breast bud. Treatment is designed according to underlying condition (1).

Polymastia/polythelia
Supernumerary tissue or accessory nipples are rare conditions and associated with cardiovascular or urinary tract anomaly. They usually exist on the chest, upper abdomen or in the inferior part of normal breast tissue (1, 2, 6). Surgery might be needed to solve cosmetic or functional problems (7).

Breast asymmetry and hypoplasia
In healthy people some breast asymmetry is normal. If asymmetry or hypoplasia is excessively visible; structural variations, hormonal diseases, chest diseases or procedures, tuberous breast anomaly should be taken into consideration (1, 2). If necessary reconstructive surgery should be delayed until the termination of puberty (8).

Juvenile or virginal hypertrophy
It is an aggregated rare form of normal breast hypertrophy mostly seen in adolescent girls, causing some physical problems such as posture disturbances, back pain or psychologic distress which are main indications for corrective surgery. As a reason, excessive end organ sensitivity to gonadal hormones is under discussion (1, 6). Using supportive brassieres, medical approach or corrective surgery are the treatment steps (1).

Infections
Mastitis may occur in newborns and adolescents. Irritation, trauma, foreign body, or anatomical defects as ductal ectasia or cystic lesions may cause infections. If fever, pain and other accompanying inflammatory findings exist, the condition is then diagnosed clinically. Ultrasonography is needed for further evaluation in doubtful cases. Antibiotics targeting staphylococcus aureus and gram-negative bacilli are initially recommended but if abscesses occur, drainage should be practiced (1, 9).

Nipple discharge
Nipple discharge is a rare condition in children. Although milky, sticky and thick discharge is mostly benign, purulent, serous or bloody discharge should be evaluated (1, 6, 8, 10). Galactorrhea might be a sign of prolactinoma, hypothyroidism, drug use and pregnancy should be kept in mind in adolescents as well. It is not infrequent in adolescent athletes to observe bloody discharge due to chronical stimulation of the nipple but cytology is essential in these cases to exclude the possibility of intraductal papilloma (1, 6, 10).

Mastalgia
In adolescents, premenstrual pains, benign growth pains or pains due to heavy exercise are observed frequently.

The use of soft brassieres, keeping warm, limitation of heavy exercise, drinking caffeine or acidic beverages and smoking are frequently workable precautions. If the pain is severe, nonsteroidal anti-inflammatory drugs or topicals are the first line drugs, and in some cases oral contraceptives are useful (1).

Breast Masses

Fibrocystic changes
Cysts are the most common masses in the pediatric population. At least 50 percent of women experience fibrocystic changes in their whole reproductive period (6, 10). Easily palpated fibrotic tissue usually exists in the upper outer quadrants of the breast usually. The size and the degree of pain vary parallel to menstrual cycle changes while the etiology of the condition is related to the imbalance between estrogen and progesterone hormones (1, 6). Mostly history and physical examination is enough for diagnosis. Breast ultrasonography is rarely required. Aspiration is performed if the gravity persists or increases; cytology is needed for bloody content. To relieve symptoms, nonsteroidal anti-inflammatory drugs especially ibuprofen is recommended in adolescents. Limiting caffeine intake can be helpful and oral contraceptives could be used in special circumstances (1, 2)

Fibroadenomas
These are most extreme breast masses in adolescents, frequently occurring in the upper outer part of breasts as an exaggerated response to estrogen stimulation. The condition accounts for 30-50 percent and 44-94 percent of adolescent breast masses in medical and surgical series respectively and accounts 50 percent of all breast biopsies (6, 11). Fibroadenomas are easily diagnosed by palpation (approximately 2-3 cm in size (ranging 1-10 cm), consistency, texture, location and tenderness as they are well-circumscribed lesions. An ultrasonography (US) examination is needed in all cases (1, 6, 8, 10-13). Mammography is not indicated in adolescents, as the intense structure of breasts limit imaging and the radiation effect on the growing tissue (8, 12, 13).

Although the course is benign, nipple discharge, trauma to breasts, family history of breast diseases/malignancy and previous history of chest radiation should be inquired in detail in every case.

Periodical follow up with physical examination and US is usually enough, but 4% of the lesions grow and need core needle aspiration (1). Surgical excision is demonstrated if the mass persists to adulthood or reaches 5 cm which can lead to risk of developing giant fibroadenoma or cystosarcoma phyllodes (1, 2, 13). However, surgery should not be performed before confirmation of the lesion by breast core needle biopsy.

Breast trauma
Trauma to the breast may be observed through childhood (e.g. traditional practices to newborns' physiologic breast enlargement, bumps to breasts, heavy exercise, seatbelt injury) resulting in fat necrosis that resemble breast mass. Differential diagnosis is frequently made by history and physical examination, but as fat necrosis mimics breast malignancy, further evaluation with ultrasonography for the typical image is needed (10, 14-16). In some of the cases which the presentation is not definitive, biopsy is the choice.

Mammary duct ectasia

The condition is the stretching of subareolar ducts with fibrosis and inflammation with sticky, multicolored fluid that appears as a dark colored mass under the nipple (blue breast) being predisposed to infection (mastitis or breast abscess). Although it is a benign course and resolves spontaneously, sometimes a residual subareolar nodule may be left (1, 2).

Cysts of Montgomery

Montgomery glands/tubercles or Morgagni tubercles are rooted, small papillary processes in periareolar region and probably play a role in lactation. Obstruction of the glands may cause inflammation, asymptomatic cyst or brownish, clear discharge (1, 2). Diagnosis is made clinically and usually resolves spontaneously. In some difficult cases ultrasonographic confirmation is needed.

Malignant masses

Primary breast cancer is very rare in the pediatric population (1, 6, 8, 16, 17). According to the data taken from Surveillance Epidemiology and End Results (SEER) of USA, from the 2011 to 2015 list, in female adolescents aged 15-19 years, invasive breast cancer incidence is declared as 0.1/100,000 (5). Juvenile secretory carcinoma made up over 80 percent of the cases, followed by intraductal carcinoma. Rhabdomyosarcoma and lymphoma also may occur as a primary tumor of the breast. Cystosarcoma phyllodes is a very rare condition having the potential of rapid growth and mimicking giant fibroadenomas (1, 12, 13). Juvenile papillomatosis has the potential of breast cancer in 15% of cases and should be treated surgically (1).

Primary finding of breast cancer in adolescents is a hard and irregular mass sometimes being fixed on underlying tissue. Also, skin or nipple involvement, retraction, discharge or skin edema (peau d'orange) and lymphadenopathy in neighbourhood could be observed (1, 17).

Risk factors such as familial history, history of previous individual cancer and exposure of the chest to radiation therapy or personal habits such as; alcohol consumption, limited physical activity or smoking, should be kept in mind.

The diagnosis is made by US with a proceeding biopsy from the mass. Accompanying lymph nodes and distant organ/system metastasis should be evaluated according to the stage of the disease (1, 17).

Metastatic cancer

Metastatic cancer to the breast are usually found due to existing states of rhabdomyosarcoma, Hodgkin and non-Hodgkin lymphoma, hepatocellular carcinoma and neuroblastomas (1,18).

Secondary cancer

Relapsing acute lymphoblastic leukemias, carcinomas of breast or previous chest radiation from another disease such as Hodgkin lymphoma are the causes of secondary cancers (1, 19, 20).

Management of breast masses in children;

1. Taking careful history; duration of the complaint, primary size or any increase in the mass, trauma, previous individual or familial breast disease or malignancy, previous chest radiation therapy, use of any drugs, pregnancy history or menstrual cycle regularity in adolescents.

2. Physical examination; location, size, being cystic/solid lesion, mobile/fixed, tender, inflammation criterion, skin changes, nipple discharge or attending lymphadenopathy or organomegaly.

3. Imaging; for persistent, atypical or extraordinary localized masses ultrasonography is preferred as the accuracy of the device in experienced hands when differentiating solid from cystic lesions is 96-100%. Mammography is not used in childhood breast diseases routinely, but for the girls who had received chest radiation for any kind of cancer are recommended to start mammography screening at 25 years of age or 8 years after therapy whichever comes last. Breast MRI can be added to the screening in these cases.

4. Surgical procedures; persistent cystic lesions need aspiration (bloody material in the aspirate needs cytologic evaluation). In the case of cystic lesions which do not resolve after aspiration, suspicious masses (unusual localization, fixed next to tissue, hard character etc.) or which, lymphadenopathy and/or hepatosplenomegaly accompany, surgical resection is demonstrated.

5. Therapy depends and varies upon the type of breast disease.

Conclusion

Breast masses during childhood are mostly benign, transient conditions. Physiologic hormonal changes, benign growth, cysts, some congenital anomaly/variants or syndromes, traumas and rarely malignancies may cause breast problems. Every physician interested in child health should implement checking of the breasts as a part of a routine physical examination and should have a command of breast physiology, development, variant conditions as well as pathological courses.

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Original Article

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Breast Cancer in Turkey; An Analysis of 20.000 Patients with Breast Cancer

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ABSTRACT

Objective: Breast cancer is the most common type of cancer and the leading cause of cancer-related deaths in women in Turkey. This study presents the characteristics of patients registered in National Breast Cancer Registry Program of Turkish Federation of Breast Diseases Societies.

Materials and Methods: The registry contains 242 variables under 10 categories and 699 questions. Patients were recorded (online and offline) from nationwide breast centers around Turkey.

Results: Twenty-thousand patients were registered between May 2005 and April 2017 at 36 centers. After data cleaning, 19,503 women were included in the study. The median age at diagnosis was 51 [14-97]; 17.2% were younger than 40 and 37.2% were premenopausal; 13.6% were nulliparous. Breast conserving surgery rate was 39.3%. Histopathology was invasive ductal cancer in 77%. Majority of patients had stage II cancer (48.3%). Estrogen, progesterone and HER-2 receptor positivity rates in invasive breast cancer were 72.5%, 62.5% and 21.8%, respectively. The mean tumor diameter was 2.5±1.7 cm. During the mean 51.6 months of follow-up, the local/regional and systemic recurrence rates were 3.7% and 5.2%, respectively; five and 10-year overall survival rates were 86% and 76%.

Conclusion: Despite increasing number of screening centers and free-of-charge mammography (ages 40 to 69) and mobile screening systems in recent years, a significant portion of patients were diagnosed at advanced stage due to lack of breast cancer awareness. In contrast with the study published 5 years ago, there was a decrease in the rate of pre-menopausal women and an increase in the breast conserving surgery.

Keywords: Breast cancer, demography, reproductive functions, pathology, survival, Turkey

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Introduction

Worldwide, there will be about 2.1 million newly diagnosed female breast cancer (BC) cases in 2018, accounting for almost 1 in 4 cancer cases among women (1). The disease is the most frequently diagnosed cancer in the vast majority of the countries (154 of 185) and is also the leading cause of cancer death in over 100 countries. Its incidence and mortality rates have been increasing mostly in developing countries including Turkey (2). Breast cancer incidence has increased almost two times in the last two years (24/100,000 in 1994 and 43.8/100,000 in 2015) in Turkey (3, 4). According to the Cancer Report 2015 data published by the Cancer Registry Unit of the Cancer Control Department, 17,183 women diagnosed with breast cancer in 2015 (4).

Maintaining an accurate and complete cancer registry program is one of the most important factors to implement national cancer control programs and assess the outcomes of screening, diagnosis and treatment. Unless accurate data are obtained and statistically assessed, prioritization cannot be achieved and sound decisions cannot be taken in the development of national health policies, national cancer strategic plans and utilization of limited resources. The Turkish Federation of Breast Diseases Societies (TFBDS) is the largest and single association of national breast societies and implementing an active specific registry in this sense; namely, the National Breast Cancer Registry Program (NBCRP). The program has been collecting data since 2005 from 36 centers scattered throughout the country. The medical secretaries at these centers were trained periodically for online and offline data accumulation and data cleaning has been performed regularly. The first results of breast cancer registry program were published in 2014 including demographic, clinical and pathological characteristics of 13.184 patients with breast cancer. This study aimed to evaluate the demographic, clinical, reproductive and histopathologic features and also survival results of 20.000 female BC patients registered into the program, and to compare them with data from other developed or developing countries.

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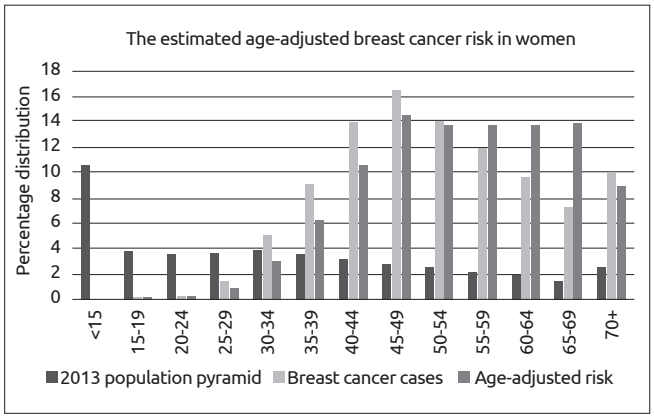

Figure 1. The estimated age-adjusted breast cancer risk in women (with 5-year intervals) according to the 2013 census data

Materials and Methods

Data recorded in NBCRP between May 1, 2005 to April 17, 2017 were evaluated. The primary outcome included overall demographic, clinical, reproductive, pathological characteristics and overall survival data of around 20,000 patients diagnosed with breast cancer in Turkey. In the scope of analysis there were 242 different variables covered under 10 main categories. The main categories were identity, history, clinical information, reproductive functions, histologic diagnosis, surgical treatment, postoperative pathology, chemotherapy, radiotherapy, hormonotherapy and follow-up. Modified Scarff Bloom Richardson histological grading was used in the morphological assessment of the degree of differentiation in breast cancer (5, 6).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences for Windows 20.0 (IBM Corp.; Armonk, NY, USA) program. Categorical variables were compared using chi-square analysis and presented as frequencies and percentage. Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Data were presented as mean and standard deviation or median and range. For non-parametric data, Mann-Whitney U test was used to compare means of two independent groups, and Kruskall-Wallis test was used to compare means of more than two independent groups. Where appropriate, continuous variables were regrouped and separately analyzed based on their cutoff points and groupings. The correlation between categorical variables was assessed using the chi-squared test, and data presented as frequencies and percentage. The comparisons between the survival times in subtypes were made through Log-Rank test. Survival rates as well as mean survival times and 95% confidence interval of averages were demonstrated in the corresponding rows for the groups compared in the tables. A p value lower than 0.05 was considered as statistically significant. The survival curves of the groups found to be statistically significant in the analysis were drawn.

Results

After data cleaning, the number of female BC was reduced to 19,503. The estimated age-adjusted breast cancer risk in women according to the 2013 census data is displayed in Figure 1. The median age of patients at diagnosis was 51 [14-97]. The age group 45-49 was the most populated group (16.5%) in the cohort for 5-year age intervals. At the time of diagnosis, 37.5% of patients were premenopausal. The mean menarche age was 13.4 (±1.0) years, the mean breastfeeding duration was 24.2 (±17.7) months, missed abortion rate was 19.4%, induced abortion rate was 29.9%, the rate of oral contraceptive use was 14.7%, and child delivery rate was 86.3% (mean number of births given was 2.4±1.8). Only 8.2% of the patients diagnosed with breast cancer received hormone replacement therapy (HRT) on a regular basis, while 27% of them received HRT for more than 5 years. 33.9% of the patients had a family history of any cancer, and 15.8% of them had a family history of breast. 3.3% of them had family history of ovarian cancer, respectively. Patients and tumor characteristics are displayed in Table 1.

Table 1. Patients and tumor characteristics

Number of patients	19503
Mean age (±SD)	51.8 (±12.6)
<40 years old	3101 (16.6%)
≥40 years old	15604 (83.4%)
Histopathologic subtype	
Invasive ductal cancer	7726 (76.9%)
Invasive lobular cancer	649 (6.5%)
Invasive mixed type	425 (4.2%)
Other	1241 (12.4%)
Histologic grade	
I	562 (7.7%)
II	3416 (46.8%)
III	3320 (45.5%)
Receptor status	
ER	5745 (72.5%)
PR	4736 (62.5%)
HER-2	1659 (21.8%)
Ki-67 (≤%14)	378 (%35.0)
Pathologic stages at the time of diagnosis	
Stage I+II	4990 (76.8%)
Stage III+IV	1728 (23.2%)
Obstetric history	
Nulliparous	1281 (13.6%)
Monoparous	1227 (13.1%)
Spontaneous abortion	1494 (19.3%)
Induced abortion	2326 (30.0%)
Molecular subtypes	
Luminal A	3326 (57.7 %)
Luminal B	1187 (50.3 %)
HER-2	555 (12.2 %)
TNG	695 (8.1 %)
5-year overall survival	3555 (85.8%)
10-year overall survival	4826 (75.7%)

ER: Estrogen; PR: Progesterone; TNG: triple negative

Breast conserving surgery rate was 39.3%, and mastectomy rate was 60.7%. Sentinel lymph node biopsy was performed for the patients who were negative for axillary involvement in clinical examination (69.4%); 55.3% of the patients underwent axillary lymph node dissection (ALND). When the surgical interventions are divided into groups regarding years before and after 2000, breast conserving surgery (BCS) rate was 25% before and 45% after the year 2000. As a result, the rate of patients with mastectomy decreased from 75% to 60.7% in the last 15 years.

Among patients with complete histopathologic diagnostic data, the majority (72.8%) of them had invasive ductal cancer (IDC); 10.1% of them had invasive lobular cancer (ILC) or invasive mixed cancers (IMC=IDC+ILC). A comparison between age groups and histopathological tumor types (IDC, ILC and IMC) revealed that the rate of IDC was 91.5% among young women (<40 years) while it was 87% for older women (≥40 years) (p<0.001).

The distribution of patients whose Modified Scarff Bloom Richardson HG were registered in the database was as follows: HG I 7.8%, HG II 46,8%, HG III 45.5%. Majority of the patients had HG II or III tumors, whereas HG declined with an inverse relation with the increase in the age at diagnosis (p<0.001). The histological grades of tumors (HG) were divided into two groups as HG I+II and HG III, and their associations with histological types (IDC and ILC/IMC) were studied. Nearly half of all patients (45.5%) had HG III. 46,4% of patients with IDC had HG III, while 37.3% of patients with ILC/IMC had HG III (p<0.001).

The distribution of the pathologic stages of these patients at diagnosis was as follows: Stage 0 (DCIS) 4.7%, Stage I 28.5%, Stage II 48.3%, Stage III 14.5% and Stage IV 4%. The rate of Stage I breast cancer was 21.9% in women aged ≤40 years; while it was 30.6% in the age group 50-59 (p<0.05). Percentage distribution of the pathological lymphatic stages according to different age groups are displayed in Figure 2. As for the association between pathologic stages and age groups, it was found that pathologic stage decreased with advancing age at diagnosis (Figure 3, p=0.002).

The mean tumor diameter was 2.5±1.7 cm, while the median tumor size was 2 cm [0.1–25 cm]. The tumor diameter in young patients (<40 years) was significantly larger (mean diameter 2.8; median diameter 2.5 cm; p<0.001). Lymph node involvement rates of patients diagnosed with invasive breast cancer were as follows: pN0 51.4%; pN1 28.1%; pN2 13.9% and pN3 6.6%. The clinical stages of patients were Stage-0 2.3%, Stage I 29.7%, Stage II 44.2%, Stage III 21.4% and Stage IV 2.4%. Associations of pathological lymphatic stages with different tumor diameter groups are displayed in Figure 4.

Estrogen receptor positivity was (72.5%). The patients were divided into two age groups (<40 y/o and ≥40 y/o) to compare ER positivity between these groups. ER positivity was 65.9% in young (<40 y/o), and 73.8% in older patients (age ≥40 y/o, p<0.001). Progesterone receptor positivity was 62.3%. PR positivity rate was higher in older patients (≥40 y/o) (62.5% vs. 60.5%, p>0.05). HER-2 receptor expression was analyzed through immuno-histochemical (IHC) and fluorescence in situ hybridization method (FISH/SISH). It was found that 21.8% of the patients were HER-2 positive.

In the cohort, rate of Ki-67 value >14% was 62.7%, while the percentage of those with a Ki-67 value of >20% was 54.2%. 59% of the

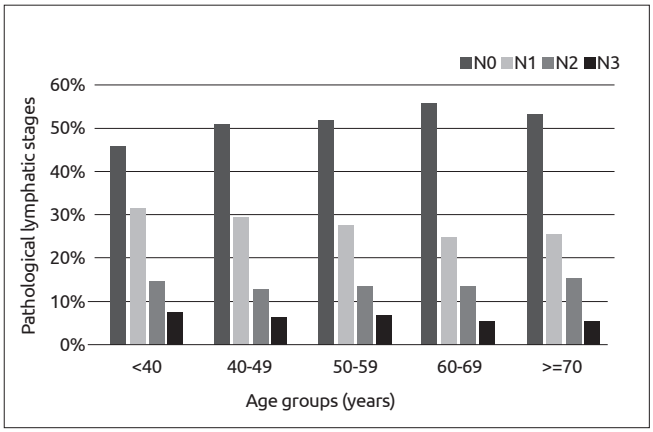

Figure 2. Pathological lymphatic stages according to different age groups

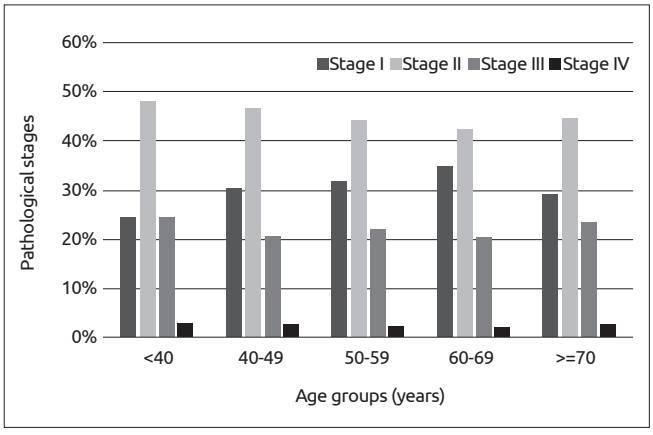

Figure 3. Pathological stages according to different age groups

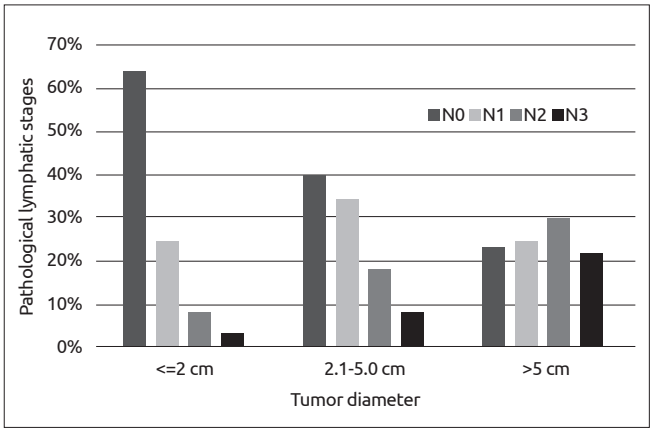

Figure 4. Associations of pathological lymphatic stages with different tumor diameter groups

patients were positive for lymphovascular invasion. Estrogen (ER), progesterone (PR) and HER-2 receptor expression were positive in 76.9%, 65.8% and 21.8% of the patients, respectively.

The mean follow-up time was 51.6 months and loco-regional recurrence rate was 3.7% in this period. The overall survival rate was 85.8% for 5-years and 75.7% for 10-years. Young age (<40 y/o, p<0.049), small tumor size (<5 cm vs. ≥5 cm, p=0.017), high HG (I+II vs. III; p=0.003), PR status (positive or negative; p<0.001), pathologic stage (Stage I vs. III, p=0.036), and triple negative and HER-2 positive

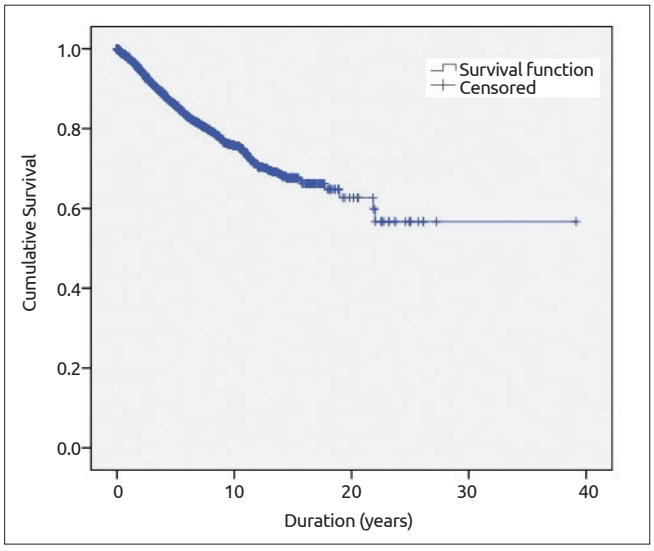

Figure 5. Overall survival rate of breast cancer patients

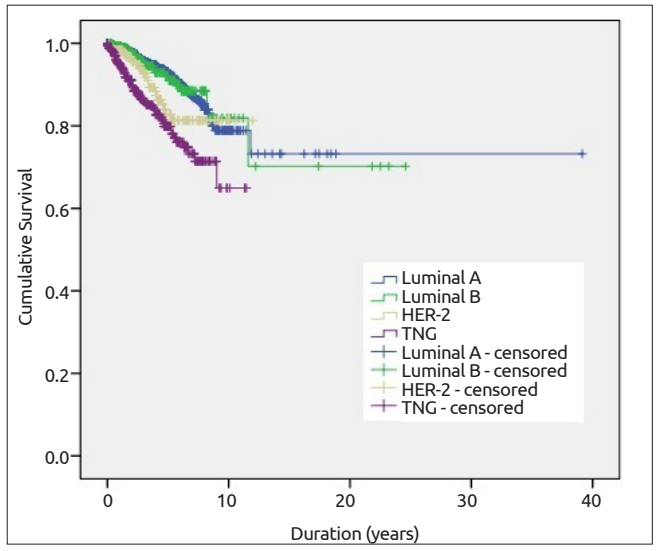

Figure 6. Overall survival according to different molecular subtypes

Table 2. Comparison of data of breast cancer patients in 2012 and 2017

	TFBDS Registry 2005-2010 13.120 patients	TFBDS Registry 2005-2015 20.000 patients	Difference in 5-years
Mean age, years	51.6±12.6	51.8±12.6	0.2
<40 years, %	17.1	16.5	0.6
>70 years, %	10	10	-
Pre-menopausal, %	45	37.7	7.3
DCIS, %	4.9	4.7	0.2
pN0, %	49.8	51.4	1.6
Mean tumor size (cm)	2.5±1.6	2.5±1.7	-
pStage I, %	26.6	29.7	3.1
BCS, %	35	39	4
5-year overall survival, %	-	86	

DCIS: Ductal carcinoma in situ, BCS: Breast conserving surgery, pStage: Pathologic stage

molecular subtypes (p<0.001; p<0.001) were found related with locoregional recurrence. Overall survival rate and overall survival according to different molecular subtypes are displayed in Figure 5 and Figure 6, respectively.

Distant metastasis rate was 9% in 4.3 years of follow-up period. Young age (<40 vs ≥40; p<0.001), type of surgery (mastectomy vs. BCS; p<0.001), pathologic lymphatic stage (pN0 vs pN1-3, p<0.001), menopausal status (pre- vs post-menopausal; p=0.013), tumor size (<2 cm vs. ≥2 cm p<0.001), histopathological type (IDC vs ILC or IMC, p=0.002), HG (I+II vs III, p=0.002), and molecular subtypes (Luminal A vs. others p<0.001; Luminal A/B vs. HER-2/TNG p<0.001; TNG vs. others p<0.001) were found to be associated with distant metastasis.

When we compared these results with our previous study, the rate of premenopausal women decreased from 45% to 37.7%, the rates of pathologic Stage I breast cancer and breast conserving surgery (BCS) increased 3.1% and 4% respectively (Table 2). The rates of DCIS and tumor size of invasive breast cancer did not change in this 5-year period.

Discussion and Conclusion

Although breast cancer mortality rates are decreasing in most high-income countries, incidence and mortality rates are increasing particularly in rapidly developing countries (7). Such increase is explained by changes in life styles (changes in the reproductive functions such as early menarche, nulliparity, delivery after 35 years old, less breast feeding, late menopause, etc.), nutritional habits (obesity, inactivity etc.), increased population growth, aging and increasing opportunistic screening (8). Although it is a possibility that improvements in access to medical care over time, might have resulted in inclusion of patients with milder disease in estimates, the reported incidence of breast cancer in Turkey increased more than 2-folds from 24/100.000 in 1993 to 50/100.000 in 2017.

Cancer registry is the starting point of cancer control. Unless accurate data are obtained and statistically assessed, prioritization cannot be achieved and sound decisions cannot be made for development of national health policies, strategic plans and utilization of limited resources. Currently, there are around 200 population-based registries maintained across the world. Under the light of these registries, IARC (International Agency for Research on Cancer) under the World Health Organization (WHO) publish global health statistics covering all countries in the world. The incidence and mortality analyses on cancer that is performed every 3-5 years are published as GLOBOCAN for the use of the scientific community. One of the most popular registries is the SEER Program (The Surveillance, Epidemiology, and End Results). It is affiliated to the National Cancer Institute (NCI) and started collecting data in 1973 as the official source of data in the USA on cancer incidence and survival (9). On the European side, in 1995, the European Commission has supported the European Network of Cancer Registries (ENCR) which was set up in 1990 (10). In Turkey, the first cancer registry was kicked off in 1982. In the late 90's, İzmir Cancer Registry became a member of the IARC, and of the ENCR. In 2002 and 2008, IARC used İzmir Cancer Registry data for GLOBOCAN, which served as an endorsement of the quality of data from the province of İzmir (11). Eventually, local initiatives created a stronger national emphasis and National Breast Cancer Database (NBCD) was launched for use in 2005. The ultimate aim is to contribute to the national cancer registry program by revealing very different characteristics of a large patient population.

Today we understand that the rapid westernization especially in the younger population, increases the breast cancer incidence in Turkey. The rate of young female (<40) and premenopausal patients with invasive breast cancer were 16.6% and 37.5%, respectively, in our study. Complete prevalence distributions of patients (with invasive breast cancer) younger than 40 and 50 years old were 1.1% and 7.5%, respectively, on January 1, 2015 according to the SEER database (12). The Ministry of Health of the Republic of Turkey has changed the screening period from 50-69 to 40-69 years of age due to the NBCD results revealing that the distribution of breast cancer cases under 50 years of age constitutes 47% of all cases in Turkey.

Breast cancer is most frequently diagnosed among women aged 55-64 in developed countries; median age at diagnosis is 62 in USA. The most populated group is 45-49 in Turkey, where the median age is 51. This can be explained by the young population age. In the United States, DCIS accounts for 20% of all newly diagnosed breast cancers (13). In Turkey, DCIS patients constituted only 5% of all patients diagnosed with breast cancer. The mean tumor diameter was 2.5±1.7 cm. It can be thought that this situation is related to the lack of community-based screening, lack of education and low breast cancer awareness. In order to demonstrate the feasibility of well-organized, continuous and invitation-driven community-based screening program in line with the social, cultural, educational and economic structure of Turkey, "Bahçeşehir Community-Based Mammographic Screening Project" was launched in Bahçeşehir for up to 10 years (2008-2018). In this Project, among patients diagnosed with breast cancer, 19% had ductal carcinoma in situ (DCIS), and 55% had stage I invasive breast cancer (14). These results indicate the possibility of a successful community-based screening in our country.

The molecular sub-type analysis of the tumors in this study showed that 57.7% of the tumors were luminal A (ER and/or PR positive, HER-2 negative), 20.6% were luminal B (ER and/or PR positive, HER-2 positive), 9.6% were HER-2 type (ER and PR negative, HER-2 positive) and 12.1% were triple negative. Studies comparing the patients with breast cancer detected through screening and symptomatic breast cancer cases found that tumor diameter is smaller and the rate of luminal A subtype of breast cancers is higher in patients diagnosed with breast cancer through screening (15, 16). In 2011, St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer recommended the clinical use of Ki-67 index (cut-off value >14%), to distinguish luminal A and B molecular subtypes (17). Many specialized breast centers updated their data based on modern definitions of molecular subtypes and some centers reported their updated results. For example, the molecular subtypes of regularly followed-up 2032 patients from Istanbul Florence Nightingale Breast Center were as follows; Luminal A and B (Ki67 >14%, HG=3) were 30,4% and 50,3%, respectively; HER-2 positive group was 8,1%; triple negative breast cancer was 11,2% (18, 19).

The mortality rates of breast cancer cases in USA decreased from 24.1 in 2005 to 21.5 in 2010 and to 20.3 in 2015; and overall 5-year survival rate is 90.9%. The 5-year survival rate was found to be 86% in this study. Thus, it is imperative that increased use of screening programs and increasing awareness will result in a reduction in the tumor diameter and regional lymphatic involvement in breast cancer patients.

This study highlights the impact of mammographic screening and the benefits of a structured national breast cancer registry. The NBCRP registry, constituting a national framework for breast cancer control, facilitates the evaluation of the improvement in screening, ongoing awareness, education and training. Despite increasing number of screening centers and free-of-charge mammography (ages 40 to 69) and mobile screening systems in recent years, a significant portion of patients were diagnosed at advanced stage due to lack of breast cancer awareness. In contrast with the study published 5 years ago, there was a decrease in the rate of pre-menopausal women and an increase in the breast conserving surgery.

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Original Article

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Imaging Findings and Clinicopathological Correlation of Breast Cancer in Women under 40 Years Old

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ABSTRACT

Objective: The aim of this study was to evaluate the clinical, imaging and histopathological features of breast cancer in patients aged under 40 years of age. The relationship between radiological characteristics and histopathological features was also investigated.

Materials and Methods: The study included 131 patients aged under 40 years, diagnosed pathologically with breast cancer. A retrospective evaluation was made of the imaging and clinicopathological findings and the relationship between pathological and imaging findings was investigated.

Results: Most of the cancers were detected from clinical symptoms, especially a palpable mass (76.3%). The most common histological type of tumor was invasive ductal carcinoma and 64.8% of the tumors were high grade tumors. The predominant features were irregular borders (92.4%), microlobulated-angulated contours (43.5%), hypo-homogeneous internal echogenicity (80.9%) on ultrasonography, and the presence of a mass (41.2%) and suspicious microcalcifications (40.2%) on mammography. Magnetic resonance imaging commonly showed mass enhancement (66.7%) with type 2 or 3 dynamic curve (92.6%). High-grade tumors were associated with posterior acoustic enhancement (p: 0.03) while low-grade tumors presented with spiculated margins more than high grade tumors (p: 0.04).

Conclusion: Breast cancer in women aged under 40 years usually presents with a self-detected palpable mass and can show different imaging findings according to the histological grade. Ultrasonography is the main modality for the diagnosis of breast cancer in young women, but mammography and magnetic resonance imaging can help in both diagnosis and evaluation of the extent of disease.

Keywords: Young women, breast cancer, radiological findings, pathology features

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Introduction

Breast cancer is less common in women under 40 years old and this age group constitutes approximately 7% of all women diagnosed with breast cancer (1, 2). However, it can have a worse prognosis and more aggressive biological behavior than breast cancer in older patients. Previous studies have shown that young women are diagnosed at a later stage with highly proliferative, poorly differentiated, estrogen receptor negative tumors with the presence of lymphovascular invasion (3-5).

The radiological findings of breast cancer in young women can vary and the diagnosis of cancer can be more challenging than in an older population as there are also different histopathological features (6, 7). Most medical associations, including the American College of Radiology and Society of Breast Imaging, recommend annual breast cancer screening starting at the age of 40 and the sensitivity of mammography is lower in young women due to denser breast tissue (8, 9). The use of breast ultrasonography (US) is preferred for women under 40 years old in the diagnosis of breast disease, but mammography or Magnetic Resonance Imaging (MRI) should be performed if there is a suspicious finding for malignancy (10).

Therefore, the aim of this study was to evaluate the clinical, imaging and histopathological features of breast cancer in patients aged <40 years. The secondary objective was to investigate the relationship between radiological characteristics and histopathological features.

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Materials and Methods

Patients

Approval for the study was granted by the Hacettepe University Ethics Commission. Informed consent was not required because of the retrospective nature of the study.

A retrospective review was made of 2619 women applied with breast core needle biopsy between June 2011 and December 2017. A total of 443 patients were under 40 years old. Those with benign pathology results were excluded from the study and thus 131 patients diagnosed with breast cancer were included for evaluation in the study.

Imaging

All patients underwent ultrasonography, 107 patients had mammography and only 27 patients had MRI. Patients aged >35 years with a family history and those with a personal history of breast cancer underwent mammography as the initial modality. For other patients, US was applied first and then mammography was performed because of suspicious findings. MRI was applied to 27 patients to evaluate the extent of breast cancer before breast-conserving surgery.

The US images were obtained using a 12 MHz linear probe on a Toshiba Aplio 400 device (Toshiba Medical Systems Corporation, Otawara, Japan). For the mammograms, standard mediolateral oblique and craniocaudal images were obtained using Seno essential mammography systems (General Electric, USA). The MRI scans were acquired with the patient in the prone position in a 1.5-Tesla MRI scanner (Signa HD, GE Medical Systems, USA) using a four-channel phased array breast coil. The imaging protocol included the following sequences: axial T2-weighted fat saturated (TR/TE 5100/90 ms, slice thickness=2 mm, flip angle 90°, matrix 256x256), axial echo-planar DWI (TR/TE 2500/72, slice thickness =3 mm, matrix 256x256, diffusion gradient with b values of 0 and 500 s/mm^2), and axial T1-weighted fast spin echo pre-contrast MR images (TR/TE 4.3/2.1 ms, slice thickness=2 mm, flip angle 90°, matrix 512x512). Dynamic breast examination was performed after the injection of intravenous contrast material (Dotarem, Guerbet, Roissy, France) through the antecubital vein at a dose of 0.1 mmol/kg using a power injector (Medrad, Bayer HealthCare, Netherlands). After pre-contrast T1-weighted images, the following 5 axial T1-weighted post-contrast dynamic sequences (TR/TE 4.5/2.1 ms, slice thickness=2 mm, flip angle 10°, matrix 512x512) were obtained at intervals of 90 seconds.

Pathological examination

The pathological reports were reviewed to determine histopathological type, tumor grade and immunohistochemical findings including Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Receptor 2 (HER 2) status. HER 2 status was defined as positive for tumors with a score of 3+ and negative for tumors with scores of 0 and 1+. In tumors with a 2+ score, gene amplification using Fluorescence in situ Hybridization (FISH) analysis was used to confirm the HER 2 status. Testing negative for all three hormone receptors was defined as triple negative breast cancer.

Statistical Analysis

Descriptive statistics including patient age, tumor size, clinical presentation, histopathological type, grade, immunohistochemical and radiological findings were presented as frequencies and percentages of categorical variables and means and standard deviations of quantitative variables. The Independent Samples t-test was performed to compare the means of two groups (grade1-2 and grade 3) and Pearson chi-square test, Yates' chi-square test or Fisher Exact tests were used to compare differences between groups for categorical variables including radiological findings and histopathological findings Spearman's rho correlation was used to examine the relationship between two quantitative variables. A value of $p<0.05$ was accepted as statistically significant. All statistically analyses were performed using The Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA).

Results

Clinical and histopathological data

The clinical and histopathological features are presented in Table 1. Most cancers were detected from clinical symptoms, especially a palpable mass (101/131, 77% symptomatic, 100/131 patients with a palpable mass). 22.9% of patients were asymptomatic and were diagnosed with breast cancer when they underwent breast US due to personal or family breast cancer history. The most common histological type of tumor was invasive ductal carcinoma, 64.8% of tumors were high-grade, and 17.6% of tumors were triple negative.

Table 1. Clinical and pathological characteristics of 131 patients

Characteristics	Number (%)
Mean age (year±SD)	34.2±3.6
Clinical presentation	
-Palpable mass	100 (76.3)
-Personal breast cancer history	10 (7.6)
-Family breast cancer history	20 (15.3)
-Bone metastasis	1 (0.8)
Histopathological type	
-Invasive ductal carcinoma	96 (73.3)
-Invasive lobular carcinoma	5 (3.8)
-Mixed carcinoma	20 (15.3)
-Mucinous type	3 (2.3)
-DCIS	7 (5.3)
Tumor Grade	
-Grade 1	4 (3.1)
-Grade 2	42 (32.1)
-Grade 3	85 (64.8)
Immunohistochemical findings	
ER positivity	87 (66.4)
PR positivity	71 (54.2)
HER 2/Cerb positivity	34 (26.0)
Triple negative	23 (17.6)

SD: Standard deviation; DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; PR: Progesterone receptor; HER 2: Human epidermal growth factor receptor-2

Table 2. Radiological findings of lesions

Findings	Number (%)
Size (±SD) mm	36.3 (±28.3)
Axillary lymphadenopathy in US	79 (60.3)
Skin thickening	24 (18.3)
Multifocality	49 (37.4)
BI-RADS category according to US-MMG	
-BI-RADS 4A	8 (6.1)
-BI-RADS 4B	16 (12.2)
-BI-RADS 4C	16(12.2)
-BI-RADS 5	91 (69.5)
US Findings (131 patients)	
-No abnormality	5 (3.8)
-Shape	
-Irregular	121 (92.4)
-Oval-round	5 (3.8)
-Margin	
-Circumscribed	2 (1.5)
-Microlobulated and angulated	57 (43.5)
-Indistinct	45 (34.4)
-Spiculated	22 (16.8)
-Posterior acoustic feature	
-No feature	76 (58.0)
-Acoustic enhancement	29 (22.1)
-Acoustic shadowing	26 (19.8)
-Echogenicity	
-Iso-homogeneous	2 (1.5)
-Hypo-homogeneous	106 (80.9)
-Heterogeneous	18 (13.8)
Mammography findings (107 patients)	
-No abnormality	17 (15.9)
-Abnormality	90 (84.1)
-Microcalcifications	43 (40.2)
-Asymmetrical density	29 (27.1)
-Distortion	7 (6.5)
-Mass	44 (41.2)
-Mass shape	
-Oval-round	9 (8.3)
-Irregular	35 (32.7)
-Mass margins	
-Circumscribed	1 (0.9)
-Microlobulated	5 (4.6)
-Indistinct	13 (12.1)
-Obscured	17 (15.8)
-Spiculated	8 (7.4)
MRI findings (27 patients)	
-Mass	18 (66.7)
-Non-mass enhancement	9 (33.3)
- Kinetic curve	
-Type 1	2 (7.4)
-Type 2 and 3	25 (92.6)
-T2W signal intensity	
-Isointense	18 (66.7)
-Hyperintense	9 (33.3)
Grade 1-2 (46)	
-Spiculated margins	12 (26.1)
-Posterior acoustic enhancement	5 (10.9)
-Heterogeneous internal echogenicity	4 (8.7)
-Microcalcifications	19 (50)
-Mass enhancement in MRI	4 (57.1)
-T2W signal intensity	1 (14.3)
Grade 3 (85)	
-Spiculated margins	10 (11.8)
-Posterior acoustic enhancement	24 (28.2)
-Heterogeneous internal echogenicity	14 (16.5)
-Microcalcifications	24 (34.8)
-Mass enhancement in MRI	14 (70)
-T2W signal intensity	8 (40)

SD: Standard deviation; US: Ultrasonography; MMG: Mammography; MRI: Magnetic resonance imaging; BI-RADS: Breast imaging reporting and data system

Imaging findings

The radiological findings of tumors are summarized in Table 2. Breast Imaging Reporting and Data System (BI-RADS) categorisation was applied according to the US and mammography findings. Most patients were categorized as BI-RADS 5, and only 8 patients as BI-RADS 4A. The mean size of tumors was 36.3 mm. 60.3% of patients had axillary lymphadenopathy, which was also proven to be malignant pathologically. Skin thickening was present in 24 (18.3%) patients, and multifocal/multicentric tumors were seen in 49(37.4%).

US

Ultrasonography was performed on all the patients. In 5 (3.8%) patients, no abnormality was determined on US and these cases were diagnosed with microcalcifications seen on mammography. The predominant features on US were irregular shape (121, 92.4%), microlobulated-angulated margins (57, 43.5%) and hypo-homogeneous internal echogenicity (106, 80.9%). Most patients (76, 58%) did not have a posterior acoustic feature, and 22.1% of patients demonstrated posterior acoustic enhancement.

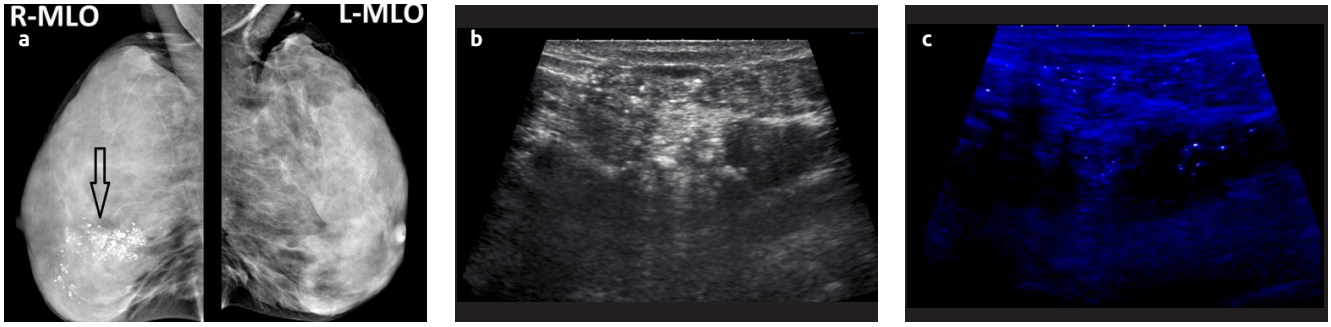

Figure 1. a-c. Malignant pleomorphic microcalcifications are seen on mammography (a), ultrasonography (b) and micropure imaging (c) in a 27-year old patient with grade 3 breast cancer

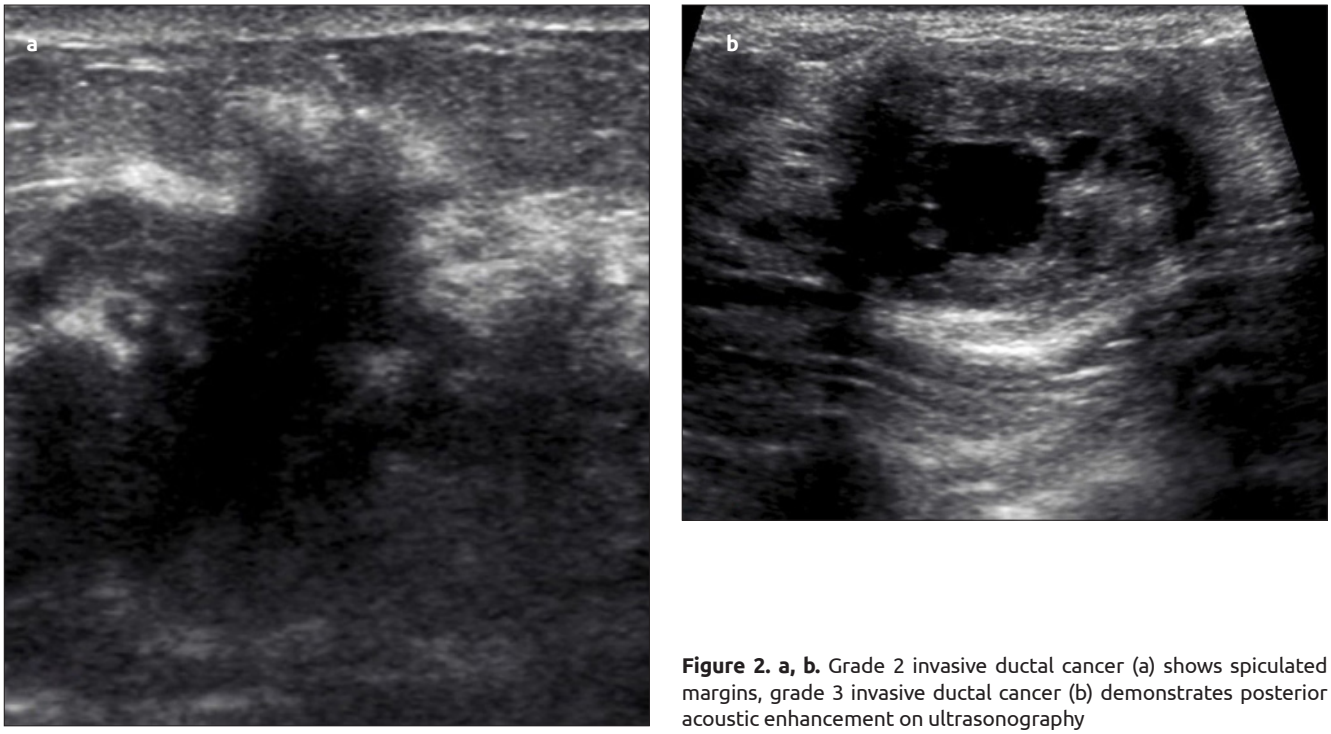

Figure 2. a, b. Grade 2 invasive ductal cancer (a) shows spiculated margins, grade 3 invasive ductal cancer (b) demonstrates posterior acoustic enhancement on ultrasonography

Mammography

Mammography was applied to 107 patients (81.6%) and on 84.1 % of these images an abnormality was determined. The most common abnormality on mammography was the presence of a mass (44/107, 41.2%), followed by suspicious microcalcifications (43/107, 40.2%) (Figure 1). In 5 patients, the diagnosis was made based on the presence of microcalcifications on mammography only. The most frequently seen shape on mammography was irregular, and the most common margin feature was obscured.

MRI

All of the patients were diagnosed with US and mammography findings. MRI was applied to 27 (20.6%) patients to evaluate the extent of the disease before surgery. Of these 27 cases, 18 (66.7%) presented with mass enhancement, and 9 (33.3%) presented with non-mass enhancement. Most patients demonstrated type 2 or 3 dynamic curve (25/27, 92.6%). In 9 of 27 (33.3%) patients the cancer was hyperintense, and the T2W signal intensity was predominantly isointense in 18 (66.7%).

Relationship between histopathological features and imaging findings

High-grade tumors were associated with posterior acoustic enhancement (grade1, 2: 10.9%, grade 3: 28.2% p: 0.03), and low-grade tumors presented with spiculated margins more than high-grade tumors (grade 1-2: 26.1%, grade 3: 11.8% p: 0.04) (Figure 2).

High pathological grade tumors showed more internal heterogeneity than grade 1 and 2 tumors (grade1-2: 8.7%, grade 3:16.5% p: 0.09) (Figure 2). On MRI, T2W hyperintensity was more commonly seen in high-grade tumors than low-grade tumors (grade1, 2: 14.3%, grade 3: 40% p: 0.3). (Figure 3). Skin thickening (grade 1, 2: 13%, grade 3: 21.2% p: 0.3) and the presence of axillary lymphadenopathy (grade 1, 2: 50%, grade 3: 65.9% p: 0.1) were more frequently seen in high-grade tumors than low-grade tumors, but these findings did not reach statistical significance.

The histopathological grade did not show any association with the other radiological findings including shape, margins, and microcalcifications. No statistically significant relationship was determined between immunohistochemical findings and imaging findings.

Discussion and Conclusion

Breast cancer in young women is uncommon but shows more aggressive histopathological features and has a poorer prognosis (5, 11, 12). In the current study, the majority of breast cancers in women under

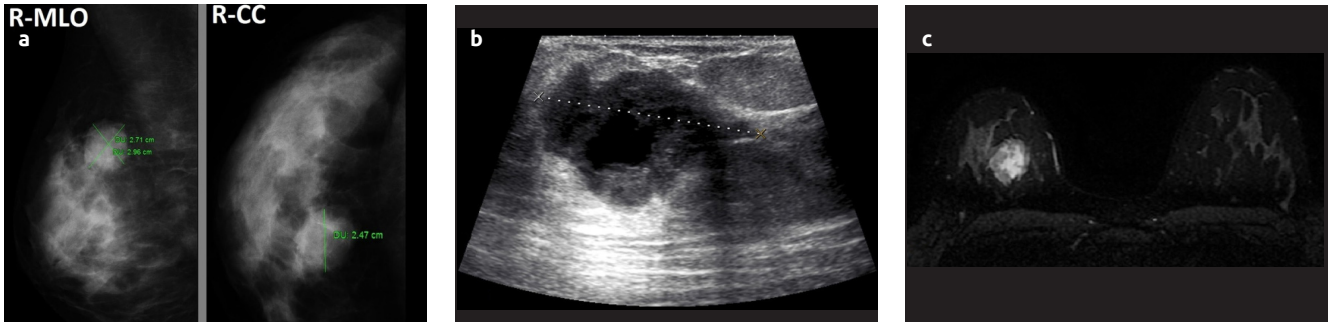

Figure 3. a-c. Imaging findings are shown of a 26-year old patient with grade 3 invasive ductal carcinoma. Mediolateral and craniocaudal mammography images (a) demonstrate round shape, ultrasonography image (b) shows internal heterogeneity and posterior acoustic enhancement and magnetic resonance image (c) indicates T2W hyperintensity

40 years old presented symptomatically especially with a palpable mass and more than half of the patients had axillary lymphadenopathy on US at the time of diagnosis. With the exception of the high-risk group, young women are not included in breast screening programs. The reason for a poorer prognosis may be a late diagnosis and axillary or distant metastasis at diagnosis. However, several studies have shown that breast cancer in young women has a higher percentage of negative ER and PR receptors, higher lymphovascular invasion, grade and expression of proliferation markers including KI-67 and cyclins (12-14). Similar to a previous study, the findings of the current study showed that breast cancer in women under 40 years old was associated with a higher histological grade (6).

Radiological diagnosis of breast cancer in young women is more challenging compared to older counterparts. Most medical associations recommend annual breast cancer screening starting at the age of 40 years old for women at average risk. Mammography is the main modality for breast cancer screening (9, 15). Breast density can hide breast cancer and therefore mammography sensitivity is decreased in young women because of the higher breast tissue density (16). Due to the higher density, overdiagnosis and accumulation of radiation in young women, ultrasonography is the primary modality for the diagnosis of breast cancer. In the current study, ultrasonography was performed on all patients and with the exception of 5 patients, there was an abnormality in all patients. Of the patients who underwent mammography, an abnormality was detected in 84.1%. Moreover, 5 patients who could not be diagnosed by US were diagnosed by mammography. On mammography the most common findings of tumors were microcalcifications and mass. The shape of the masses was usually irregular, which was consistent with the findings of previous studies (6, 17). The predominant margin features were microlobulated-angulated on US and obscured in mammography. In contrast to the current study, Bullier et al. (17) found a predominance of spiculated margins in women with breast cancer aged <40 years. The lower rate of spiculated margins in the current study could be attributed to the higher percentage of high-grade tumors.

Magnetic Resonance Imaging was performed on patients for evaluation of the extent of cancer before breast cancer conserving surgery. Most patients showed mass enhancement, T2 isointensity and type 2 or 3 dynamic curves similar to the results of previous studies (6, 17, 18). Dynamic curves (92.6 % of patients have type 2/3 curves) in particular could help the radiologist in the diagnosis of breast cancer in young women whose diagnosis can be more challenging than in an older population.

The association between radiological findings and histological grade was also investigated. High-grade tumors were related to posterior acoustic enhancement, while low-grade tumors were related to spiculated margins. Moreover, on MRI T2W, hyperintesity was more commonly seen in high-grade tumors than in low-grade tumors, but this finding could not reach statistical significance probably due to the low number of patients with MRI findings. The results of previous studies supported the current study findings and it has been reported that high-grade and triple negative tumors can mimic benign lesions with circumscribed margins and posterior enhancement (17, 19). High-grade tumors are known to demonstrate higher cellularity and necrosis, which could be the reason for the internal heterogeneity, posterior acoustic enhancement and T2W hyperintensity. However, low-grade tumors usually show higher stromal reaction and desmoplasia which may cause spiculated margins (17, 20, 21). Women under 40 years old show a diverse distribution of histological grades, as 64.8% of our patients had higher grade tumor. Therefore, due to the different imaging findings of high-grade tumors, breast cancer under 40 years old can show distinct radiological findings from their older counterparts.

There were some limitations of the current study. The major limitation was the retrospective design. Second, the number of patients evaluated with MRI was low and this may have caused the lack of statistical significance. Finally, although the immunohistochemical findings were investigated, molecular subtypes could not be evaluated due to the lack of Ki 67 data in some patients.

In conclusion, breast cancer in women under 40 years old usually presents with a self-detected palpable mass and can show different imaging findings including posterior enhancement, T2W hyperintensity and less spiculated margins due to a higher histological grade. US is the main modality for diagnosis of breast cancer in young women, but mammography and MRI can help both diagnosis and evaluation of the extent of the disease. Awareness of imaging and clinicopathological findings of breast cancer in young women helps the radiologist to make an early and accurate diagnosis, and the clinician to provide the correct treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hacettepe University School of Medicine.

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

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Original Article

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3D Automated Breast Ultrasound System: Comparison of Interpretation Time of Senior Versus Junior Radiologist

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ABSTRACT

Objective: This study aimed to compare the automated breast ultrasound system (ABUS) reading time of breast radiologist to a radiology resident independent of the clinical outcomes.

Materials and Methods: One hundred women who underwent screening ABUS between July and August 2017 were reviewed retrospectively. Each study was examined sequentially by a breast radiologist who has more than 20 years of experience in breast radiology and third year resident who has 6 months of experience in breast radiology. Data were analyzed with Spearman' correlation, Wilcoxon Signed Ranks Test and Kruskal-Wallis Test and was recorded.

Results: The mean age of patients was 42.02±11.423 years (age range16-66). The average time for senior radiologist was 223.36±84.334 seconds (min 118 max 500 seconds). The average time for junior radiologist was 269.48±82.895 seconds (min 150 max 628 seconds). There was a significant difference between the mean time of two radiologists (p=0.00001). There was a significant difference regarding the decrease in the reading time throughout study with the increase of number of cases read by the breast radiologist ($p<0.05$); but not with the resident radiologist (p=0.687). There was a correlation between BI-RADS category and reading time for both the breast radiologist and the resident (p=0.002, p=0.00043 respectively) indicating that patients who had findings caused longer reading times.

Conclusion: ABUS reading time may differ according to the experience of the user, however the times of an experienced and non-experienced user is comparable.

Keywords: Automated breast ultrasound, breast ultrasonography, breast cancer, interpretation time of ABUS, average time of ABUS

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Introduction

Mammography is the gold standard for breast cancer screening yielding 30% reduction in breast cancer mortality among women aged 50-74 years (1). Mammographic sensitivity for breast cancer decreases significantly with increasing breast density. To overcome this, ultrasonography (US) has been studied as an adjunct to mammography in dense breasts and studies showed significant increase in detection of small cancers when added to mammography (2, 3).

Hand Held Ultrasound (HHUS) is widely available and a well-tolerated method which allows detailed evaluation of the breast and the axilla and has the availability of color Doppler and elastography modes (4, 5). On the other hand, HHUS has several disadvantages. It is time consuming, operator-dependent, not reproducible and requires high level of skill and experience. It has high false positivity rate, lacks standardized techniques, allows only two-dimensional (2D) imaging with a small field of view (FOV) (4, 6-8).

Automated three-dimensional (3D) breast ultrasound (ABUS) was developed to obtain an operator independent system. It is reproducible and obtains three dimensional (3D) high resolution imaging with a large FOV. ABUS is reported as a comfortable and time-efficient technique (7-10). Multiple studies have demonstrated similar sensitivity, cancer detection rate, diagnostic accuracy rates and image quality for both ABUS and HHUS (11-16). The new generation ABUS provides better detection of architectural distortions, lesion localization and typical hyperechoic rim on coronal planes (9, 17, 18). Thick hyperechoic rim is suspicious sonographic finding which suggests

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the presence of invasive cancer. However, ABUS has some limitations such as 10% lower cancer detection rate, higher false positive results and recalls, shadowing artefacts, incompatibility for US guided biopsy, limited evaluation of axilla, absence of elastography or Doppler techniques for further characterization of the lesions and relatively higher cost compared to HHUS (4, 18-20).

To our knowledge, limited studies of reading time of US have been reported in the English literature (4, 21-23). The average total time to complete a HHUS is 19 minutes (23). The aim of this study was to assess ABUS reading time and compare the reading times of a breast radiologist and a radiology resident independent of the clinical outcomes.

Materials and Methods

Institutional review board approval (No: 2018-2/9) was obtained for this study by Acıbadem Mehmet Ali Aydınlar University ethics committee. Additional informed consent was obtained from all patients for which identifying information is included in this article. One hundred women (age range 18-66 years; mean 42.02±11.423 years) who underwent screening ABUS examination between July and August 2017 were reviewed retrospectively.

We excluded twelve patients who were already diagnosed with breast cancer and had a breast surgery history, skin disorders, inflammatory conditions of the breast, breastfeeding woman and pregnancy. Patients with larger breasts which needed more than three positions were also excluded from the study. ABUS images of one hundred women were evaluated by two readers.

Automated Three-Dimensional (3D) Breast Ultrasound (ABUS)
Automated breast ultrasound studies were performed using the ABUS (Invenia™ ABUS, GE Healthcare) scanner by two well-trained radiology technicians with one month of experience on automatic ultrasound. The examination was performed in the supine position with the ipsilateral arm above the head. A hypoallergenic lotion and a disposable membrane were used to aid an acoustic coupling. Each breast was examined in three different positions; i) anteroposterior (AP), ii) lateral (LAT) including the pectoral muscle and iii) medial (MED). A nipple marker was placed on the coronal view to locate the nipple position for accurate location in each position.

Automated breast ultrasound system acquires 15.4 cm x17.0 cm area with the volume from the skin to the chest wall up to 5 cm deep. The frequency of transducer varied between 6-15 MHz.

Each study included bilateral anteroposterior, medial, and upper-outer quadrant positions.

For the lateral position, the breast tissue was pushed from axilla towards the sternum and covered the upper outer breast. For the medial position, the breast tissue was pushed from sternum toward the axilla, covering the inner inferior part of the breast. Minor compression was performed to the breast to avoid breast movement and obtain better view of the volume.

All positions included the nipple as a landmark. The scanning time for the sweeping of the probe the whole volume of interest was one minute per view.

Data were sent from the ABUS to the dedicated workstation. Multiplanar compounded images in three planes (coronal, sagittal and axial reconstructions) were reviewed.

Data Evaluation
Each study was examined sequentially by a breast radiologist who has more than 20 years of experience in breast radiology, three months of experience in ABUS reading prior to the study (senior radiologist) and third year resident (junior radiologist) who has 6 months of experience in breast radiology, one-month experience in ABUS reading prior to the study blinded to each other's results. Junior radiologist had a training for ABUS for one month prior to the study. Two radiologists participated in ABUS training via online webinars. A standard review protocol was used by both readers, which included, evaluation of coronal and transverse planes of each volume. Each plane was evaluated in the same order. The cases were evaluated in the same sequence. The reading environment was same.

Patient's age, reading time of 2 radiologists and American College of Radiology Breast Imaging Reporting and Data System (BIRADS) Atlas category for each patient were noted. The results were classified as: BIRADS 0 (incomplete), BIRADS 1 (negative), BIRADS 2 (benign findings).

Statistical Analysis
Data were analyzed with Statistical Package for the Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA). Spearman' correlation, Wilcoxon Signed Ranks Test and Kruskal-Wallis Test were recorded. P value <0.05 was considered for statistical significance for all tests. Wilcoxon Signed Ranks Test was used for significant difference between the mean time of two radiologists. Spearman' correlation was used for significant difference regarding the decrease in the reading time throughout study with the increase of number of cases read by the breast radiologist. Kruskal-Wallis Test and Spearman' correlation were used for correlation between BI-RADS category and reading time for both the breast.

Results

The average time for evaluating the ABUS data for the senior radiologist was 223.36±84.334 seconds (min 118 max 500 seconds). The average time for junior radiologist was 269.48±82.895 seconds (min 150 max 628 seconds) as detailed on Table 1. There was a significant difference between the mean time of two radiologists (p=0.00001). There was a significant difference regarding the decrease in the interpretation time throughout study with the increase of number of cases read by the breast radiologist (p<0.05); but not with the resident radiologist (p=0.687) (Figure 1). The reading time of the breast radiologist decreased throughout the study (Figure 2).

Table 1. The average time for evaluating the ABUS data for the senior and junior radiologist

Descriptive Statistics	Minimum	Maximum	Mean	Std. Deviation
Age	16	66	42.02	11.423
Senior radiologist (seconds)	118	500	223.36	84.334
Junior radiologist (seconds)	150	628	269.48	82.895
Average time (seconds)	139.5	458.5	246.424	67.0528

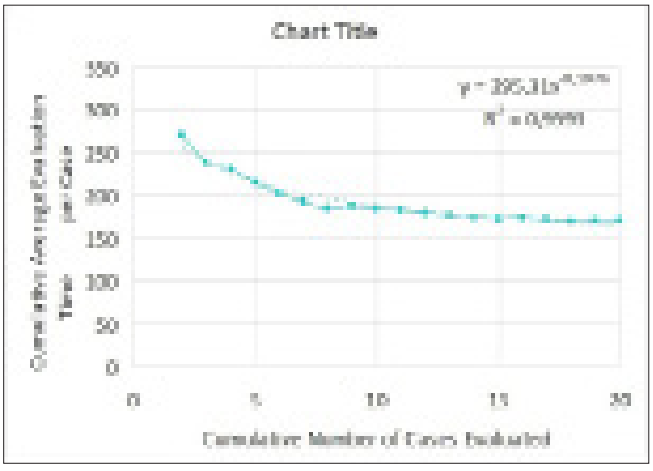

Figure 1. The reading time of the senior breast radiologist decreased throughout the study

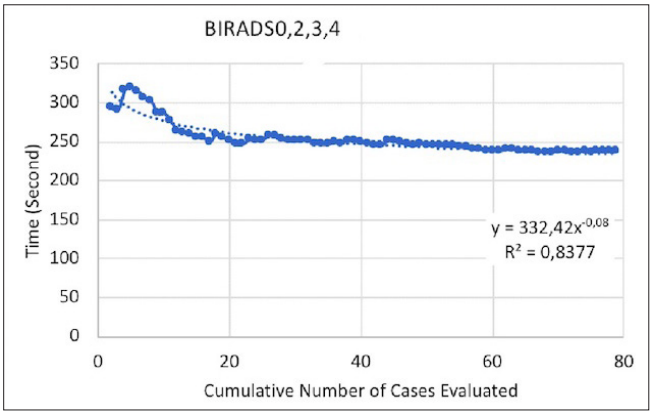

Figure 2. Learning curve of breast radiologist

We classified cases according to American College of Radiology BIRADS Atlas category; including BI-RADS category I in 20 patients (20%), BI-RADS category II in 65 patients (65%), BI-RADS category 0 in 15 patients (15%). All BI-RADS category 0 patients were examined with second look HHUS. Two of these changed to BI-RADS 2, seven to BI-RADS 3 and six to BI-RADS 4. One of six BI-RADS 4 cases proved to be an invasive carcinoma with a diameter of 6 mm which was detected by both readers. There was a correlation between BI-RADS category and reading time for both the breast radiologists and the resident (p=0.002, p=0.00043 respectively) indicating that patients who had findings resulted with longer reading times (Table 2). This finding was evident for the resident compared to the findings of the breast radiologist taking the BIRADS category into consideration.

Discussion and Conclusion

This study highlights the interpretation time of 3D ABUS by two radiologists with different experiences. Junior radiologist showed to be inferior to senior radiologist, particularly in the average time and learning curve. Our study showed that inexperienced radiologist's learning curve and the reading time is longer, however the mean time difference is 46 seconds.

Average time for 2 radiologists in 100 cases was 246.424±67.0528 (min 139.5, max 458.5) seconds. We observed that ABUS reading is fast and shortens during the time span of learning curve. This interpretation time is agreeable when compared to hand-held bilateral screening ultrasound examination which is reported to take an approximately 19 min (23) particularly in practices where the radiologist performs. We believe that ABUS can be a good alternative as a less time-consuming examination for a radiologist in breast screening programs particularly in centers with high patient flow.

Table 2. Kruskal Wallis Test, correlation between BI-RADS category and reading time

Ranks		
BIRADS N		**Mean Rank**
Reding Time for Breast Radiologist	0	66.50
	1	27.48
	2	54.27
	3	56.64
	4	64.57
Reading Time for Breast Radiologist	0	62.75
	1	36.00
	2	47.59
	3	74.07
	4	84.00
Mean Time (second)	0	65.25
	1	28.05
	2	50.89
	3	69.64
	4	80.71

We observed a significant reading time difference between BI-RADS 1 and other BIRADS categories (BI-RADS 0,2). It would take less time to read a completely normal exam (BIRADS 1) than an abnormal exam (BIRADS 0 and 2).

Automated breast ultrasound is more promising for breast screening purposes where majority of women are BI-RADS category 1. Thus, recall is needed for category 0 lesions which will be higher in diagnostic studies but will be low in screening. Many studies have documented that the ABUS technique is independent of an operator, has standardized views, is faster to acquire images. ABUS requires less training than HHUS. Total examination time is about 10-15 minutes by a trained sonographer (7, 8, 24-27). The interpretation time of ABUS varies between 2,9 and 9 minutes (24-26). The reason of this variability may be the differences in experiences, presence of abnormalities, and to the filled reports or protocols (25, 26). Our study showed that readers with different experiences can perform interpretation of the images in comparable durations. However, a recent study demonstrated an average ABUS interpretation time of less than 3 minutes with 3 different experienced readers. Their study included patients with ACR BI-RADS 4 breast density classifications of C or D which in line with our findings (28).

To assess or compare radiologists' performance in the detection of breast cancer with 3D ABUS were not part of this study. However, in another related study, the addition of ABUS to screening mammog-

raphy has been found to increase in cancer detection in line with our findings (29).

Our study has several limitations: First, the number of study participants was relatively limited. Second, it would have been more objective to compare reading time with varied experienced more than 2 radiologists. A multicenter study with several readers may help to show the variability of reading times. Third, this study was a retrospective study and the clinical outcome was not included in the analysis.

In conclusion, ABUS reading time may differ according to the experience of the user; however, the times of an experienced and non-experienced users are comparable.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (2018-2/9).

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

Peer-review: Externally peer-reviewed.

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

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Original Article

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The Effect of Mini-Latissimus Dorsi Flap (MLDF) Reconstruction on Shoulder Function in Breast Cancer Patients

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ABSTRACT

Objective: The aim of this study is to investigate the effect of mini latissimus dorsi flap (MLDF) reconstruction on ipsilateral shoulder functions.

Materials and Methods: Those included in the study are the patients aged between 23 and 73, who were operated with the diagnosis of early breast cancer (cT1-3)N0). The first group includes the patients who had sentinel lymph node biopsy (SLNB) with partial mastectomy. The second group consists of the patients who had axillary lymph nodule dissection (ALND) with partial mastectomy. The third group includes the patients who had SLNB and MLDF with partial mastectomy. The fourth group includes the patients who had ALND and MLDF with partial mastectomy. Patients' Quick Disabilities of the Arm, Shoulder and Hand (Q-DASH) score work model point were recorded.

Results: 174 patients were included in this study. According to Q-DASH score, no functional change was detected in 69.5% of the patients, whereas slight functional loss was identified in 23.6%, moderate functional loss in 5.7%, severe functional loss 1.1%. In the comparison of Q-DASH scores in surgery groups, while these four groups were being analyzed, a significant difference was determined (p=0.007). When dual analyses were made, it was also established that the difference resulted from the group to which ALND and MLDF were applied together.

Conclusion: We conclude that MLDF application for reconstruction purposes after breast surgery has a negative impact on shoulder functions of the patients who had both of partial mastectomy and ALND.

Keywords: Breast reconstruction, latissimus dorsi flap, shoulder functions

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Introduction

Breast cancer is the most common cancer type among women and can lead to death (1). According to World Health Organization data, the frequency and mortality of breast cancer has increased substantially in developing countries (2, 3). Although the breast cancer incidence has increased, the general survival rate at 5 years for Stage I breast cancer has reached 100% and for Stage II has reached 93% due to early disease recognition and advanced treatment methods (4). Increase in length of life has helped to provide better cosmetic appearance of the breast and to have an increase in breast-conserving surgery. As a result, the number of studies dedicated to reducing the morbidity of surgical treatment is increasing (5-7). Treatment for early stage breast cancer is usually initiated by surgical intervention and it is necessary to fill the cavity occurring after partial mastectomy (8-10). There are two different fundamental approaches available regarding breast reconstruction after breast cancer. The first approach refers to volume replacement procedures, which combine resection with immediate reconstruction of the defect using autologous tissue (local fasciocutaneous flaps and latissimus dorsi mini-flaps) (11) and the second approach is repre-

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sented by volume-displacement procedures, which combine resection with a variety of different breast-reduction and reshaping techniques, according to the location of the tumor (12-15). This method is often applied just after mastectomy and its positive psychological effect has been demonstrated (16, 17). In spite of positive effects, complications of latissimus dorsi flap (LDF) reconstructions cannot be ignored. These complications are seroma formation, wound infection, flap necrosis and shoulder dysfunction (18). For decreasing these complications, a part of latissimus dorsi muscle should be used that called mini-latissimus dorsi flap (MLDF), which is less invasive then LDF.

Latissimus dorsi flap effects shoulder mobility and upper extremity daily living activities negatively due the decreasing stability of shoulder joint however adequate information cannot find on effects of MLDF to shoulder functions in our literature search. Because of this reason he aim of this study was to investigate the effect of MLDF in partial mastectomy on upper extremity functionality.

Materials and Methods

174 patients who were treated with breast-conserving surgery (BCS) due to breast cancer at the Istanbul Florence Nightingale Breast Health Center were included in this study. A cross-sectional descriptive study was planned. The necessary sample size was determined by including all patients who fulfilled the inclusion criteria who applied to our clinic between 2014-2017. Approval was obtained from the Istanbul Science University Ethics Committee before the study. Written informed consent was obtained from all patients.

Inclusion criteria for the patient group was set as follows: being over 18 years old, having BCS with a diagnosis of stage I or stage II breast cancer, having received radiotherapy and chemotherapy, having no neurologic, orthopedic or rheumatic diseases affecting upper extremity function, and not having any disability related to the upper extremities before the surgery. Exclusion criteria were rejecting to participate in the study, having mastectomy, having operation on the same breast previously and/or having applied LDF, having treatment with a muscle relaxant or having treatment forming a neuromuscular block, not having radiotherapy or chemotherapy, having disability of the shoulder joint before the operation and having a disease affecting shoulder and upper extremity functions.

Patients were divided into 4 groups according to the surgical procedures applied. These groups were: I. Group: patients having sentinel lymph node biopsy (SLNB) with partial mastectomy (n=50), II. Group: patients having axillary lymph node dissection (ALND) with partial mastectomy (n=37), III. Group: patients having partial mastectomy + SLNB + LDF (n=50), IV. Group: patients having partial mastectomy + ALND + LDF (n=37). After having recorded the demographic information of the patients, joint movements and examinations were performed to complete the quick disabilities of the arm, shoulder and hand (Q-DASH) form for functional assessment.

In the MLDF surgical reconstruction procedure, the tumor is removed from the breast within clean surgical margins and the tumor bed is marked with clips. The patient is placed in the semi-lateral decubitus position, and the incision performed for SLNB or ALND is slightly extended laterally in order to find the lateral edge of the latissimus dorsi muscle. This muscle is drawn and separated from the chest wall, and the point where thoracodorsal vessels enter the muscle is found. Since the blood supply of the flap is from this vascular bundle, careful attention is required not to injure it. The latissimus dorsi muscle is separated from teres major and minor muscles superficially. To fill the space occurring in the breast tissue, the lower part of the tissue excised from axillary apex is measured and 5 cm is added on to it. This 5-cm-excess, which is added in order to have the necessary amount of muscle, is used to give a better shape to the breast. It forms pre-muscular fascia in the anterior, lumbosacral fascia in dorsal and rib arcuate limit in inferior. This area becomes free from muscle structures with the help of bipolar scissor and electrocautery. The muscle is prepared from the inferior according to the amount of muscle needed. The superior part of the muscle is separated from the humerus adherence point. During this process, utmost care is taken not to rotate the muscles in order to prevent vascularity. Muscle tissue is transported through the subcutaneous tunnel opening towards the excision cavity from the axillary region. Muscle tissue is here fixed to the pectoralis muscle and then shaped.

Upper extremity functional assessment was carried out with Q-DASH. Q-DASH is a regional result criterion that was developed for upper extremity musculoskeletal system disease. It evaluates all upper extremity functions, is filled out optionally and includes sport and musician modules. It contains eleven questions. To calculate the score of the criterion that can be used instead of Q-DASH, at least 10 questions out of 11 must be answered. Each question is graded on a 5-point- Likert scale. The total score of the questionnaire is calculated in such a way that the total points of the marked questions is divided by the number of questions marked, and then 1 is subtracted from the result, and the result multiplied by 25. Point total between 0-20 indicates normal, 21-40 indicates slight, 41-60 indicates moderate, and 61-80 indicates severe disability. The business model investigation survey of Q-DASH contains 4 questions intended for the assessment of problems that the patient has with his/her arms while working. Difficulty level is scored between 1 and 5. The total score of the questions is divided by 4, then 1 is subtracted from the result and then this result is multiplied by 25 (19). The validity and reliability of this scale was confirmed by Düger et al. (20).

The reasons why we have selected the Q-DASH survey for our study are that the survey's Turkish cultural adaptation has been done, that measurement features have been tested, that it is a survey especially for upper extremities and that it gives an idea about whole upper extremity functionality.

Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA) package has been used for statistical analysis. In descriptive statistics of the data, average, standard deviation, minimum and maximum values, median, rate and frequency values have been used. Distribution analysis of the variables has been controlled and tested by Kolmogorov- Smirnov test. Mann-Whitney U test and Kruskal Wallis test have been used for quantitative data analysis. For qualitative data analysis, Chi-Square test has been used, however, when it did not give results, Fisher test has been used. In correlation analyses, Pearson and Spearman tests have been used. Significance level was accepted as $p<0.05$.

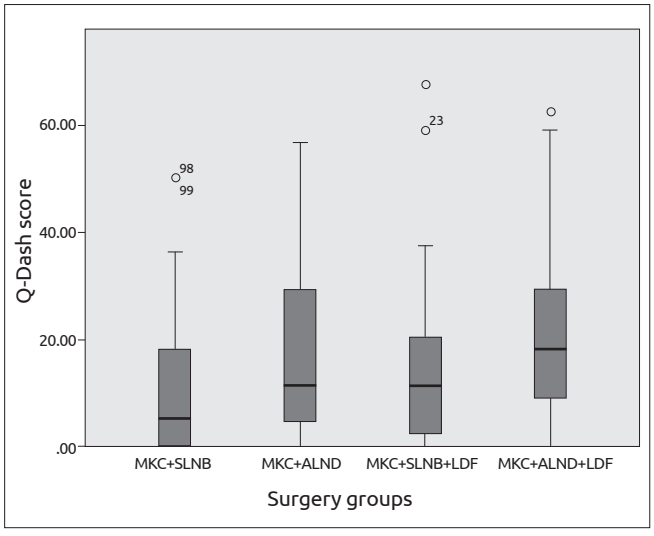
Results

174 patients were involved in this study. The mean age of the patients was 50.32±10.18, the mean body mass index (BMI) was 26.7±5.8 and the median value of the time passed after the surgery was 24 (3-108) months. 57.4% of the patients had surgery on the dominant side. The distribution of patient demographic data by surgery groups is provided in Table 1.

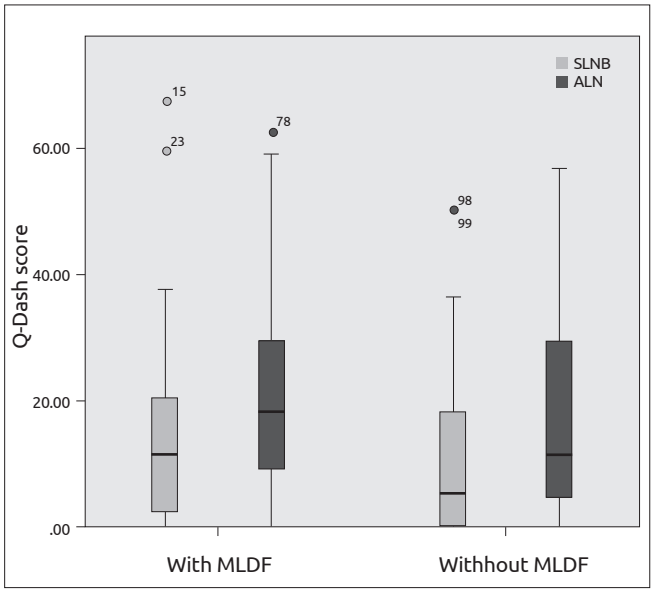
Table 1. Demographic data between groups

	MCS+SLNB (n=50)	MCS+ALND (n=37)	MCS+MLDF+SLNB (n=51)	MCS+MLDF+ALND (n=37)	p
BMI (kg/m²)	25.5 (18.5-37)	28.4 (18.6-57.7)	24 (19.1-33)	25 (20-38.3)	0.003
Age (year)	51.5 (30-71)	51 (23-73)	48 (33-70)	47 (35-72)	0.80
Elapsed time after operation (month)	24 (3-128)	29 (5-108)	21 (3-108)	34 (4-78)	0.248

Mann-Whitney U Test
MCS: Mastectomy; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection; MLDF: Mini Latissimus dorsi flap; BMI: Body mass index



Graphic 1. Comparison of between surgery groups and Q-Dash scores



Graphic 2. Comparison of between reconstruction performed with/ without MLDF and Q-Dash

According to Q-DASH score, no functional change was observed in 69.5% of the patients. On the other hand, slight functional loss, moderate functional loss and severe functional loss were detected in 23.6%, 5.7% and 1.1% of the patients, respectively. It was determined that having surgery on the dominant side did not have any impact on the arm functions (p=0.567).

Having compared Q-DASH scores in the surgery groups, a significant difference was established across the four groups analyzed (p=0.007) (Graphic 1). Dual analyses also revealed a difference resulting from the group in which ALND and MLDF were applied together. This significant difference disappeared once the three groups were reassessed after excluding those that were subjected to concomitant application of ALND and MLDF (p=0.22).

Although the findings suggested that reconstruction performed with MLDF did not have any statistically significant impact (p=0.17, p=0.12) on upper extremity functions when patients were classified as SLNB and ALND by lymph node surgery, Q-DASH scores were found to be relatively higher in patients to whom MLDF was applied than those who did not have MLDF application in both groups (Graphic 2).

In the comparison of Q-DASH business model scores of the patients in whole groups, no significant difference was determined (p=0.11).

In the evaluation of questions one by one in the groups, a significant breakdown (p=0.032, p=0.048) was found only in carrying a bag and opening a new or tight jar cap functions, whereas no significant difference was identified for the other nine questions.

No significant correlation was found in the comparison of functionality questions and the time passed after surgery (p=0.903).

Discussion and Conclusion

Reconstruction with mini-latissimus dorsi after partial mastectomy has begun to be implemented as one or two-stage procedures from the 1990's (21-24). Especially for patients who have a small breast and a large tumor or who are diagnosed with multifocal breast cancer, MLDF after partial mastectomy has been implemented in our clinic since 2010 and this has increased our breast protective surgery rate by 12.5% (3, 10, 25-27).

According to Spears et al. (28) article published in 2005, concerning stabilization and power of the shoulder joint, joint range of motion and functionality decrease after latissimus dorsi muscle transfer within the first 4 weeks after the implementation of LDF, there was a 30% decrease in shoulder function. These restraints affect daily life and free time activities negatively for the first 3 months after surgery. General functionality will return to the patients 6-12 months after surgery (28). Glassey et al. (29) assessed preoperative, postoperative, 6th week, 6th month and 1st year shoulder joint movement, power, pain and functionality levels of 22 patients who had LDF. In the results they obtained, they found that the assessments covering the period up to 6 months were poor, however after the first year, shoulder function recovered to a significant level (29). Button et al. (19) evaluated

preoperative, postoperative, 6th week, 3rd, 6th, 12th, 18th, 24th and 36th month shoulder functions of 58 patients who had LDF. Although they saw that Q-DASH scores decreased in each subsequent period, they reported that functional disability continued even in the long term, and that the patients receiving physiotherapy had better scores. They also reported that patients returned to preoperative values completely after 3 years (19). The relation of shoulder functions with the time given in these studies was not determined in our study. The reason for this is that while the LDF method has been used in the mentioned studies, we have used the MLDF method, which is less invasive.

Koh and Morrison (30) assessed latissimus dorsimuscle-skin reconstruction results in various patient groups (breast, upper extremity, head and neck patients) with the Q-DASH investigation form. 33% of the patients had changed their lifestyles because of dysfunction, and a clear majority of the patients stated that they had difficulty in overhead activities. It has been reported that this decrease in terms of functionality became clear especially between 6-12 months after the surgery (30). In our study, a serious functional loss in the upper extremity was found in 1.1% of the patients. In follow-ups 1 year after the operation for 22 patients diagnosed with breast cancer who had latissimus dorsi muscle-skin reconstruction, Glassey et al. (29) demonstrated that those who were operated on the dominant side recovered functionality over a longer time without having a decrease in muscle force or joint range of motion (29). In a prospective study, Forthomme at al. (31) evaluated 20 patients with whom they applied unilateral mastectomy and LDF reconstruction at the pre-operation, and post-operation 3rd and 6th months, and they reported that there was a restriction in overhead movements, especially among patients who were operated on the dominant side, and that there was no decrease in fine motor skills (31). In our study, we determined that having the operation on the dominant side had no impact on functionality.

Gosselink et al. (32) stated that 27% of 76 women with breast cancer who had ALND had continuous upper extremity functional disorders for 3 months after the surgery. In their studies in which shoulder functions of women to whom ALND was applied and only SLNB or no surgery were compared, Mansel et al. (33) determined that shoulder functions of women to whom ALND was applied were worse at the post-op 6th and 12th months. According to the results of our study, for all patients to whom BCS was applied, surgical interventions performed on axilla (SLNB/ALND) and MLDF affected shoulder functions and functionality in daily life activities adversely for up to one year. This exposure rate changed based on the type of surgical intervention performed. The gradation of surgical interventions affecting the upper extremity functions from minimum to maximum were as follows: Partial mastectomy + SLNB, Partial mastectomy + ALND, Partial mastectomy + SLNB + MLDF and Partial mastectomy + ALND + MLDF.

In conclusion, MLDF was applied to patients having a high tumor/breast ratio and diagnosed with multifocal/multicentric breast cancer as an alternative to reconstruction with subcutaneous mastectomy and prosthesis. Although with this method, which uses less latissimus dorsi muscle than latissimus dorsi muscle skin flap, led to less upper extremity functional disorders, the use of MLDF may cause upper extremity functional disorders in patients who require ALND.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Istanbul Science University (04.11.2014/25-17).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.D., Z.E.I.; Design - Z.E.I., A.S.I.; Supervision - V.O., F.A.; Resources - V.O., Z.E.I., A.S.I., C.O., A.O.; Materials - Z.E.I., A.O.; Data Collection and/or Processing - T.D., Z.E.I.; Analysis and/or Interpretation - A.S.I., F.E.; Literature Search - T.D., M.U.; Writing Manuscript - T.D., C.O., Z.E.I.; Critical Review - V.O., F.A.; Other - F.E., G.A.

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Original Article

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The Oncotype Dx Assay in ER-Positive, HER2-Negative Breast Cancer Patients: A Real Life Experience from a Single Cancer Center

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ABSTRACT

Objective: To determine the influence of the Oncotype Dx assay on the treatment of patients with Estrogen Receptor (ER)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative, axillary lymph node-negative or micrometastatic carcinoma of the breast in a single cancer center. In addition, patients with intermediate Oncotype Dx recurrence scores were analyzed to assess the factors influencing therapeutic decisions for adjuvant chemotherapy.

Materials and Methods: Data from medical records of women diagnosed with carcinoma of the breast and qualified for the Oncotype Dx assay were extracted (OncoDx cohort). Patient demographic and cancer characteristics, genomic report, and course of treatment data, including survival outcomes and treatment decision-making, were analyzed. A matched cohort of patients with similar tumor stage and biology (ER-positive, HER2-negative) from the era before the introduction of the Oncotype Dx assay was analyzed for comparison (pre-OncoDx cohort).

Results: Two hundred and one patients were included in the OncoDx cohort and one hundred and sixty patients were included in the pre-OncoDx cohort. Oncotype Dx recurrence score (RS) was low (<11) in fifty-six patients (28%), intermediate (11-25) in one hundred and twenty-three patients (61.5%) and high (>25) in twenty one patients (10.5%). Demographic and cancer clinicopathologic characteristics between OncoDx and pre-OncoDx cohorts were similar. Overall, 10.9% of the patients in the OncoDx cohort received adjuvant chemotherapy, versus 23.8% of the patients in the pre-OncoDx cohort (Fisher exact p=0.003). Fewer patients were recommended adjuvant chemotherapy in the OncoDx era compared to the pre-OncoDx era (17.9% vs 30.6%, respectively, Fisher exact p=0.006). The decision to recommend chemotherapy within the intermediate-risk cohort was influenced by the patient's RS. The mean RS of patients in the intermediate-risk cohort who did not receive chemotherapy was 21.5 while the score of those that received chemotherapy was 24.6 (p=0.000). The series confirmed excellent PFS and OS for both OncoDx and pre-OncoDx cohorts.

Conclusion: This single cancer center analysis confirms the avoidance of chemotherapy in the great majority of patients with early ER-positive, HER2-negative, lymph node-negative or micrometastatic carcinoma of the breast since the introduction of the Oncotype Dx assay. A higher recurrence risk score within the intermediate group may influence the decision for chemotherapy inclusion in the adjuvant treatment plan. A lower PR percentage by IHC and higher grade may predict higher Oncotype Dx scores.

Keywords: Oncotype Dx, breast cancer, recurrence risk, prediction, retrospective

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Introduction

Carcinomas of the breast with the estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative phenotype represent the most common subtype of breast cancer, accounting for 75% of the total breast cancer patient population (1, 2). Many of these patients present with localized and axillary lymph node-negative disease, which would usually suggest a good prognosis (3). Yet, some patients possess a significant risk of disease recurrence. Indeed the ER-positive, HER2-negative subset of breast cancers contains two genomically distinct groups, termed luminal A and luminal B, with the latter having a decreased response to hormonal therapies and a worse prognosis (4). Thus, the underlying genetics of the tumor may be more important in predicting its behavior than a patient's individual characteristics or the overall stage and grade of the malignancy at the time of presentation.

Several new genomic tests, which examine the genetic content of the tumor cells and incorporate the results into a prognostic recurrence risk, have been created and validated (5-9). One of these tests is the Oncotype Dx by Genomic Health Inc. (Redwood City, CA), a twenty-

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one-gene assay which examines the simultaneous expression of sixteen genes, together with five control genes, by Polymerase Chain Reaction (PCR), in an individual patient's breast cancer tissue, and returns a recurrence risk score (RS) and a percentage risk of distant disease recurrence at ten years if hormonal therapy (tamoxifen) alone is used as systemic therapy in the adjuvant setting (10-12). The test has been validated in ER-positive, HER2-negative, lymph node-negative or micrometastatic patients and allows for predicting which patients would derive minimal or no benefit from adjuvant chemotherapy and may be safely spared from it, thus avoiding toxicity and cost, without compromising outcomes (13).

Our study examined the influence of Oncotype Dx testing in the adjuvant therapy of patients with early ER-positive, HER2-negative breast carcinomas treated at a community cancer program and compares treatment decisions and outcomes of these patients with a cohort of similar patients treated in the same center in the era before the introduction of Oncotype Dx testing. Factors that may affect therapeutic decisions and may predict Oncotype Dx stratification are also discussed.

Materials and Methods

Two hundred and one breast cancer patients who had the Oncotype Dx assay were identified in the database at our cancer center, and their records were retrieved and reviewed. Four hundred and fifty-one patients who were diagnosed at our center with carcinoma of the breast in the period prior to the introduction of the Oncotype Dx assay were also identified. After exclusion of two hundred and ninety-one patients that would not qualify for the Oncotype assay because of more advanced stage or other receptor phenotypes, one hundred and sixty patients with ER-positive, HER2-negative carcinoma of the breast were retained in the pre-OncoDx cohort.

The patients' demographic and tumor characteristics were extracted from medical records. The course of treatment, including decision-making regarding the adjuvant treatment plan, as well as disease recurrence and survival outcomes were recorded. The details of the Oncotype Dx report were also recorded, including distant recurrence risk at ten years and RS, as well as ER, Progesterone Receptor (PR) and HER2 scores.

Group comparisons were performed using the cut-off points according to the TAILORx study (low-risk group RS <11, intermediate group RS 11-25, high-risk group RS >25) (10).

Statistical analysis was performed with the Fisher exact test or the x^2 test for comparison of ratios, the t-test for comparison of mean differences of continuous variables, and the Log-Rank test for comparison of Kaplan-Meier plots. All p values were considered significant at the level <0.05. Calculations were carried out using online statistical calculators (www.socialstatistics.com and https://merser.shinyapps.io/survival) and using STATA software. The protocol for this research was approved by the Ethics Committee of the institution. As this was a retrospective study, no informed consent was obtained from individual patients.

Results

Comparisons according to TAILORx cut-offs in the OncoDx Cohort

We assessed the OncoDx cohort using the TAILORx study cutoffs. Table 1 shows the characteristics of the three groups of patients classified as per these cut-offs (low-risk group: RS <11, intermediate-risk group: RS=11-25, high-risk group: RS >25) and compares the high-risk group with the two others combined. According to the TAILORx cutoffs, fifty-six patients (28%) belonged to the low-risk group, 123 patients (61.5%) belonged to the intermediate-risk group, and 21 patients (10.5%) belonged to the high-risk group. The comparison of the high-risk group per the TAILORx cutoff versus the two other groups showed statistically significant differences in grade, and ER and PR staining intensity (Table 1). The difference in PR staining with a cutoff of >20% by immunohistochemistry (IHC) between the low-risk and intermediate-risk cohorts based on the TAILORx cutoffs were statistically significant. 3.6% of patients in the low-risk cohort had ≤20% of PR positivity, while this ratio was 35% in the intermediate-risk cohort (Fisher exact test p=0.000). However, there were no statistically significant associations between the low and intermediate-risk cohorts in mean age at presentation, the percentage of patients above age 65, the percentage of post-menopausal patients, or in the size, histology and node status of the tumors, and in the percentage of patients with ER ≥90% scores or whether HER2 negativity was confirmed by either IHC or Fluorescence in itu hybridization (FISH) (Table 1).

Using the TAILORx cut-offs, eighteen of twenty-one patients (85.7%) in the high-risk cohort were recommended chemotherapy. Three patients were not recommended chemotherapy due to co-morbidities or advanced age, in the context of a RS at the lower margin of high-risk. Twelve of twenty-one patients (57.1%) accepted the recommendation and received adjuvant chemotherapy (Table 2).

The most important function of the Oncotype Dx assay is to help with the chemotherapy decision, and virtually all patients in our study were recommended chemotherapy if they were in the TAILORx high-risk group and their general status allowed. Therefore, an analysis was performed among factors that were statistically significant in the high-risk group comparison with the two other groups to identify an optimal combination of factors predicting membership in the high-risk group. Among the factors with the most significant difference in the comparison between the high-risk group and the two other groups, the combination of grade III and PR staining percentage of ≤20% when both present predicted membership in the high-risk group in eleven of nineteen patients (57.9%). Conversely, presence of none or one of these factors predicted membership in the low or intermediate TAILORx groups in one hundred and seventy-one of one hundred and eighty-one patients (94.5%). The addition of ER positivity data did not add to the sensitivity or specificity of the PR/grade index, as a significant majority (96%) of the high-risk cohort had high ER positivity (≥90% of tumor cells).

Therapeutic recommendations and outcomes in the OncoDx Cohort

In our series, no patients with a RS of less than 18 were recommended adjuvant chemotherapy, consistent with the intent of the Oncotype Dx assay. We examined, next, therapeutic recommendations in patients with RS between 18 and 31. In this group, twenty-seven of the sixty patients (45.0%) were recommended adjuvant chemotherapy (Table 3). The decision to recommend chemotherapy within this cohort with intermediate-risk was heavily influenced by the patient's RS (Table 3). Specifically, twenty-three (69.7%) patients were not recommended adjuvant chemotherapy because their RS was considered to confer a recurrence risk similar to the low-risk cohort. In eight patients (24.2%), no specific rationale was noted for not recommending adjuvant chemotherapy. In two patients (6.1%), adjuvant chemotherapy was not recommended due to their significant comorbidities.

Table 1. Demographic and clinicopathologic characteristics of patients in the Oncotype cohort, with low (RS <11), intermediate (RS 11-25), or high (RS >25) risks according to the TAILORx risk category. The two last columns provide comparisons between the low and intermediate risk groups and between low + intermediate risk and high risk groups. The Fisher exact test in grade refers to comparison between combined grades I and II versus grade III. Bolded is statistically significant (p<0.05)

Parameter	Category	Total (n=201)	Low Risk (<11) (n=56)	Intermediate Risk (11-25) (n=123)	High Risk (>25) (n=21)	p (Low+Intermediate vs. High)
AGE	Mean	65.1	66.7	64.5	64.4	0.08 (t)
	≤65	93 (46.3)	24 (42.9)	59 (48.0)	9 (42.9)	0.81 (Fisher)
	>65	108 (53.7)	32 (57.1)	63 (52.0)	12 (57.1)	
MENOPAUSE STATUS	Pre-/peri-	22 (10.9)	4 (7.1)	14 (11.4)	4 (19.0)	0.25 (Fisher)
	Post-	179 (89.1)	52 (92.9)	109 (88.6)	17 (81)	
PRIMARY SIZE	<1 cm	37 (18.4)	12 (21.4)	23 (18.7)	2 (9.5)	0.08 (χ^2)
	1-2 cm	116 (57.7)	35 (62.5)	70 (56.9)	10 (47.6)	
	>2 cm	48 (23.9)	9 (16.1)	30 (24.4)	9 (42.9)	
HISTOLOGY	Ductal	139 (69.1)	40 (71.4)	83 (67.5)	16 (76.2)	0.89 (χ^2)
	Lobular	26 (12.9)	4 (7.1)	20 (16.3)	2 (9.5)	
	Mixed	20 (10.0)	6 (10.7)	12 (9.8)	2 (9.5)	
	Other	16 (8.0)	6 (10.7)	8 (6.4)	1 (4.8)	
GRADE	I	57 (28.3)	21 (37.5)	35 (28.5)	1 (4.8)	0.000 (χ^2)
	II	101 (50.3)	30 (53.6)	66 (53.7)	4 (19.0)	
	III	43 (21.4)	5 (8.9)	22 (17.8)	16 (76.2)	
ER STAINING	<90%	8 (4.0)	1 (1.8)	2 (1.6)	5 (25.0)	0.000 (Fisher)
	≥90%	191 (96.0)	54 (98.2)	121 (98.4)	15 (75.0)	
PR STAINING	≤20%	59 (30.0)	2 (3.6)	43 (35.0)	13 (61.9)	0.001 (Fisher)
	>20%	141 (70.0)	53 (96.4)	80 (65.0)	8 (38.1)	
HER2 STATUS	IHC 0-1+	115 (58.1)	35 (63.6)	67 (55.4)	12 (57.1)	1.0 (Fisher)
	FISH-	83 (41.9)	20 (36.4)	54 (44.6)	9 (42.9)	
LYMPH NODE STATUS	Negative	184 (94.4)	51 (96.2)	112 (93.3)	20 (95.2)	1.0 (Fisher)
	Micrometastatic	11 (5.6)	2 (3.8)	8 (6.7)	1 (4.8)	
SURGERY TYPE	Lumpectomy	157 (78.9)	40 (71.4)	98 (81.0)	18 (85.7)	0.57 (Fisher)
	Mastectomy	42 (21.1)	16 (28.6)	23 (19.0)	3 (14.3)	

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; FISH: fluorescent in situ hybridization; Fisher: Fisher's exact test

Table 2. Patients' decisions on accepting adjuvant chemotherapy recommendation in the high-risk cohort (RS >25) as per TAILORx cutoffs, and mean recurrence score (RS)

Therapeutic Decision	Number of Patients (n=21) (%)	Mean RS
Chemotherapy not recommended	3 (14.3)	27
Chemotherapy recommended—Accepted recommendation	12 (57.1)	35
Chemotherapy recommended—Rejected recommendation	6 (28.6)	

For those patients who were recommended chemotherapy (Table 3), twenty-six (96.3%) recommendations were influenced primarily by the recurrence risk being on the upper margin of the intermediate range. Only one of the twenty-seven patients was recommended adjuvant chemotherapy on the explicit basis of both her Oncotype Dx RS and the characteristics of her malignancy (i.e. grade III, 2.2 cm tumour with a PR staining positivity at 15%). However, these characteristics may have influenced decision-making in other patients, even without being explicitly stated in the patient's chart.

Table 3. Recommendations and rationale for or against adjuvant chemotherapy in patients with a recurrence score (RS) of 18-31

Therapeutic Recommendation	Rationale	Number of Patients (n=60) (%)
Adjuvant chemotherapy		27 (45.0)
	Recurrence score confers sufficient risk	26 (96.3)
	Totality of tumour risk factors	1 (3.7)
No adjuvant chemotherapy		33 (55.0)
	Recurrence score marginally above low risk	23 (69.7)
	No specific rationale noted	8 (24.2)
	Significant patient comorbidities	2 (6.1)

Table 4. Patients' ultimate decision on accepting or rejecting the adjuvant chemotherapy recommendation in the group of patients with recurrence score (RS) of 18 to 31, and comparison of mean RS between those for whom chemotherapy was recommended and those for whom it was not recommended

Therapeutic Decision	Number of Patients (n=60) (%)	RS	p
Chemotherapy not recommended	33 (55.0)	21.5	0.000 (t)
Chemotherapy recommended—Accepted recommendation	16 (26.67)	24.6	
Chemotherapy recommended—Rejected recommendation	11 (18.33)		

Sixteen patients (26.7%) ultimately accepted the chemotherapy recommendation (Table 4). Five patients (45.5%) rejected the recommendation for adjuvant chemotherapy due to concern for the toxicity the chemotherapy regimen would entail. The remaining six patients did not have data on the reason for their rejecting the recommendation. Patients within the cohort with a RS of 18 to 31 who received adjuvant chemotherapy had a statistically significant higher mean RS than the patients within the cohort who did not receive chemotherapy (Table 4).

Overall, twenty-two (10.9%) patients in the entire OncoDx cohort received chemotherapy. The most commonly used regimens were the FEC-D (3 cycles of 5-Fluorourcacil-Epirubicin-Cyclophosphamide, followed by 3 cycles of Docetaxel) regimen and the DC (4 cycles of Docetaxel-Cyclophosphamide) regimen.

With a mean follow-up for the whole OncoDx cohort of 33.9 months, progression-free survival (PFS) and overall survival (OS) were favorable in both the low and intermediate-risk cohorts (Figure 1). The low-risk cohort had a mean follow-up of 34.65 months compared to 32.09 months in the intermediate-risk cohort. This was not a statistically significantly difference (p=0.22). There were no statistically significantly differences between the low-risk and intermediate-risk cohorts in PFS or OS either (LogRank test p=0.41 and 0.44, respectively). Three patients (1.5%) had a disease recurrence, one of whom was in the low-risk cohort and two in the intermediate-risk cohort. Seven patients (3.5%) died, four of whom were in the low-risk cohort and three in the intermediate-risk cohort. Only one (14.3%) of these patients died due to progression of her breast cancer, while the remaining six patients died from other diseases.

Comparisons, OncoDx and Pre-OncoDx Cohorts

The pre-OncoDx cohort consisted of one hundred and sixty patients (Table 5). The mean age was 64.9 years (SD 12.75). This was not statistically significantly different from the OncoDx cohort. Most patients had carcinoma of the breast that was stage I, tumor size between 11 and 22 mm, ductal histologic type, and histologic grade II. None of these parameters were statistically significantly different from the OncoDx cohort. Most patients were also post-menopausal and had no evidence of axillary lymph node micrometastases. However, a greater ratio of patients in the OncoDx cohort had breast-conserving therapy with lumpectomy than in the pre-OncoDx cohort (Fisher exact test p<0.000). As a result, a greater ratio of patients in the OncoDx cohort received adjuvant radiation compared to the pre-OncoDx cohort (Fisher exact test p<0.000). Additionally, ER staining percentage of ≥90% of tumor cells was statistically significantly higher in the OncoDx cohort compared to the pre-OncoDx cohort (Fisher exact test p=0.001). Finally, 10.9% of patients in the OncoDx cohort received adjuvant chemotherapy, while this percentage was 23.8% of patients in the pre-OncoDx cohort (Fisher exact test p=0.001).

With a mean follow-up of 87.3 months in the pre-OncoDx cohort, twenty-eight patients died (17.5%), ten of whom (58.8%) died due to progression of their breast cancer. Eleven patients (6.9%) had a recurrence of breast cancer. There was no statistically significant difference in overall survival and progression-free survival between the OncoDx and pre-OncoDx cohorts (Log-Rank p=0.35 for PFS (Figure 2a) and p=0.83 for OS (Figure 2b)).

The rationale used to recommend chemotherapy in the pre-OncoDx era was documented in the patients' records in only 46.4% of cases (Table 6). The single-most influential element of the recommendation was that the Adjuvant! online prediction tool (currently not available) favored the addition of adjuvant chemotherapy (26.5% of cases). Similarly, in recommending against chemotherapy, the rationale was documented in only 43.9% of cases (Table 6). The most influential

Table 5. Demographic and clinicopathologic characteristics patients in the pre-OncoDx cohort. Last column provides comparisons between the pre-OncoDx and OncoDx patients. Bolded is statistically significant (p<0.05)

Parameter	Category	Pre-OncoDx Cohort (n=160) (%)	OncoDx Cohort (n=201) (%)	p
AGE	Mean	64.9	65.1	0.43 (t)
	≤65	75 (46.9)	93 (46.3)	
	>65	85 (53.1)	108 (53.7)	
MENOPAUSE STATUS	Pre-/peri-	33 (21.3)	22 (10.9)	
	Post-	122 (78.7)	179 (89.1)	
PRIMARY SIZE	<1 cm	35 (26.5)	37 (18.4)	0.11 (x^2)
	1-2 cm	62 (47.0)	116 (57.7)	
	>2 cm	35 (26.5)	48 (23.9)	
HISTOLOGY	Ductal	113 (72.9)	139 (69.1)	0.68 (x^2)
	Lobular	19 (12.3)	26 (12.9)	
	Mixed	10 (6.5)	20 (10.0)	
	Other	13 (8.4)	16 (8.0)	
GRADE	I	34 (23.1)	57 (28.3)	0.44 (x^2)
	II	75 (51.0)	101 (50.3)	
	III	38 (25.9)	43 (21.4)	
ER STAINING	<90%	19 (14.2)	8 (4.0)	0.0016 (Fisher)
	≥90%	115 (85.8)	191 (96.0)	
PR STAINING	≤20%	44 (32.8)	59 (30.0)	0.55 (Fisher)
	>20%	90 (67.2)	141 (70.0)	
HER STATUS	IHC 0-1+	95 (67.4)	115 (58.1)	0.09 (Fisher)
	FISH-	46 (32.6)	83 (41.9)	
LYMPH NODE STATUS	Negative	135 (95.1)	184 (94.4)	0.81 (Fisher)
	Micrometastatic	7 (4.9)	11 (5.6)	
SURGERY TYPE	Lumpectomy	84 (53.2)	157 (78.9)	<0.000 (Fisher)
	Mastectomy	74 (46.8)	42 (21.1)	

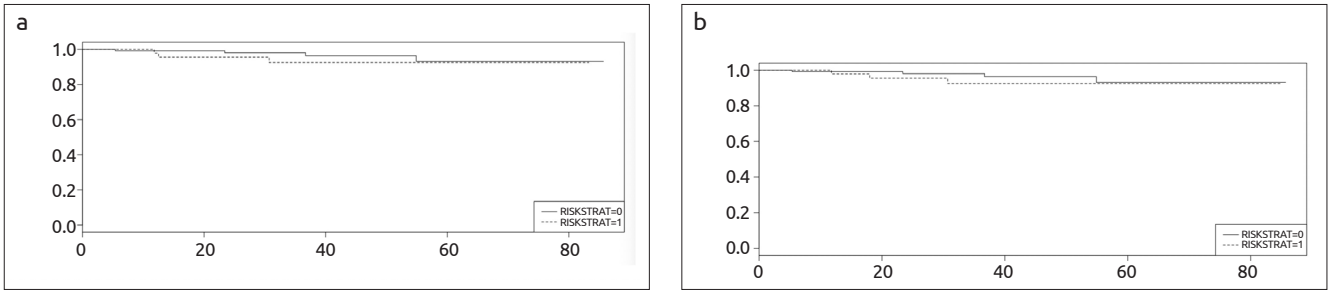

Figure 1. a, b. Kaplan-Meier progression-free survival (PFS) curves (a) and overall survival curves (b) in months, of patients in the low recurrence risk (riskstrat=0) cohort versus patients in the intermediate recurrence risk cohort (riskstrat=1). LogRank test p=0.41 and 0.44 respectively

reason for not recommending chemotherapy was either that the specific characteristics of the tumor were considered to confer a low risk of recurrence (13.1% of cases) or because the Adjuvant! online prediction tool showed a minimal benefit from the addition of adjuvant chemotherapy (11.2% of cases).

Overall, adjuvant chemotherapy was recommended to forty-nine of one hundred and sixty (30.6%) patients (Table 6). 77.6% of the patients who were recommended chemotherapy accepted the recommendation. The reason for patient's rejecting the recommendation was not mentioned in the records in any of the cases.

Our analysis demonstrates that the addition of the Oncotype Dx assay at our cancer center resulted in decreased use of adjuvant chemotherapy while maintaining very good survival outcomes.

Table 6. Recommendations to receive or not receive adjuvant chemotherapy, the rationale, and the patients' ultimate decision in the pre-OncoDx cohort, percentage of total number of patients in the pre-OncoDx cohort

Therapeutic Recommendation and Decision	Rationale	Number of Patients (n=160) (%)
Adjuvant Chemotherapy		49 (30.6)
	No specific rationale noted	26 (53.6)
	Online prediction tools supported benefit	13 (26.5)
	Totality of tumour characteristics	9 (18.4)
Accepted Recommendation		38 (77.6)
Rejected Recommendation		11 (22.4)
No Adjuvant Chemotherapy		111 (69.4)
	No specific rationale noted	60 (56.1)
	Totality of tumour characteristics	14 (13.1)
	Online prediction tools did not support benefit	12 (11.2)

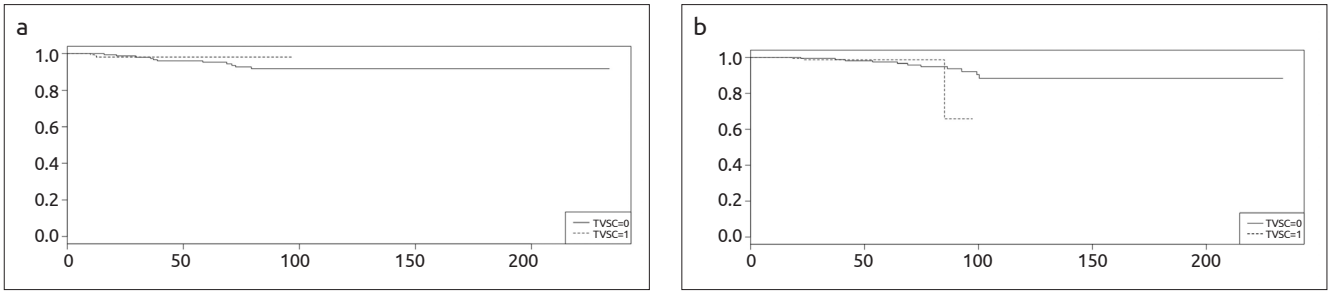

Figure 2. a, b. Kaplan-Meier progression-free survival (PFS) curves (a) and overall survival curves (b) in months, of patients in the pre-OncoDx cohort (TvsC=0) versus patents in the OncoDx cohort (TvsC=1). LogRank test p=0.35 and 0.83 respectively

Discussion and Conclusion

Before the advent of genomic assays, clinical and pathologic parameters, such as the patient's age and general state of health, menopause status, and size and grade of the tumor at the time of presentation had been used to determine risk of disease recurrence in patients with early ER-positive, HER2-negative carcinoma of the breast. Estimated higher risk suggested the need for the addition of adjuvant chemotherapy to adjuvant hormonal therapy in the treatment plan. However, the underlying genetic lesions of the tumor may be more important in predicting its behavior than a patient's individual characteristics or the overall stage and grade of the malignancy at the time of presentation. This new knowledge was corroborated by the introduction of genomic profiling, which categorized breast cancers in distinct approximated but not completely overlapping groups, with the groups defined by IHC for ER, PR, and HER2 receptors (14). Two ER-positivity and HER2-negativity breast cancer sub-types with overlapping IHC profiles have been defined by genomic profiling, termed luminal A and luminal B. Both have distinct prognosis and response to hormonal therapy but are difficult to predict clinically given the overlapping clinicopathologic profile (15). Several genomic tests have been introduced and validated in the clinical setting attempting to predict outcomes of cancers in the ER-positive, HER2-negative spectrum, based on expressions of a subset of genes, ranging from a few to several dozen in the tumor genome. Genomic tests include the 70-gene signature, the PAM50 test, the BCI, and the Oncotype Dx assay, the latter of which has been used in our cancer center and is the subject of this report.

The Oncotype Dx assay is a proprietary RT-PCR-based test that examines expression of sixteen genes along with five controls. The genes included in the assay are involved in tumor proliferation and invasion as well as hormone and growth factor signaling (13). In addition to providing a RS and a numeric estimation of ten-year distant recurrence risk if only hormonal therapy (tamoxifen) is used in the adjuvant setting, the Oncotype Dx assay provides an estimation of the benefit of adding adjuvant chemotherapy to adjuvant hormonal therapy. Excellent results have been reported in low RS patients treated only with adjuvant hormonal therapy (16). Moreover, a decrease in the use of chemotherapy in the ER-positive, HER2-negative, lymph node-negative population has also been reported (11). These results confirm that the assay succeeds in decreasing the use of chemotherapy without compromising survival outcomes.

Patients with a high RS from the Oncotype Dx assay derive benefit from adjuvant chemotherapy due to their higher risk of disease recurrence, and the patients in the low RS category conversely do not accrue further benefits with the addition of adjuvant chemotherapy. However, the optimal approach for patients with intermediate RS has been uncertain, given the higher risk of recurrence but only minimal benefit of adjuvant chemotherapy (10, 11). In practice, most treating physicians would consider all patients with a high Oncotype Dx RS > above 30 and most patients above 25 to be candidates for chemotherapy. This practice has been recently validated by the results from the intermediate group of the TAILORx study that confirmed minimal, if any, benefit from chemotherapy in the intermediate group with a RS of 11 to 25 (17). An exemption may

be for patients below age 50 and a RS of 20 to 25 who may derive some benefit from adjuvant chemotherapy.

In our retrospective analysis of women diagnosed with carcinoma of the breast at our cancer center, we observed the avoidance of adjuvant chemotherapy in low and low-intermediate recurrence risk patients with early ER-positive, HER2-negative, lymph node-negative or micrometastatic disease. The decision to offer adjuvant chemotherapy in most intermediate-risk patients seemed to be influenced by the patient's RS from the Oncotype Dx assay. This result is similar to the conclusion of another study in Ontario (11). Additionally, our analysis demonstrated that a higher RS in the intermediate-risk cohort predicted use of adjuvant chemotherapy. The PR staining intensity was also statistically different for the low and intermediate-risk cohorts, which is consistent with the degree to which a lower PR staining by IHC correlates with recurrence risk. This is consistent with the results reported by other series (18-20). Finally, we found that survival outcomes were favorable in both low and intermediate-risk cohorts.

Prediction of a RS above 25 may be of special clinical interest in settings where the Oncotype Dx assay is not available, given that patients in this range could actually be among the subgroup who would benefit from the addition of adjuvant chemotherapy. In our analysis, the three pathological factors most significantly associated with a RS >25 were high grade and a low positivity for ER (<90%) and for PR (≤20%). These results concord with another investigation that proposed a combination of ER, PR, and Ki67 immunohistochemical score as a valid predictor of the Oncotype Dx RS (18). The two component (PR/grade) predictor we propose is simpler and avoids the inclusion of Ki67, which may not be universally available, and has a similar discriminatory value (21).

Compared with the pre-OncoDx cohort, our analysis demonstrated a decrease in the use of adjuvant chemotherapy in the Oncotype era (89.1% versus 76.3%, respectively, Fisher exact test p=0.0016). In addition, fewer patients were recommended adjuvant chemotherapy in the Oncotype era compared to the pre-Oncotype era (17.9% versus 30.6%, respectively, Fisher exact test p=0.0059). Both cohorts were largely similar from a demographic and clinicopathologic characteristics perspective. Our study also demonstrated that both cohorts had favorable survival rates, with no statistically significant differences in the comparisons of Kaplan-Meier plots, though there was an absolute higher number of death and progression in the pre-Oncotype cohort. This is likely partially related to a longer follow-up in this cohort. From limited available data, the most significant influence on recommending adjuvant chemotherapy in the pre-OncoDx cohort was the use of Adjuvant! online prediction tool. Thus, in both the Oncotype and pre-Oncotype era, recommendations on the addition of adjuvant chemotherapy relied on predictive tools to complement clinical judgment.

Besides the general disadvantages of retrospective and non-randomized comparisons, our analysis is limited by the fact that the rationale for the chemotherapy recommendation in the pre-Oncotype era was not well documented, making a comparison of decision-making changes between pre-OncoDx and OncoDx cohorts incomplete.

In conclusion, the addition of the Oncotype Dx assay at our cancer center resulted in decreased use of adjuvant chemotherapy while maintaining excellent survival outcomes. This, together with the fact that genomic tests seem to be cost effective, suggests continued utility in clinical practice [22]. Future investigations will aim at providing even better prognostic and therapy predictive tools to further advance personalized oncology.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Sault Area Hospital.

Informed Consent: Informed consent was not taken due to retrospective design of the study.

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Original Article

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Our 20-Year Institutional Experience with Surgical Approach for Breast Hamartomas

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ABSTRACT

Objective: Hamartomas are rare, slowly-growing breast tumours. Clinical, radiological and histopathological examination together increase the diagnostic accuracy. To evaluate the clinicopathologic features of hamartomas and outline our clinical approach to hamartomas in our 20-year experience at our Breast Clinic.

Materials and Methods: Between 1995 and 2015, 24 cases were retrospectively analyzed with a diagnosis of breast hamartoma at our Breast Clinic followed by excisional biopsy. Data was obtained on patient demographics, clinical examination, radiological findings and histopathological subtypes.

Results: Of 1338 benign breast tumours excised from January 1995 to January 2015, 24 (1.8%) were identified as breast hamartoma. Median age of patients was 42 (range, 13-70), whereas the median tumour size was 5 cm (1-10 cm). On preoperative imaging, hamartoma was most commonly misdiagnosed as fibroadenoma. Pathological examination of the 24 biopsy specimens revealed 3 cases with pseudoangiomatous stromal hyperplasia, and another hamartoma associated with a radial scar within the centre of the lesion. Of those, one patient was diagnosed with malignant phylloides tumour in the same breast. At a median follow-up 58.4 months, none of the patients recurred or developed malignancy.

Conclusion: Hamartomas can often be missed by clinicians, due to its benign nature which is poorly understood. Despite their slow growth, hamartomas can reach large sizes and can cause breast asymmetry. Although it is rare, hamartoma can be seen along with malignancy, as it is formed from similar components of breast tissue. Therefore, careful diagnosis and appropriate management including surgery are required.

Keywords: Breast disease, hamartoma, phyllodes tumor

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Introduction

Hamartomas were first defined as mastomas by Pyrm (1). Before the term hamartoma came in to use in 1971 by Arrigoni, the lesion was also described as an adenolipoma and fibroadenolipoma. At present, some authors accept adenolipomas, adenohibernoma and myoid hamartomas as variants of hamartoma (2-4). Breast hamartomas are rare benign tumors comprising 0.7-1.2% of benign breast lesions in women. It is most commonly seen in perimenopausal period (5-7).

Hamartomas are slowly-growing lesions with a mean diameter ranging from 2 cm to 5 cm. However, sometimes hamartomas can reach giant dimensions (8). Patients usually present with a painless mass or breast anisomastia (7, 9-12). Hamartomas may be missed by physical examination. Mammographically, these lesions can be seen as mass containing fibrous and fatty tissue (9, 10). Furthermore, an excisional biopsy is generally required to distinguish hamartoma from other benign breast lesions such as fibroadenoma, lipoma and cystosarcoma phyllodes (12). Similar to what the breast epithelial cells do, the stromal cells also express estrogen and progesterone receptors (13). Despite hamartomas are considered as benign disease, it can be uncommonly seen along with a breast malignancy (14-16).

In this report, we aimed to evaluate the clinicopathologic features of hamartomas and outline our clinical approach to hamartomas in our 20-year experience at our Breast Clinic.

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Materials and Methods

Between January 1995 and January 2015, 1338 patients who underwent surgery with a diagnosis of benign breast disease at the Breast Clinic of the Department of Surgery, İstanbul University School of Medicine, were retrospectively analyzed. Of those, 24 cases (1.8%) were identified with a definitive pathology of hamartoma. A database was created for patient demographics, clinical findings including physical examination and radiological findings, surgery, and histopathological characteristics. All patients underwent excisional biopsy. Clinical follow-up data was also obtained. Statistical Packages for the Social Sciences (SPSS) version 17 (SPSS Inc.; Chicago, IL, USA), and Fisher's exact test was used for categorical analysis. Spearman's correlation test was used to examine the associations between parameters. Mann Whitney-U test was used for continuous variables. Ethics committee approval was obtained for this retrospective analysis.

Results

Of the 24 patients, 8 were diagnosed from 1995 to 2005, and 16 patients were diagnosed between the years 2005-2015. Of those, there was only one male patient (4.2%), whereas the remaining were female (95.8 %). The median age of patients was 42 (range, 13 - 70 years), and 17 were premenopausal (74%). Five patients (20.8%) had a family history of breast carcinoma. The majority of the patients (n=15, 62.5%) presented with a soft painless mass, whereas 4 presented with a breast lump and pain (Table 1). Nevertheless, 2 patients were asymptomatic who were diagnosed during routine screening.

All patients were examined by ultrasound imaging, whereas 16 (66.7%) had a mammogram. Ultrasonography frequently showed an oval-shaped, well-defined, heterogeneous mass containing cystic areas defining a diagnosis of hamartoma in 9 cases (37.5 %). Other common findings were associated with a diagnosis of fibroadenoma in 7 patients (29%), and cystosarcoma phyllodes in 2 patients (8.3 %). Mammography mostly revealed a nodular opacity (n=11, 68.8%) or an asymmetric density (n=2, 12.5%), or BIRADS IV microcalcifications (n=2, 12.5%).

Seven cases (29.1 %) were diagnosed as likely fibroadenoma on imaging. For masses of large size on radiological examination, a misleading preliminary diagnosis of phyllodes tumour was established. The mammography and ultrasonography findings of the cases are given in Table 2. For 11 patients with radiological less than 5 cm and 13 patients with a radiological mass greater than 5 cm, hamartoma was identified as a possible diagnosis in 18.2% and 46.2% respectively (p=0.21). Mammographic image of hamartoma was shown in Figure 1.

For preoperative diagnosis, fine needle aspiration (FNA) was performed in 10 patients (41.7%), whereas 4 patients had only core biopsy (16.7%). Furthermore, 5 patients had both FNA and core biopsy, whereas the remaining underwent excisional biopsy for diagnosis. None of the FNA finding predicted the final pathology of hamartoma. Of patients with a core biopsy (n=9), the core biopsy revealed fibrolipomatous cell fragments in 3 patients (33.3%) that was concordant with a diagnosis of hamartoma. However, hamartoma diagnosis could not be confirmed in 6 patients where the pathological finding was stromal fibrosis in 3 patients, fibrosis/adenosis in 1 patient, myxoid tumor in 1 patient and fibrocystic changes in 1 patient.

On pathological examination of the excisional biopsy specimens of hamartoma cases, pseudoangiomatous stromal hyperplasia was present in 3 specimens. In one case, fatty necrosis was identified, whereas fibro-hyaline stroma were present in another case (Figure 2). Furthermore, histopathological examination established multiple foci of microcalcification in 4 cases (16.6%). Both foci of adenosis and sclerosing adenosis were present in 2 cases. Interestingly, hamartoma was associated with a radial scar in one case.

Table 1. Demographic and Clinical and Tumor Characteristics of Patients

Patient and Tumor Characteristics	N	%
Median age	42 (range, 13-70)	
Age groups		
≤20	2	8.3
20-30	3	12.5
30-40	6	25
40-50	5	20.8
50-60	4	16.7
60-70	4	16.7
Premenopausal	17	74
Postmenopausal	6	26
Family history	5	20.8
Gender		
Female	23	95.8
Male	1	4.2
Presenting symptoms		
Pain	2	8.3
Pain & palpable mass	4	16.6
Palpable mass	15	62.5
Palpable mass & anisomastia	1	4.2
Screening	2	8.3
Imaging techniques		
Ultrasound	24	100
Mammogram	16	66.7
Magnetic Resonance Imaging	6	25
Preoperative Diagnosis		
Fine Needle Aspiration (FNA)	10	41.7
Core Biopsy	4	16.7
FNA & core biopsy	5	20.8
Excisional biopsy	5	20.8
Median tumor size	5 cm (range, 1-10 cm)	
Associated lesions with hamartoma		
Pseudoangiomatosis hyperplasia	3	12.5
Radial scar	1	4.2
Malignancy	1	4.2

Unknown data were excluded from the analysis

Table 2. Mammography and ultrasonography findings

Ultrasonography Sign	n:24	100%
Heterogenous mass containing cystic areas	9	37.5
Fibroadenoma	7	29
Cystosarcoma phloides	2	8.5
Non-descriptive findings	6	25
Mammography sign	n:16	100
Nodular opacity	11	68.8
Asymmetrical density	2	12.5
Microcalcifications	2	12.5
Non-descriptive findings	1	6.2

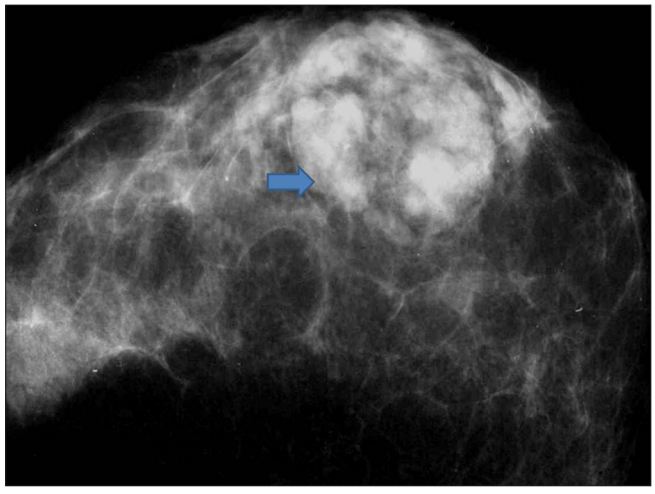

Figure 1. Mammographic appearance of a hamartoma who underwent surgery for diagnostic purposes

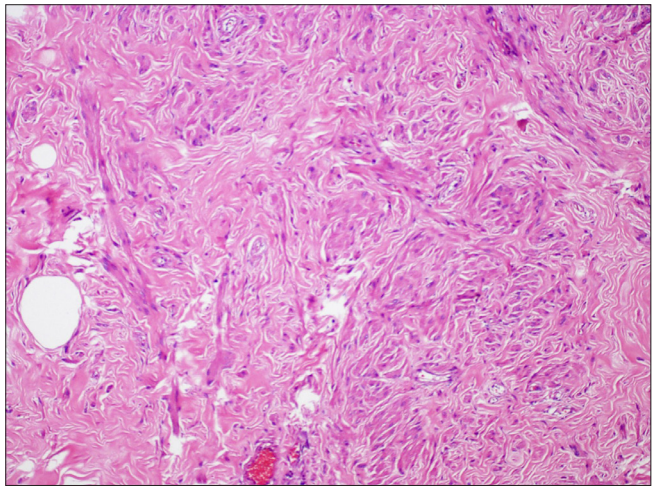

Figure 2. Microscopic findings of hamartoma in a patient who underwent excisional biopsy for diagnosis and therapy (hematoxylin & eosin staining, 4X)

The median tumour size was 5 cm (1-10 cm). The patient's age and tumour size were negatively correlated (r=-0.414; p=0.045). However, no significant difference could be found in the mean tumour size between premenopausal and postmenopausal patients (premenopausal, 5.58±2.82, vs postmenopausal, 4.31±2.92; p=0.309).

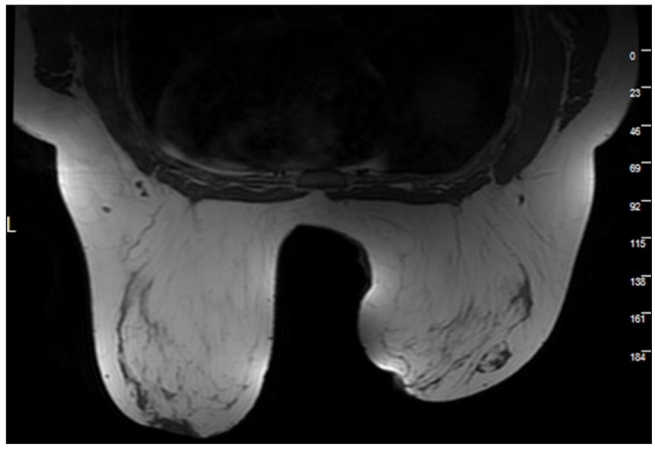

Figure 3. Pre-contrast fat-suppressed T1-weighted images in Magnetic Resonance imaging (MRI) of hamartoma showing a hyperintense fatty signal

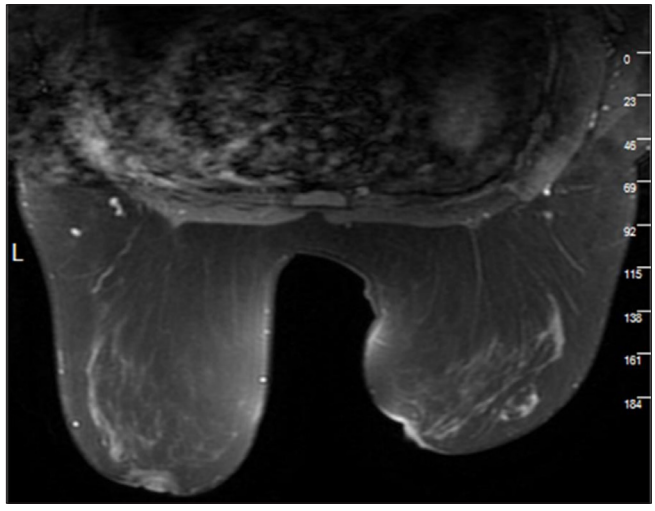

Figure 4. Postcontrast MRI images of ovoid shaped-hamartoma in the lower upper quadrant of the right breast as a lesion having both a fatty density fat-suppressed and contrast-enhanced glandular component inside

The only male case was 65-year old patient with a diagnosis of prostate cancer who presented with a mass in the right upper quadrant of his breast. Even though a metastatic lesion to the breast was suspected, ultrasonographic findings revealed a solid mass with a size "47x20 mm" with a preoperative diagnosis of fibroadenoma. Interestingly, the definitive pathology of the excisional biopsy showed pseudoangiomatous stromal hamartoma.

In another case, a 21-year old female presented with mass following an excision for a malignant phyllodes tumour at another institute. There was suspicion of residual disease on imaging and re-excision was therefore completed at our institution. No residual tumour could be detected in the surgical specimen. However, the pathological examination of the 6x9 cm mass unexpectedly revealed a diagnosis of hamartoma.

The median follow-up of these patients was 58.4 months (1-186 months). There was no recurrence of hamartoma or no malignancy was detected during the follow-up period.

Discussion and Conclusion

Hamartomas are very rare benign tumours. Breast cancer screening programs and breast cancer awareness activities in Turkey have gained momentum in recent years. This situation increased the number of women undergoing examinations, breast ultrasonography, and mammography. As a result, the detection of benign diseases as well as those of breast malignancies has increased. Our 20-year clinical experience have also shown only 2% of patients with benign lesions underwent surgery for hamartomas. Of 24 patients revealed in the 20-year study, 8 of them were diagnosed between 1995 and 2005, whereas 16 of them were detected between 2005 and 2015. In a study conducted in 1978, 10000 mammograms were recorded in a 9-year period and there were only 16 diagnoses of breast hamartoma identified (17). In another study, the authors stated they found 41 hamartomas in 5834 patients undergoing breast biopsy (5). The present study included 1338 patients operated for benign breast disease, of which 24 (1.8 %) were breast hamartoma. One of our patients was male which is relatively rare. The male patient firstly presented with concerns that the breast mass was metastasis of his prostate cancer. However, an ultrasound finding indicated that the mass present in the breast was a fibroadenoma. The patient then underwent excisional biopsy with a final pathology of hamartoma. There are very few published cases of male hamartoma. In a study by Gupta et al. (18), there were only three reported cases of male breast hamartoma. Ravakhah et al. (19) identified a hamartoma in a 36 -year-old male patient with a complaint of slow-growing mass in the left breast.

Hamartomas are seen in middle-aged women as a painless mass of soft consistency or present as a complaint of breast asymmetry. Hamartomas are most commonly seen between the ages 40 to 45 (9, 10, 18). In our case series, the median age was 42 years. Of those, 15 (62.5%) presented with a painless palpable breast mass. The average diameter of a hamartoma is reported at 2 to 5 cm (20). In the literature, breast hamartomas have been detected in very large sizes (21, 22). Weinzweig et al. (22) described a young female patient in the post-lactational period who was diagnosed with a giant size hamartoma followed by an excisional biopsy and required mastopexy. The median size was 5 cm ranged from 1 cm to 10 cm in our study.

Histopathologic features of hamartoma are not characteristic. Breast hamartomas consist of breast ducts and lobules, fibrous stroma, adipose tissue and smooth muscle in varying quantities (23). Clinically, fibroadenomas and phyllodes tumours are often indistinguishable from hamartomas. Especially breast hamartomas are mostly diagnosed as fibroadenomas (12, 20, 24). In our study, the ultrasound findings have shown that hamartoma was most commonly misdiagnosed as fibroadenoma in 7 cases, and secondly phyllodes tumour in 2 cases.

In mammography, presence of peripheral lucent halo, and normal breast pattern are indicators of hamartoma. Therefore, it's described as "breast within a breast". The mammographic findings of hamartoma are the presence of fat and soft tissue density, a mass with a well-defined border, and the presence of a thin radiopaque border (pseudocapsule). Hamartoma contains fatty, glandular or fibrous tissue in varying quantities seen as a mammographic opacity. Although not often, microcalcifications can be seen with hamartoma (10, 13, 17, 25, 26). The ultrasonographic findings revealed that hamartomas were seen as oval, well-defined mass with heterogeneous echogenicity. Furthermore, in general, echogenic or echolucent halo and posterior strengthening was seen in hamartoma (27). Fibroadenoma appears to be encapsulated and well-defined lesion in USG. It is usually homogenous and hypoechoic as compared to the normal breast parenchyma, and sometimes there may be low-level internal echoes. Characteristically, the transverse diameter is greater than the anteroposterior diameter. Calcifications may occur and uncommonly, the mass may appear complex, isoechoic, or hyperechoic. Cystosarcoma phyllodes are a mass with well-defined boundaries that have a non-homogeneous echogenic structure with generally cystic areas. (28)

In 9 of our 24 hamartoma cases, ultrasonography indicated a diagnosis of hamartoma, that might be helpful in differential diagnosis. Although not statistically significant, ultrasonography was found to be more diagnostically useful in patients with a mass greater than 5 cm compared to those other smaller lesions. In 5 cases (20.8%), mammography results correlated with USG findings, and both USG&MMG were found to be useful in diagnosis of breast hamartomas. In our current practice, breast MRI has been commonly used as a diagnostic imaging tool to confirm hamartomas in addition to ultrasound and mammogram as reported before (29). MRI has been especially helpful to determine whether excisional biopsy is required for diagnostic and therapeutic purposes. Patients with a radiological diagnosis of hamartomas can be conservatively followed without surgery with 6-month intervals without performing surgery for at least 2 years. The appearance of the breast hamartoma with MRI is shown in Figure 3 and 4.

There is no specific histological findings in the diagnosis of hamartoma and the pathological diagnosis is often difficult. Many studies have pointed out that there is a limited role in the diagnosis of fine needle aspiration cytology and core biopsy. Core or fine needle biopsy usually provides an inadequate or nonspecific biopsy result. Core biopsy seems to be more important to exclude malignancy (4, 9, 11). Our results suggest that, fine needle and core biopsy have been useful to confirm a benign lesion, however they may not be adequate for diagnostic purposes.

Tse and colleagues reported 25 cases of hamartoma. On histopathological examination of these cases, all contained the fatty tissue, whereas interlobular fibrosis was seen in 21 patients and pseudoangiomatous stromal hyperplasia was detected in 8 patients (11). In a further study, of 27 cases analyzed, pseudoangiomatous stromal hyperplasia was identified in 25.9% (10). In this study, 3 cases contained pseudoangiomatous stromal hyperplasia (12.5%), and two cases (8.3%) were found to have both sclerosing adenosis and adenosis. Foci of microcalcification were detected in 4 of our cases (16.6 %). A radial scar was identified in one case of hamartoma. Papillomas, fibrocystic disease, epithelial changes, ductal ectasia and atypical lobular hyperplasia frequently accompany hamartomas (10, 11).

Uncommonly, hamartomas are reported with invasive ductal and invasive lobular breast carcinoma (14, 15, 24). Albawardi et al. (23) reported mammary hamartomas to be associated with columnar cell changes including flat epithelial atypia. In our study, invasive ductal or lobular carcinoma was not detected with hamartoma. In addition, there were no cases diagnosed with ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) within hamartoma. However, one of our cases in this series was interestingly diagnosed with malignant phyllodes tumour that was found in the same breast as hamartoma, which has not been described in the literature before.

Daya et al. (3) noted in 25 patients, there were 2 cases of recurrence at 7 and 18 months postoperatively. In many studies, an emphasis

has been given to the need to complete a total excision to avoid recurrence. In this study, at a median follow-up period of 58.4 months postoperatively, no recurrence was detected or none of them developed malignancy.

In conclusion, due to the development of radiological methods in recent years, the diagnosis of hamartoma can easily be made. This could be more valid and reliable if confirmed by core-needle biopsy. For those patients in this situation, surgical excision is unnecessary, and follow-up is appropriate as the hamartoma is benign. However, surgical excision is required in patients with suspected malignancy who cannot be determined hamartoma on radiographically.

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

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Original Article

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Can Radiologist and Pathologist Reach The Truth Together in The Diagnosis of Benign Fibroepithelial Lesions?

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ABSTRACT

Objective: Benign fibroepithelial lesions (BFL) lesions of the breast are various and predominantly benign, although a few can be locally aggressive. Definitive diagnosis of some BFL can be challenging from core needle biopsy (CNB). Radiological findings can help guide the management of the lesions. The aim of this study was to investigate the accuracy rate of CNB results and evaluate the radiological findings of the most common BFL according to the final excision pathology results. The secondary aim was to assess the contribution of the imaging findings to CNB results.

Materials and Methods: A retrospective review was made of 266 patients diagnosed with suspicious BFL, conventional fibroadenoma, complex fibroadenoma, cellular fibroadenoma and benign phyllodes tumor (PT). The study included 132 patients who underwent surgical excision. The radiological and histopathological findings were evaluated.

Results: While 66 patients were diagnosed with more descriptive results on CNB, the other 66 patients were diagnosed with suspicious BFL. Agreement between CNB and excisional pathology was good, when CNB provided a definite diagnosis. While conventional and complex fibroadenoma were observed to have hypo or normal vascularity, cellular fibroadenoma and PT showed hypervascularity. Oval shaped and homogeneous internal echo pattern were significantly associated with conventional fibroadenoma. A heterogeneous internal echo pattern was seen in complex fibroadenomas and PT.

Conclusion: CNB often reaches the correct diagnosis alone when it gives a definite diagnosis. The radiological findings which help in the differentiation of BFL are hypervascularity, oval shape and internal heterogeneity. More accurate results can be obtained when histopathological and radiological findings are evaluated together.

Keywords: Benign fibroepithelial lesions, fibroadenoma, phyllodes tumor, histopathological findings, radiological findings

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Introduction

Benign fibroepithelial lesions (BFL) of the breast are characterized by proliferation of both epithelial and stromal components. BFL are various and predominantly benign, although a small percentage can be locally aggressive (1). Fibroadenoma is the most common benign neoplasm among BFL. Fibroadenomas have variants including cellular and complex fibroadenoma. Complex fibroadenoma is a variant of the fibroadenoma harboring at least 1 of the following features: sclerosing adenosis, cysts, papillary apocrine metaplasia and epithelial calcifications. Cellular fibroadenoma is another variant of fibroadenoma with remarkable cellularity. These different characteristics of fibroadenoma can cause misdiagnosis histopathologically (2-4).

To distinguish between fibroadenoma and phyllodes tumor (PT) is clinically important due to different clinical management. While fibroadenomas can be followed up safely with conservative methods, surgical excision is recommended for PT. Definitive diagnosis of some of the BFL can be challenging from core needle biopsy (CNB) due to increased cellularity and complex structures. They can be upstaged to phyllodes tumor on excision pathology (5). If there is histopathological uncertainty, the World Health Organization working group proposes using the term of benign fibroepithelial neoplasm in order to avoid overtreatment (6, 7). On the other hand, National Comprehensive Cancer Network guidelines suggest excisional biopsy for palpable, large (>3 cm) and rapid growing lesions which are diagnosed as fibroadenoma or are indeterminate on CNB (8).

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There can also be overlapping findings in the radiological diagnosis of BFL (9). However, more accurate results can be obtained when histopathological and radiological findings are evaluated together. The main aim of this study was to investigate the accuracy rate of CNB results and to evaluate the radiological findings of the most common BFL according to the final excision pathology results. The secondary aim of the study was to assess the contribution of the imaging findings to CNB results.

Material and Methods

Approval for the study was granted by the Hacettepe University Ethics Commission. Informed consent was not taken due to the retrospective nature of the study.

Patients

A retrospective review was made of 266 patients diagnosed with BFL on CNB between January 2014 and June 2018. The study included 132 patients who underwent surgical excision with a diagnosis of conventional fibroadenoma, complex fibroadenoma, cellular fibroadenoma and benign PT. As the excisional pathology results are gold standard in the diagnosis of the BFL, we excluded the 121 patients who did not undergo surgical excision. There were only 5 patients diagnosed with borderline and malignant PT. We excluded the borderline and malignant PT, because of the limited number and more aggressive nature of these lesions. Uncommon BFL including pseudoangiomatous stromal hyperplasia, lactating adenoma, adenomyoepithelioma and tubular adenoma were also excluded due to lower numbers. The total number of these patients was 8.

The patients diagnosed with suspicious fibroepithelial lesion and PT in CNB and the patients categorized as BIRADS 4B and 4C underwent surgical excision. 26 patients underwent excisional surgery due to positive family history or their own request.

Imaging

All patients underwent ultrasonography (US), 45 patients had mammography and only 8 patients had magnetic resonance imaging (MRI).

The US images were obtained using a 12 MHz linear probe on a Toshiba Aplio 400 device (Toshiba Medical Systems Corporation, Otawara, Japan). For the mammograms, standard mediolateral oblique and craniocaudal images were obtained using Seno essential mammography systems (General Electric, USA). The MRI scans were acquired with the patient in the prone position in a 1.5-Tesla MRI scanner (Signa HD, GE Medical Systems, USA) using a four-channel phased array breast coil. The imaging protocol included the following sequences: axial T2-weighted fat saturated (TR/TE 5100/90 ms, slice thickness=2 mm, flip angle 90°, matrix 256x256), axial echo-planar DWI (TR/TE 2500/72, slice thickness=3 mm, matrix 256 x 256, diffusion gradient with b values of 0 and 500 s/mm^2), and axial T1-weighted fast spin echo pre-contrast MR images (TR/TE 4.3/2.1 ms, slice thickness=2 mm, flip angle 90°, matrix 512x512). Dynamic breast examination was performed after the injection of intravenous contrast material (Magnevist, Bayer Schering Pharma AG, Berlin, Germany) through the antecubital vein at a dose of 0.1 mmol/kg using a power injector (Medrad, Bayer HealthCare, Netherlands). After pre-contrast T1-weighted images, the following 5 axial T1-weighted post-contrast dynamic sequences (TR/TE 4.5/2.1 ms, slice thickness=2 mm, flip angle 10°, matrix 512x512) were obtained at intervals of 90 seconds.

Pathological examination

The patients with suspicious histopathological or radiological findings underwent surgical excision. Some patients underwent surgery due to family history and their own request for surgery, although the CNB pathology results and radiological findings were benign.

All CNBs were performed under US guidance using a 14-gauge cutting needle. All needle biopsies were performed using an automated biopsy gun and at least 4 core specimens were obtained from each lesion.

The pathological reports were reviewed. The lesions with a final pathological diagnosis of conventional fibroadenoma, complex fibroadenoma, cellular fibroadenoma and benign PT were assessed.

Statistical Analysis

Mean and standard deviation were presented for continuous variables; number and proportion were presented for categorical variables. Yates' Chi-square test or Fisher Exact tests were used to examine the relationship between two categorical variables. The Kappa coefficient was obtained to assess the agreement between CNB and excisional pathology results.

A p value of 0.05 was accepted as statistically significant. Data analysis was performed by Statistical Package for the Social Sciences version 23.0 (IBM Corp., Armonk, NY, USA) software package.

Results

Clinical and histopathological data

The mean age of patients was 41±10 years and the mean size of the lesions was 19±11mm.

While 66 patients were diagnosed with more descriptive results as conventional fibroadenoma, complex fibroadenoma, cellular fibroadenoma, benign phyllodes on CNB, the other 66 patients were diagnosed with suspicious BFL and excision was recommended. According to the excisional pathological results, the numbers of conventional fibroadenoma, complex fibroadenoma, cellular fibroadenoma and benign PT were 64 (48.5%), 24 (18.2%), 12 (9%) and 32 (24.3%), respectively.

Although all patients diagnosed with cellular fibroadenoma were under 35 years of age, there was no statistical significance between the types of BFL and age (p=0.5) Lesion size was larger in PT than in the other BFL, but not at a level of statistical significance (p=0.3).

Radiological findings

The radiological characteristics of the lesions are shown in Table 1. Most lesions had an oval shape (75%), circumscribed margin (53%), homogeneous internal echo pattern (62.1%), hypo or normal vascularity (75.8%) and were BI-RADS 4A (85.6%) category. There was no statistically significant difference between types of BFL and the features of the margins (p=0.6), size increase (p=0.4) and BI-RADS category (p=0.3). There was no relationship between the types of BFL and MRI, and mammography findings (p>0.05 for all findings).

We analysed BIRADS category and pathology results. From 113 lesions reported as BIRADS 4A category, 58 lesions diagnosed with suspicious fibroepithelial lesion and 29 lesions diagnosed with PT in CNB. The other 26 patients underwent to the excisional surgery due to positive family history or their own request. From 17 lesions reported as BIRADS 4B category, 7 lesions diagnosed with suspicious fibroepithelial lesion and 4 lesions diagnosed with PT on core needle biopsy. There were only 2 patients categorized as BIRADS 4C. And from these two patients, one was reported as suspicious

Table 1. Imaging characteristics of lesions

Radiological Findings	n (%)
Ultrasound Features	
Shape	
Oval	99 (75.0)
Round	24 (18.1)
Irregular	9 (6.8)
Margins	
Circumscribed	70 (53.0)
Microlobulated	48 (36.4)
Indistinct	14 (10.6)
Internal echo pattern	
Homogeneous	82 (62.1)
Heterogenous	50 (37.9)
Vascularity	
Hypovascular and normal vascularity	100 (75.8)
Hypervascular	32 (24.2)
Size increase	33 (25)
Mammography Features	
Patients underwent mammography	45 (34)
No features on mammography	15 (33.3)
Asymmetric density	5 (11.1)
Mass	25 (55.5)
Calcification within the lesion	2 (4.4)
MRI Features	
Patients underwent MRI	8 (6.0)
Type 1 dynamic curve	5 (62.5)
Type 2 and type 3 dynamic curve	3 (37.5)
Homogeneous contrast enhancement	6 (75)
Heterogenous contrast enhancement	2(25)
BI-RADS	
BI-RADS 4A	113 (85.6)
BI-RADS 4B	17 (12.9)
BI-RADS 4C	2 (1.5)

MRI: magnetic resonance imaging; BI-RADS: breast imaging reporting and data system

fibroepithelial lesion while the other one was reported as complex fibroadenoma.

While conventional and complex fibroadenoma have hypo or normal vascularity, cellular fibroadenoma and PT show hypervascularity on Doppler ultrasonography (p=0.0001). An oval shape (85.9%) and homogeneous internal echo pattern (57%) are significantly associated with conventional fibroadenoma (p=0.002 for shape, p=0.001 for internal echo pattern). A heterogeneous internal echo pattern is seen in complex fibroadenomas (62.5%) and PT (68.8%) (p=0.001). The significant radiological findings of BFL are shown in Table 2 and Figure 1.

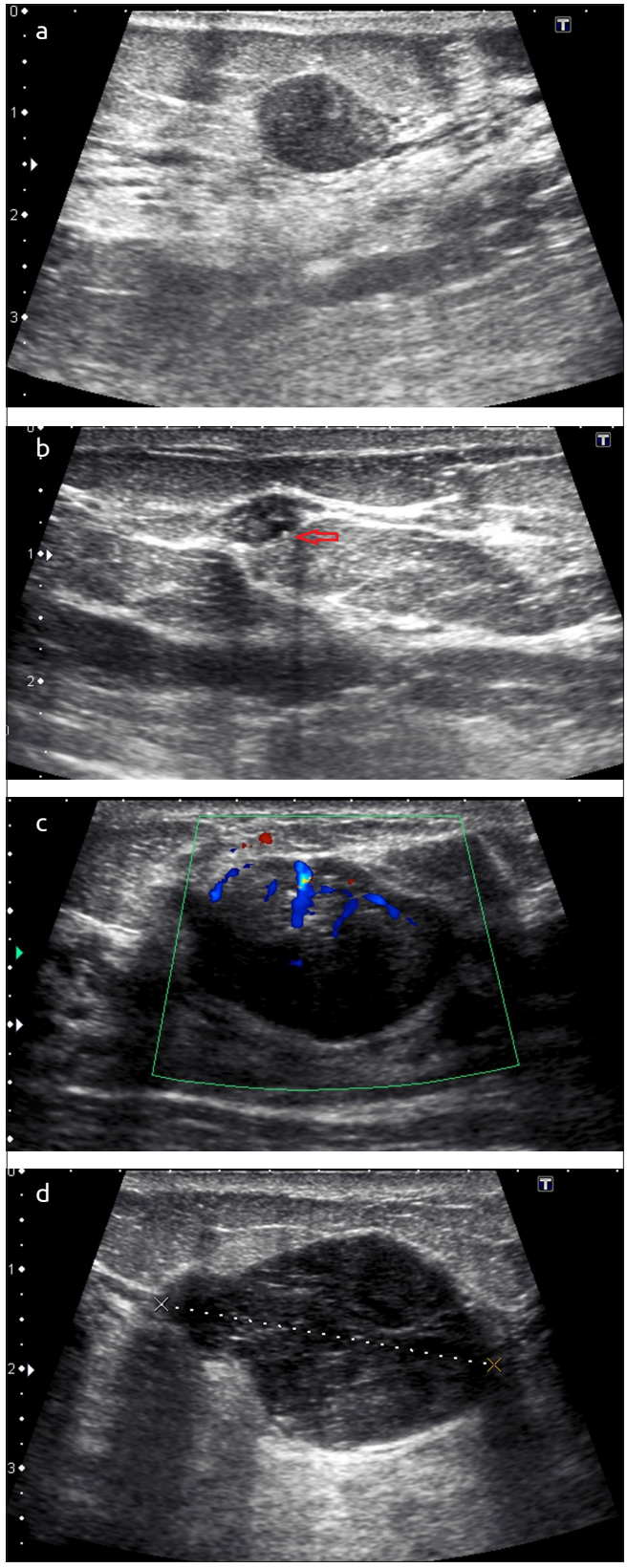

Figure 1. a-d. Oval shaped and homogeneous internal echo pattern benign fibroepithelial lesions diagnosed with conventional fibroadenoma is shown in US (a). US shows small solid lesion with heterogeneous internal echo pattern due to the millimetric cyst. It was diagnosed as complex fibroadenoma histopathologically (b). Doppler US demonstrates hypervascularity within the cellular fibroadenoma (c). Heterogenous solid lesion diagnosed with phyllodes tumor is shown in US (d).

Table 2. The significant ultrasonography findings of benign fibroepithelial lesions are given with their percentages

	Shape/ (%)/p	Internal echo patern/(%)/p	Vascularity/(%)/p
Conventional fibroadenoma (n=64)	Oval/(85.9)/0.002	Homogeneous/(57)/0.001	Hypovascular or normal/(9.8)/0.0001
Complex fibroadenoma(n=24)	Oval/(62.5)/0.1	Heterogeneous/(62.5)/0.001	Hypovascular or normal/(95.8)/0.0001
Cellular fibroadenoma(n=12)	Oval/(75)/0.1	Homogeneous/(50)/0.3	Hypervascularity/(75)/0.0001
Benign phyllodes(n=32)	Oval/(62.5)/0.1	Heterogenous/(68.8)/0.001	Hypervascularity/(56.3)/0.0001

Table 3. Agreement between core needle biopsy and excisional pathology

		Excisional Pathology Results			
		Conventional fibroadenoma n (%)	Complex fibroadenoma n (%)	Cellular fibroadenoma n (%)	Benign phyllodesn (%)
Core Needle Biopsy Results	Conventional fibroadenoma (%)	19 (63.3)	1 (9.1)	0 (0)	1 (4.3)
	Complex fibroadenoma (%)	1 (3.3)	9 (81.8)	0 (0)	0 (0)
	Cellular fibroadenoma (%)	0 (0)	0 (0)	1 (50)	1 (4.3)
	Benign phyllodes (%)	10 (30.4)	1 (9.1)	1 (50)	21 (91.4)
	Total n (%)	30 (100)	11 (100)	2 (100)	23 (100)

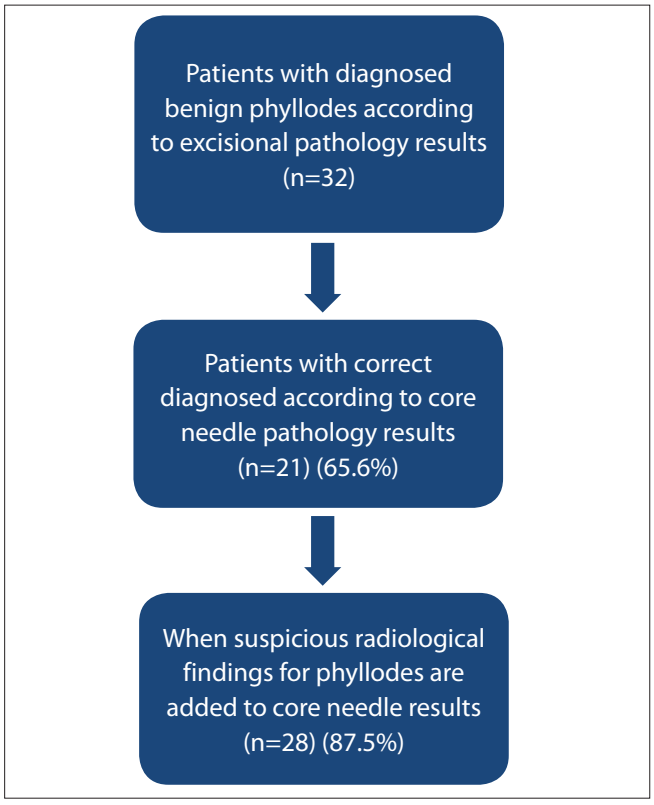

Figure 2. The diagram shows evaluation of core needle biopsy results with radiological findings in phyllodes tumors

Agreement between CNB and excisional biopsy

Agreement between CNB and excisional pathology was good (kappa=0.641 p<0.001). Agreement was evaluated in 66 patients who got a definite diagnosis in CNB and underwent surgical excision. Table 3 shows the agreement in detail.

Evaluation of core needle biopsy results with radiological findings

From 32 patients with diagnosed with PT accordingly to excisional pathology result, 21 patients got correct diagnosis in CNB at the rate of 65.6%. When statistically significant radiological findings including hypervascularity and heterogeneous internal echo pattern were added to CNB findings, additional 7 patients got accurate diagnosis although CNB could not give exact correct diagnosis. So, accuracy rate of diagnosis PT increased to 87.5% (Figure 2).

Half of the patients were diagnosed with a suspicious BFL on CNB. Figure 3 shows the excisional pathology results and the percentages of significant radiology features of the patients who could not be definitively diagnosed from CNB.

Discussion and Conclusion

The major findings of the current study are that first, CNB often reaches the correct diagnosis alone, when it gives a definite diagnosis. Second, radiological findings including oval shape, presence of vascularity and internal echogenicity of the lesions can help in the diagnosis of BFL (p<0.05). Finally, when the radiological findings and CNB are evaluated together, more accurate results can be provided than by separate evaluation.

Benign fibroepithelial lesions encompass a heterogeneous group of neoplasms exhibiting epithelial and stromal proliferation. Although most BFL are conventional fibroadenoma, PT and subtypes of fibroadenoma including cellular fibroadenoma, complex fibroadenoma are other common BFL (1, 2). Awareness of the different BFL is important because of the requirement for different management. However, the evaluation of BFL in CNB is challenging because of their heterogeneous nature. In PT, areas with marked overgrowth and stromal cellularity with leaflike stromal fronds may be present only as minor foci within a seemingly fibroadenoma. And insufficient samples including

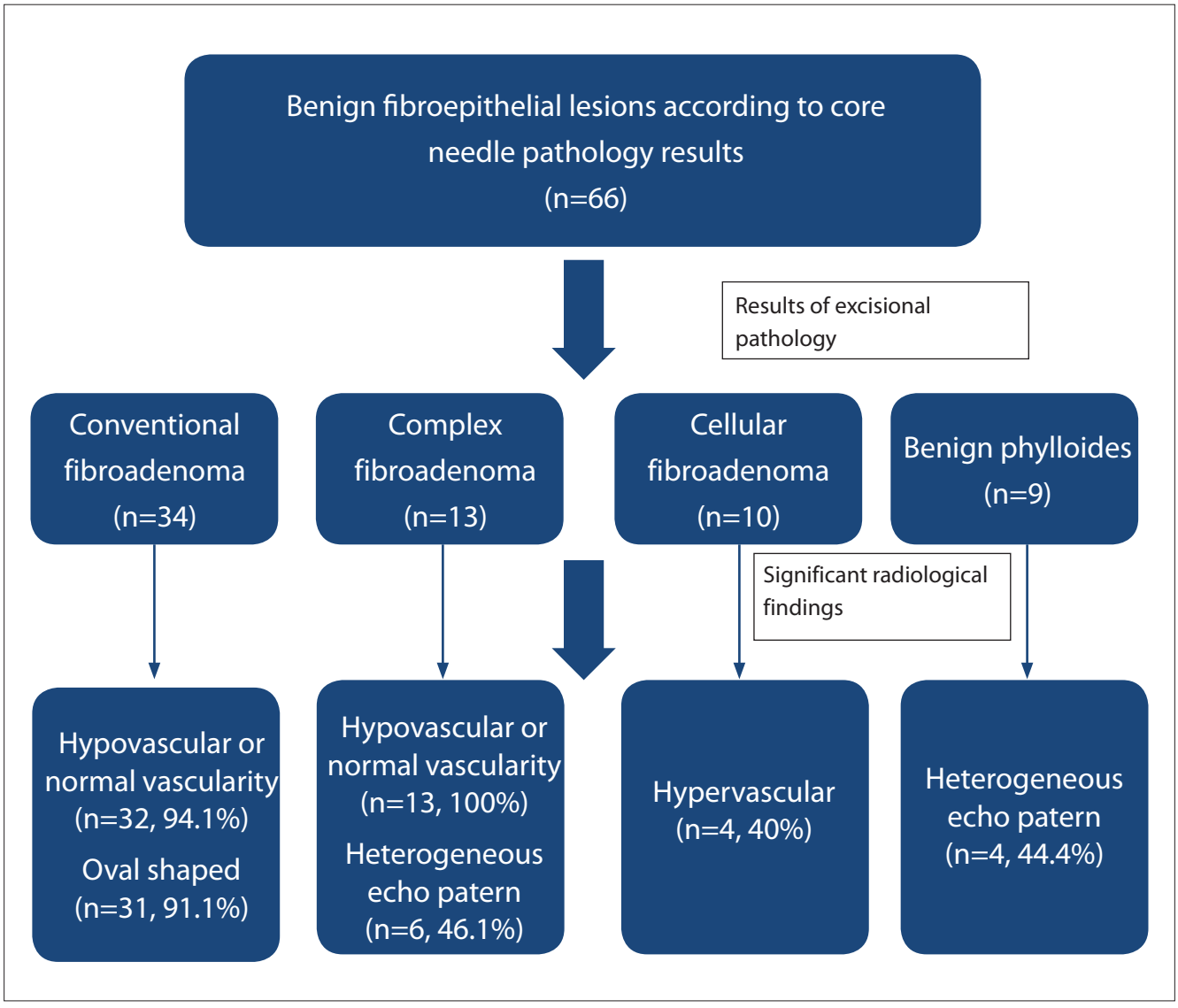

Figure 3. The diagram demonstrates the excisional pathology results and the percentages of significant radiology features of the patients who could not get definite diagnosis on CNB

torn-cracked samples prevent the accurate diagnosis in CNB. So, adequate samples with additional sampling of the areas showing heterogeneous internal echo on US may help in diagnosis of BFL in CNB. In the current study, the agreement between CNB and excisional pathology was good, if CNB provided a definite diagnosis (kappa=0.641 p<0.001) but the CNB diagnosis was of a suspicious BFL without a definitive diagnosis in half of the patients. And, also according to the results of current study, the core biopsy showed an overestimation. Because only 2 benign phyllodes tumor were reported as fibroadenoma, while 12 fibroadenomas were reported as benign phyllodes in core needle biopsy.

In CNB, the lesion most frequently misdiagnosed as PT is cellular fibroadenoma due to its increased stromal cellularity. Cellular fibroadenoma is usually seen in young women and surgical excision is recommended because of the larger size (10). In the current study, all the patients diagnosed with cellular fibroadenoma were younger than 35 years old. Nevertheless, no statistical relationship was determined between age and cellular fibroadenoma, which could be attributed to an insufficient number of patients. Furthermore, the accuracy of the CNB results could not be optimally evaluated due to surgical excision of most of the cellular fibroadenomas without preoperative CNB.

Complex fibroadenoma is another variant of fibroadenoma harboring one or more complex features. Previous studies have shown that complex fibroadenomas are usually smaller than other BFL and are seen in older patients (3, 4). However, in this study, no statistical significance could be determined between subtypes of BFL and age, or size. PT is usually seen in older patients than simple fibroadenomas such as complex fibroadenoma (11, 12). According to the current study results, CNB often gives the diagnosis of complex fibroadenoma and PT correctly. Evaluation of the age, size and radiological findings together may help in the diagnosis of suspicious BFL in CNB. And when there is a radio-pathological discordance, second look US and re-biopsy can be performed.

Most of the lesions in this study were categorized as BI-RADS 4A. There was no significant finding among BFL on mammography and MRI. This was probably due to the limited number of patients applied with mammography and MRI. Some previous studies have shown that high density and absence of intratumoral calcification were as-

sociated with PT on mammography (9, 13, 14) and other studies have reported that PT and other fibroadenomas could not be precisely differentiated on breast MRI (15, 16). In the current study, the features of margins and size increase could not differentiate benign fibroepithelial lesions from each other, whereas hypervascularity (p=0.0001), internal echo pattern (p=0.001) and shape (p=0.002) were able to help differentiate the different types of BFL. While conventional and complex fibroadenoma have hypo or normal vascularity, cellular fibroadenoma and PT show hypervascularity on Doppler ultrasonography. An oval shape and homogeneous internal echo pattern are significantly associated with conventional fibroadenoma. Moreover, a heterogeneous internal echo pattern is seen in complex fibroadenomas and PT. Similar to the current study results, Duman et al. (16) found hypervascularity to be associated with PT. Increased cellularity in PT and cellular fibroadenoma may be the cause of the hypervascularity seen on Doppler US. The reason for the heterogeneous internal echo pattern in complex fibroadenoma may be the complex pathological nature of it including calcification and cystic changes. Wiratkapun et al. (14) reported that PTs often showed sonographic heterogeneity, similar to the observations of the current study. This can be explained by the presence of cystic changes representing areas of focal necrosis and dilated glands (1).

Although CNB often reaches the correct diagnosis alone, it could not provide a definitive diagnosis in half the patients. When CNB gives a diagnosis of suspicious BFL, close follow-up may be selected in cases of benign radiological findings. Furthermore, when suspicious radiological findings for PT including hypervascularity and internal heterogeneity were added to the results of CNB in the current study, the diagnostic accuracy rate increased from 65.6% to 87.5%.

There are some limitations to this study. First, it was a retrospective study and the radiological findings were only assessed from the recorded images. The retrospective nature of the study limited the determination of US and Doppler US characteristics. Second, the small number of cellular fibroadenoma and the small number of masses evaluated by mammography and MRI limited the statistically significance of the results. Finally, due to the very small number of borderline, malignant PTs and uncommon benign fibroepithelial tumors including pseudoangiomatous stromal hyperplasia, lactating adenoma, adenomyoepithelioma and tubular adenoma, these were not included in the study. Therefore, the range of BFL for which the radiological and histopathological features were evaluated, was limited.

In conclusion, CNB often reaches the correct diagnosis alone when it gives a definite diagnosis (kappa= 0.641 and p<0.001). The radiological findings which can help in the differentiation of BFL are hypervascularity, oval shape and internal heterogeneity. More accurate results can be obtained when histopathological and radiological findings are evaluated together. When the suspicious radiological findings were added to the results of the CNB, the diagnostic accuracy of rate increased from 65.6 % to 87.5 %. The presence of suspicious radiological findings can predict PT, even if CNB results show fibroadenoma or suspicious BFL. Nevertheless, close follow-up may be preferred for cases with benign radiological findings in BFL.

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

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Original Article

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Cost effectiveness of Gene Expression Profiling in Patients with Early-Stage Breast Cancer in a Middle-Income Country, Turkey: Results of a Prospective Multicenter Study

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ABSTRACT

Objective: Breast cancer is a heterogenous disease, and genetic profiling helps to individualize adjuvant treatment. The Oncotype DX is a validated test to predict benefit of adjuvant systemic treatment. The aims of this study are to determine the costs of chemotherapy in government hospitals in Turkey and evaluate the cost-effectiveness of the Oncotype DX from the national insurance perspective.

Materials and Methods: A Markov model was developed to make long term projections of distant recurrence, survival, quality adjusted life expectancy, and direct costs for patients with ER+, HER2-, node-negative or up to 3 node-positive early stage breast cancer. Turkish decision impact study patient data were captured for model reference. In that study, ten academic centers across Turkey participated in a prospective trial. Of 165 patients with pT1-3, pN0-N1mic, ER-positive, and HER-2 negative tumors, 57% had low recurrence score (RS), 35% had intermediate RS, and 8% had high RS, respectively. The overall rate of change in chemotherapy treatment decisions following Oncotype DX was 33%.

Results: The cost of adjuvant chemotherapy in public hospitals was estimated at $3.649, and Oncotype Dx test was $5.141. Based on the cost-effectiveness analysis, Oncotype DX testing was estimated to improve life expectancy (+0.86 years) and quality-adjusted life expectancy (+0.68 QALYs) versus standard care. The incremental cost-effectiveness ratio (ICERs) of Oncotype DX was estimated to be $7207.9 per QALY gained and $5720.6 per LY gained versus current clinical practice.

Conclusion: As Oncotype DX was found both cost-effective and life-saving from a national perspective, the test should be introduced to standard care in patients with ER+, HER-2 negative early-stage breast cancer in Turkey.

Keywords: Early breast cancer, genetic profiling, oncotype-Dx, cost, markov model.

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Introduction

Invasive breast carcinoma is the most commonly seen malignancy and leading cause of cancer related death in Turkish women. An analysis of 13.240 patients in the National Breast Cancer Database established within the Turkish Federation of Breast Diseases Societies showed that 50% patients had N0 and 27% had Stage I breast cancer, respectively. Overall, 80.7% of patients had luminal molecular subtype

Despite available data on chemotherapy efficacy in locally advanced and metastatic breast cancer, it is not possible to predict who will benefit from adjuvant treatment in early stage breast cancer based on traditional clinical pathological features. The major pathological and clinical features including age, menopausal status, tumor size, histologic grade, ki 67 proliferative index, estrogen (ER) and progesteron receptor (PR) and human epidermal growth factor receptor 2 (HER-2) expression are commonly used by clinicians to guide chemotherapy treatment decisions; however, in cases with equivocal features, the decision to recommend adjuvant chemotherapy may be uncertain. Furthermore, challenges remain regarding the inter- and intra-laboratory standardization of a number of clinical risk factors.

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Table 1. Summary of changes in adjuvant therapy recommendations with Oncotype DX testing in the modelling analysis

	Initial recommendation		Post Oncotype DX net change in CT use
Recurrence Score	HT (%)	HT+CT (%)	HT+CT (%)
Low	30.9 (51/165)	25.5 (42/165)	-21.0
Intermediate	11.5 (19/165)	23.6 (39/165)	1.9
High	1.8 (3/165)	6.7 (11/165)	4.8
Total	44.2 (73/165)	55.8 (92/165)	

CT: chemotherapy; HT: hormone therapy

As early stage breast cancer incidence is increasing with improved cancer screening methods, with half of breast cancer cases presenting as stage pN0 in Turkey, suboptimal evaluation for treatment planning may lead to many patients unnecessarily exposed to chemotherapy and associated toxicity and may increase health expenses. Besides, patients who may derive a substantial benefit from chemotherapy to prevent distant recurrence may not receive chemotherapy.

The emergence of genomics and transcriptomics techniques and the ability to measure various genes led to the identification of tumor-biology based prognostic and predictive determination. The Oncotype DX RS is one of the best-validated prognostic assays and may identify patients who are most and least likely to derive benefit from adjuvant chemotherapy (1, 2).

The Oncotype-DX test is validated for patients with node-negative early breast cancer as well as limited node involvement (pNmic/pN1), ER(+), HER-2(-) negative breast cancer to identify whether a patient who will receive at least a five-year course of endocrine therapy is likely to derive benefit from chemotherapy. (3, 4). The validity of Oncotype DX has been demonstrated in several studies both for prognosis and prediction of adjuvant chemotherapy (5, 6).

In two different analyses from the same patient cohort from 10 academic centers in Turkey, we demonstrated that only high Ki67 (>14%) and low PR (20%) levels were correlated with high Oncotype DX-RS in multivariate analysis, and Oncotype-DX RS may further change physician decisions for adjuvant treatment (7, 8). In a Turkish Oncotype-Dx Decision Impact Study involving patients with T1-3, ER+, HER-2(-), N0-1mic breast cancer, adjuvant chemotherapy treatment recommendations of enrolled patients were collected before and after availability of the RS. Changes in treatment decisions based on the information provided by the RS were then analysed. Of 165 patients; 57% had low RS, 35% had intermediate RS, and 8% had high RS, respectively. The overall rate of change in chemotherapy treatment decisions was found to be 33%. For the most part, recommendations changed from chemotherapy plus hormonotherapy to hormonotherapy alone, resulting in 19% absolute reduction in chemotherapy use (8).

Currently Oncotype DX is not frequently used by Turkish Physicians due to its prohibitive cost for patients and also it is not currently reimbursed by the Turkish Social Security Administration. The cost-effectiveness is a matter of policy interest. Several developed countries have revealed the cost-effectiveness of testing based on analyses of the local use and impact of the test. Although the benefit was clearly established in these trials, in some European countries, Oncotype DX reimbursement is limited to selected patients. The question remains as to the optimal approach to implementing Oncotype DX testing.

In this study, we aimed to evaluate the cost-effectiveness of Oncotype DX in a developing country using our patient population as a model reference.

Materials and Methods

Model overview

The model used in this analysis is generated via local adaption of a Markov model, that was developed in Microsoft Excel, based on an original model by Hornberger, to evaluate the long-term costs and clinical outcomes associated with introducing Oncotype DX testing to inform decisions about adjuvant chemotherapy for patient with ER+, node-negative or single node positive early-stage breast cancer for an analysis for England and Wales (9). The model made projections of life expectancy, quality-adjusted life expectancy and direct costs, based on recurrence rates for low, intermediate and high-risk patients as well as country-specific mortality data. The risk was adjusted by reference models as demonstrated on Table 1, 2 and 3.

The model structure is outlined in Figure 1. There are three states in the model: *recurrence-free* (in which all patients start the simulation), *recurrence* (following a distant recurrence event) and *dead* (following a mortality event). The model had a 1-year cycle length. The base case time horizon was set to 30 years to capture long-term recurrence risk. All patients start the simulation in the *recurrence-free* state. In each 1-year cycle of the simulation, patients are exposed to the risk of competing mortality and recurrence. Patients who have a mortality event transition to the *dead* state, who experience a distant recurrence event transition to the *recurrence* state occurs, where they are exposed to the risk of breast cancer mortality in each subsequent year of the simulation. All cost-analyses were analysed according to Social Security Instution of Turkey (SGK).

Clinical parameters

To ensure that the modelling analysis was in line with the standard clinical care pathways in Turkey, patients were assumed to receive standard endocrine therapy and chemotherapy regimens in line with local practices evidenced in the Turkish Oncotype-Dx Decision Impact Study and the Turkish Cost-Effectiveness Analysis of Screening in Breast Cancer (8, 10). The model cohort age was assumed to be 49.9 years based on the mean age from Turkish Oncotype-Dx Decision Impact Study cohort (8). In this patient group, 108 patients (65.4%) had pT1 tumors, and the median tumor size was 2 cm. Only 11 (6.7%) patients had micrometastasis in axillary lymph nodes (pN1mic). The

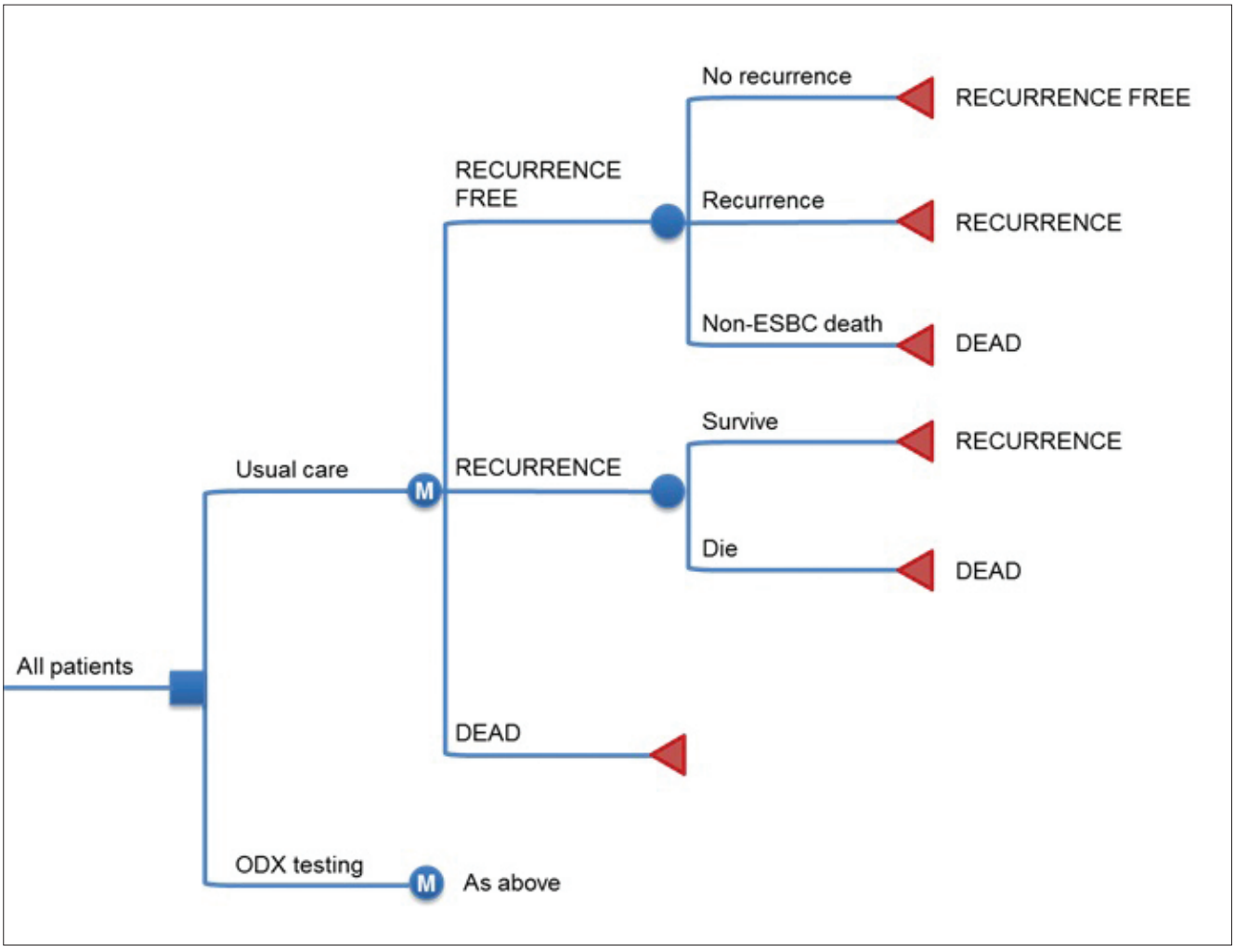

Figure 1. Overview of the Oncotype DX cost-effectiveness model structure

majority (53.5%) of the patients had a ki67 score of <20%, 60.4% patients were considered to have luminal B molecular type. The change in the chemotherapy decision between pre and post RS assay treatment plans was analysed using McNemar's test (Table 1).

In each cycle of the model, the risk of recurrence was evaluated for each simulated patient based on their RS defined category of low, intermediate or high risk as reported for the NSABP B-20 cohort (4) (Table 2). Risk was adjusted based on whether patients were receiving chemotherapy as per the initial recommendations (in the usual care arm) and based on the Oncotype DX Recurrence Score (in the Oncotype DX arm). Non-breast cancer death was captured as a competing risk in the model, based on Turkey life tables (Turkish Statistical Institute) for females in 2013 (11).For patients experiencing distant recurrence, survival was assumed to be 3.3 years (12).

Costs of treatment

In the cost-effectiveness model the costs of endocrine therapy, chemotherapy, adverse events associated with chemotherapy and the cost of distant recurrence were accounted. All costs were taken from Turkey-specific sources as Turkish lira, converted and expressed as dollars in the analysis, using the currency conversion rate as of February 2016 when the data collection was conducted. A summary of cost variables used in the model is provided in Table 3.

All the medicine costs, follow-up costs, mammogram costs and other cost items are taken from Turkish Cost-Effectiveness Analysis of Screening in Breast Cancer (10).

The cost of endocrine therapy is incurred over 8 years, at different rates over the initial 5 years and later 3 years to reflect varying treatment patterns. For those patients receiving chemotherapy, the costs of chemotherapy and endocrine therapy are both incurred in the first year. Based on 4-6 cycles of chemotherapy, there is thus an overlap of costs of approximately 3.5 months.

Costs of all drugs related with treatment and toxicities, costs of follow-up (mammography, ultrasound, biopsy, CT-scans etc.) are taken from Turkish Cost-Effectiveness Analysis of Bahcesehir Breast Cancer Screening Program (10). The cost of chemotherapy evaluated the chemotherapy regimens, number of cycles, doses of chemotherapeutics, concomitant medications used to prevent or treat adverse events, diagnostics etc; the frequency and duration. Adverse events associated with chemotherapy; the cost of screening, diagnostics, treatment and follow-up for adverse events associated with treatment were based on the Turkish Oncotype-Dx Decision Impact Study cohort (8).

Risk of recurrence associated with endocrine therapy and relative risk reduction associated with chemotherapy were both taken from the Paik et al. (4) NSABP B-20 study of Oncotype DX. Local recurrences

Table 2. Summary of clinical variables in the cost-effectiveness modelling analysis

Variable	p	Reference
Age (years)	49.9	Turkish Oncotype-Dx Decision Impact Study8
Net change in chemotherapy use with low RS (%)	–20.9	Holt et al. 201113
Net change in chemotherapy use with intermediate RS (%)	1.90	Holt et al. 201113
Net change in chemotherapy use with high RS (%)	4.76	Holt et al. 201113
10-year risk of recurrence (low RS) on HT (%)	3.20	Paik et al. 20063
10-year risk of recurrence (intermediate RS) on HT (%)	9.10	Paik et al. 20063
10-year risk of recurrence (high RS) on HT (%)	39.5	Paik et al. 20063
RRR with chemotherapy (low RS) (%)	0	Assumed based on Paik et al. 20063
RRR for chemotherapy (intermediate RS) (%)	39.0	Paik et al. 20063
RRR for chemotherapy (high RS) (%)	74.0	Paik et al. 20063
Post-recurrence survival (years)	3.3	Thomas et al. 200912
Mortality rates	-	TÜİK (2013)11

HT: hormone/endocrine therapy; RRR: relative risk reduction; RS: Recurrence Score

Table 3. Summary of cost variables in the cost-effectiveness modelling analysis

Item	Mean cost (USD)	Reference
Oncotype DX test	5141	Genomic Health Ltd. Turkey branch
Endocrine therapy (years 1–5)	256.5	Turkish Cost-Effectiveness Analysis of Screening in Breast Cancer
Endocrine therapy (years 6–8)	289.6	Turkish Cost-Effectiveness Analysis of Screening in Breast Cancer
Chemotherapy	1436	Turkish Oncotype-Dx Decision Impact Study
Distant recurrence (monthly)	98.08	Turkish Oncotype-Dx Decision Impact Study and Turkish Cost-Effectiveness Analysis of Screening in Breast Cancer
Chemotherapy adverse events	468.5	Turkish Oncotype-Dx Decision Impact Study

are not captured in the model.The cost of recurrence was generated from Bahcesehir Breast Cancer Screening Program (11).

Rate of non-cancer related death is taken from Turkish life-tables.

Quality of life

Quality of life utility scores were based on the published literature. Patients that were in the recurrence-free state and in the recurrence state accrued utility scores. Health utility scores range from death (0) to perfect health (1) and quantify the particular health situation. Published utility scores were used, with a disutility of 0.07 was applied to capture the health-related QALY (14). and annual utility scores of 0.60 and 0.78 were applied for patients with and without recurrence respectively (15, 16) Health utility associated with one year in the recurrence free state was assumed to be the same during and after endocrine therapy (16).

Endocrine therapy costs

In the model, all endocrine regimens were considered, consistent with current practices in Turkey: tamoxifen for 5 years, AI for 5 years, tamoxifen and AI sequential use and extended adjuvan treatment beyond 5 years.

The probability of treatment with each regimen was derived from the Turkish Cost-Effectiveness Analysis of Screening in Breast Cancer, with pharmacy costs for all interventions, follow up and mammograms were taken from the SGK Appendixes. In the model the annual per patient cost of treatment and follow up was calculated to be $256.5 for the first 5 years and $289.6 for years 5-8.

Adverse event rates and costs for endocrine therapy were not included in the model.

Chemotherapy costs and adverse events

The chemotherapy regimens, number of cycles, doses of chemotherapeutics, concomitant medications used to prevent or treat adverse events and diagnostic tests etc were taken from Turkish Oncotype-Dx Decision Impact Study cohort.

Chemotherapy-related adverse event rates were generated from Turkish Oncotype-Dx Decision Impact Study cohort (Table 4).

The majority of costs associated with chemotherapy are due to adverse event and monitoring rather than the acquisition costs of chemotherapy agents.

Table 4. Frequencies and costs of chemotherapy-related adverse events

	Maximum frequency in various chemotherapy regimens (% per cycle)		Cost per event (USD)	
Adverse event	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Anaemia	12.9%	21.0%	477.57	920.94
Neutropenia	36.5%	19.4%	391.05	393.12
Febrile neutropenia	32.8%	5.9%	1475.55	2099.04
Infection	8.7%	4.6%	615.58	1707.98
Thrombocytopenia	8.0%	1.4%	77.75	155.51
Nausea/vomiting	39.4%	12.5%	80.69	412.55
Diarrhea	25.1%	50.3%	63.0	413.08
Motor neuropathy	8.0%	0%	230.62	308.03
Cardiac toxicity	8.0%	2.0%	71.42	615.9

Table 5. Summary of cost-effectiveness results for the base case analysis

	Usual care	**Oncotype DX testing**	**Difference**
Cost	$3649.3	$8568.6	$4919.3
Life Expectancy (years)	24.84 LY	25.70 LY	0.86 LY
Quality-Adjusted-Life Expectancy (QALYs)	19.26 QALY	19.94 QALY	0.68 QALY
ICER (USD per life year gained)	$5720.6 per LY gained		
ICER (USD per QALY gained)	$7207.9 per QALY gained		

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; LYs: life years

The total cost of chemotherapy drugs, administration and monitoring was $1436.07 ($507.7+$432.3+$495.9).

Sensitivity analyses

A series of one-way sensitivity analyses were performed to identify key drivers of model outcomes. Most clinical and cost parameters inputs the model were varied by +/- 25%. ICERs were reported for all one-way sensitivity analyses.

Results

Base-case analysis

Oncotype DX was projected to cost an additional $1.492 per patient compared with current clinical practice over a 30-year time horizon ($5.141 versus $3.649) (Table 5). The increase in costs was associated with an improvement in life expectancy of 0.86 years (24.84 years versus 25.70 years) and an increase in quality-adjusted life expectancy of 0.68 QALYs (19.26 QALYs versus 19.94 QALYs). The incremental cost-effectiveness ratio (ICERs) was estimated to be $7207.9 per QALY gained and $5720.6 per LY gained for Oncotype DX versus current clinical practice in Turkey.

Sensitivity analyses

One-way sensitivity analysis showed that the base case outcomes were most sensitive to variation in patient age, the cost of Oncotype DX testing and the change in chemotherapy recommendations for low risk patients (Table 6). Increasing the baseline age for patients in the simulation by 25% increased the ICER for Oncotype DX testing versus current care to $7971.72 per LY gained. This was due to competing mortality, which meant that patients were not alive long enough to accumulate the full benefit of Oncotype DX testing. In contrast, reducing the baseline age improved the cost-effectiveness of Oncotype DX ($5213.7 per LY gained).

Discussion and Conclusion

Contrary to developed countries, the rate of breast cancer incidence and mortality has been increasing in Turkey and other developing countries due to changing life style, ageing, increase in population size and mammography screening (17). Breast cancer incidence has more than doubled in last two decades in Turkey (1). In our breast cancer registry database, nearly half of the patients had node negative disease and 76.9% had ER positive breast cancer at diagnosis, making these patients good candidates for molecular testing to potentially spare them from unnecessary adjuvant chemotherapy (1). Overtreatment is a big problem due to chemotherapy toxicity and its cost to breast cancer patients (18). Gene expression profiling assays may provide an emerging paradigm to predict chemotherapy benefit based on expression levels of specific tumors. Several multigene assays are currently available for early breast cancer patients, of which Oncotype DX has the most compelling evidence of adding value to standard prognostic factors regarding the benefit of adjuvant chemotherapy for patients with early breast cancer (2).

The MINDACT trial revealed that Mammaprint (70 gene signature test) may identify subsets of patients who have a low likelihood of

Table 6. Summary of one-way sensitivity analysis results

	ICER($perLYgained) for Oncotype DX testing versus usual care	
Parameter/scenario	**–25%**	**+25%**
Base case	5720.6	
Cohort		
Age	5213.7	7971.7
Cost		
Cost of chemotherapy treatment	5780.3	5661.0
Cost of recurrence	5725.5	5715.8
Cost of Oncotype DX testing	4226.2	7215.5
Clinical parameters		
Post-recurrence survival	5705.1	5736.5
Net change in the use of chemotherapy in the low Recurrence Score group	8521.7	4330
Net change in the use of chemotherapy in the intermediate Recurrence Score group	5742.4	5699.6
Net change in the use of chemotherapy in the high Recurrence Score group	5836.8	4615.8

ICER: incremental cost-effectiveness ratio

distant recurrence despite high-risk clinical features. In this trial, 6693 women, approximately 80 percent of whom had lymph node-negative disease, underwent risk assessment by clinical criteria (using Adjuvant! Online) and by the 70-genetic profile. Patients with discordant clinical and genomic predictions were randomly assigned to receive or not receive adjuvant chemotherapy. Among patients in the intention-to-treat population who had a high clinical risk of recurrence but a low risk by Mammaprint, a non-significant benefit of chemotherapy with respect to distant metastasis-free survival (DMFS) and a significant benefit of chemotherapy with respect to DFS were seen (19).

The TAILORx trial was designed to determine whether Oncotype DX that analyzes the expression of genes that are associated with risk of recurrence among women with early stage breast cancer could be used to assign patients to the most appropriate treatment choice. In the lowest risk group, the TAILORx trial provided prospective evidence that patients with RS 0-10 may be spared chemotherapy. Among these patients who were uniformly treated with ET, rates of distant recurrence at 5 and 9 years were <1% and 3% respectively. Furthermore, adjuvant endocrine therapy and chemoendocrine therapy was shown to have similar efficacy in women with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer who had a midrange 21-gene recurrence score (RS 11-25), although benefit of chemotherapy was found in some women 50 years of age or younger (20).

The precision medicine achievable via the use of molecular analysis for early breast cancer patients has been shown to change treatment recommendations. Oncotype DX testing was associated with a notable change in treatment recommendations based on the data reported by Holt et al. (13), with approximately half of all patients originally recommended chemotherapy being recommended endocrine therapy after Oncotype DX testing. In our study, overall adjuvant treatment decisions changed for 33% of patients after Oncotype Dx RS results were discussed in multidisciplinary tumor conference.

The present study is the first multicenter analysis to demonstrate cost-effectiveness of Oncotype DX in Turkey using a Markov model. Real-world patient data was used in the model based on the Turkish Oncotype-Dx decision impact study (8).

In several developed countries, Oncotype DX cost-effectiveness has been demonstrated in the early stage breast cancer setting. All studies concluded that Oncotype DX has an ICER less than $100,000 per QALY, however the results were disparate with each other (21).

A study which looked at use of the test in a community "real-world setting," found that the likely cost-effectiveness ratio for Oncotype DX testing was higher than the ratios for the most commonly accepted diagnostic and preventive interventions. Their simulation model compared 25-year incremental costs and quality-adjusted life-years (QALYs) for Oncotype DX use in the community from 2005 to 2012 with costs and QALYs of usual care in the time period before testing (2000 to 2004). The patients who underwent testing were younger and were most likely to have stage l than stage ll disease. Patients who underwent testing and who were younger than age 50 years had lower chemotherapy rates than patients in the same age group who were not tested (53.0% vs 63.6%). In contrast, older patients who were tested had higher rates of chemotherapy compared with the untested cohort (age 50 to 64 years: 36.5% vs 30.8%; age ≥ 65 years: 17.6% vs 8.2%) (22).

In a recent analysis reviewing multiple clinical studies simulation models, demonstrated that cost-effectivity studies has a wide range of heterogenity in terms of model structure. Some studies did not use the real-world RS distributions and rely on database, some did not evaluate the patients' risk status independent of Oncotype DX. When cost of chemotherapy were used in simulation models, treatment related toxicity were ignored in some studies. Despite the heterogenity of these trials, the simulation model revealed that the problematic issues that were identified in the analyses do not change the conclusion that

Oncotype DX is cost-effective for the clinically intermediate or high-risk group but not for the clinically low-risk groups (21).

Cost-effectiveness analysis (CEA) is increasingly important in public health decision-making especially in low- and middle-income countries. When cost-effectiveness is evaluated for developing countries, willingness to pay may be at lower ICER thresholds, with many health interventions deemed cost-effective but not accepted as affordable by local authorities. This multicenter prospective trial showed that Oncotype DX is cost-effective and improves QALY in a developing country model.

By leading to changes in adjuvant chemotherapy decision and modifying long-term risk of distant recurrence, Oncotype DX was projected to improve life expectancy (+0.86 years) and quality-adjusted life expectancy (+0.68 QALYs) versus standard care. The incremental cost-effectiveness ratio (ICERs) of Oncotype DX was estimated to be $7207.9 per QALY gained and $5720.6 per LY gained versus current clinical practice.Sensitivity analysis showed that the cost-effectiveness of Oncotype DX testing was not sensitive to variations in several clinical and economic parameters. In all sensitivity analyses, Oncotype DX was associated with ICERs in the range that would be considered cost-effective by commonly quoted standards.

Oncotype DX was estimated to improve quality-adjusted life expectancy versus standard care, due to chemotherapy avoidance in low-risk patients in addition to survival benefits in high-risk patients. In this analysis, data of patients who were recruited from state hospital and academic centers were taken into account where all costs are reimbursed by general health insurance. However, there are considerable amount of patients who apply to private hospitals and take the Oncotype DX with their personal expense. If it was possible to add these patients' data to the analysis, we believe that the cost-effectiveness of the test would be more favorable.

Oncotype DX provides additional information to improve personalized chemotherapy treatment in early stage breast cancer patients and changed adjuvant chemotherapy treatment decisions in 33% of patients. The test was found cost-effective from a national perspective, with improvements in quality of life and may be introduced to routine clinical practice in patients with ER+, HER-2 negative early-stage breast cancer in Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University İstanbul School of Medicine (2014/800; 09.05.2014-09).

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

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Case Report

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Intramammary Nodal Metastasis from Ovarian Cancer: A Case Report

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ABSTRACT

Intramammary metastasis from ovarian cancer is rare. It is usually associated with poor prognosis. We present a 56-year-old female with advanced ovarian cancer in whom a metastatic intramammary lymph node was discovered after finishing the first line of neoadjuvant chemotherapy.

Keywords: Breast neoplasms, ovarian cancer, metastasis, lymph nodes

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Introduction

Breast metastasis from solid tumors is a rare event. Melanoma, lung cancer, soft tissue sarcoma and ovarian carcinoma are the most common primaries. Intramammary metastases do not show a unique clinical or radiological pattern. Yet, accurate diagnosis and differentiation from primary breast tumors is very important to choose the appropriate treatment strategy and to avoid unnecessary interventions (1).

Case Presentation

A 56-year-old female, diabetic & hypertensive, with previous surgical history of appendectomy, complained from progressive abdominal enlargement. Pelvi-abdominal ultrasonographic (US) evaluation revealed bilateral adnexal neoplastic soft tissue masses with internal vascularity. The right one was seen inseparable from the surrounding intestinal loops, it measured 8x13 cm. The left one was seen inseparable from the uterus with the possibility of infiltration, it measured 10x14 cm. Multiple hyperechoic subcapsular hepatic peritoneal deposits were detected, the largest one measured 2.3 cm in diameter. Also amalgamated intestinal loops with sheet like omental cake and moderate ascites were observed. Serum carbohydrate antigen 125 (CA 125) value was 195 U/mL. Post contrast Magnetic Resonance Imaging (MRI) of the abdomen and pelvis showed mildly enlarged liver with non-enhanced focal lesion at segment VII of right lobe, it measured 1.5 cm in diameter. Large heterogeneously enhanced pelvic soft tissue mass was seen infiltrating the uterus and compressing posterior wall of the urinary bladder as well as recto-sigmoid colon with no line of separation in-between, it measured 10.5x14.5x10.5 cm in APXTRXH respectively. Another similar soft tissue mass was seen at right lower abdominal cavity, compressing and displacing surrounding intestinal loops, it measured 8x13x10 cm. Multiple variable sized enhanced nodular and sheet-like peritoneal deposits were seen scattered in the abdomen as well, the largest deposit measured 3.5x4 cm. Neoplastic lower para aortic and left iliac lymph nodes were also noted, the largest lymph node diameter was 2.5cm. The patient underwent US guided aspiration from the ascitic fluid. Microscopic examination of the aspirated sample (Figure 1) revealed clusters of rounded or hyperchromatic nuclei with overlapping in background of Red Blood Cells (RBCs). Some cells exhibited cytoplasmic vacuoles. The cell block revealed papillary & acinar structures with thin vascular connective tissue and covered by cuboidal cells showing rounded vesicular nuclei. Psammoma bodies were seen as well. This led to the diagnosis of metastatic papillary carcinoma mostly of ovarian origin. Immunohistochemical staining (IHC) showed positive nuclear staining for Estrogen Receptor (ER), negative staining for tumor protein P53, and focal nuclear positivity for Wilms tumor gene product (WT1). These results confirmed the diagnosis of metastatic papillary carcinoma of ovarian origin. The patient received 6 Taxol & Carboplatin cycles as neoadjuvant therapy with stationary course of the disease. Upon breast sonomammographical evaluation (Figure 2), the left

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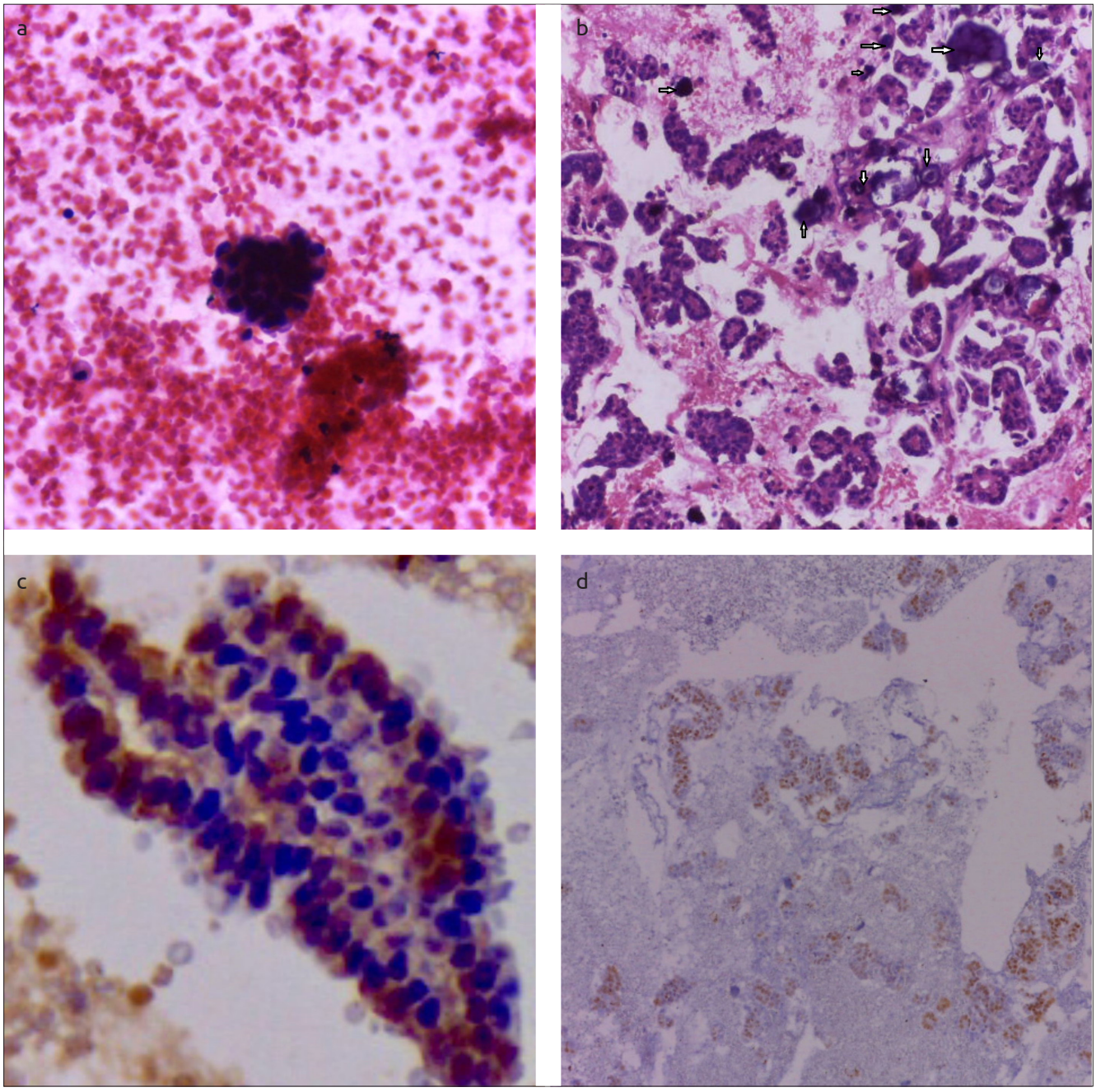

Figure 1. a-d. Microscopic examination of aspirate from ascites. Smear showing a 3D appearance of a morula of malignant epithelial cells (Hx&E, x400) (a). Highly cellular cell block showing papillary structures lined by malignant epithelial cells with evident Psammoma bodies (marked by arrows) (Hx&E, x200) (b). Cytoplasmic and focal nuclear staining of tumor cells for WT1 (x400) (c). Nuclear ER staining of tumor cells (x100) (d)

breast showed an oval hypoechoic lesion with foci of calcification measuring 11x4.3 mm at 12 o'clock in zone C, which was reported to be likely a suspicious intramammary lymph node. US guided core needle biopsy from the breast lesion was performed. Microscopic examination (Figure 3) revealed cores of lymphoid tissue showing infiltration by papillary structures covered by atypical epithelial cells showing mild degree of atypia and pleomorphism. IHC studies for WT1, Cytokeratin 7 (CK7) and ER showed positive reaction in atypical cells, while (Progesterone Receptor) PR, mammaglobin and P53 showed negative reaction in tumor cells. This supported the diagnosis of metastatic ovarian carcinoma. The patient was prepared for receiving second line neoadjuvant therapy. Informed consent was obtained from the patient reported in this study.

Discussion and Conclusion

Secondary tumors to the breast are rare. They account to 0.2-2% of all breast neoplasms. The most common primary sites are contralateral breast, melanoma, lung cancer and ovarian cancer. Diagnosis of intramammary metastasis is a diagnostic challenge as it may resemble primary breast tumors clinically, radiologically and even pathologically (2-5). Proper evaluation and accurate pathological examination is recommended to avoid the possibility of unneeded breast intervention (e.g., mastectomy) (4, 6-10).

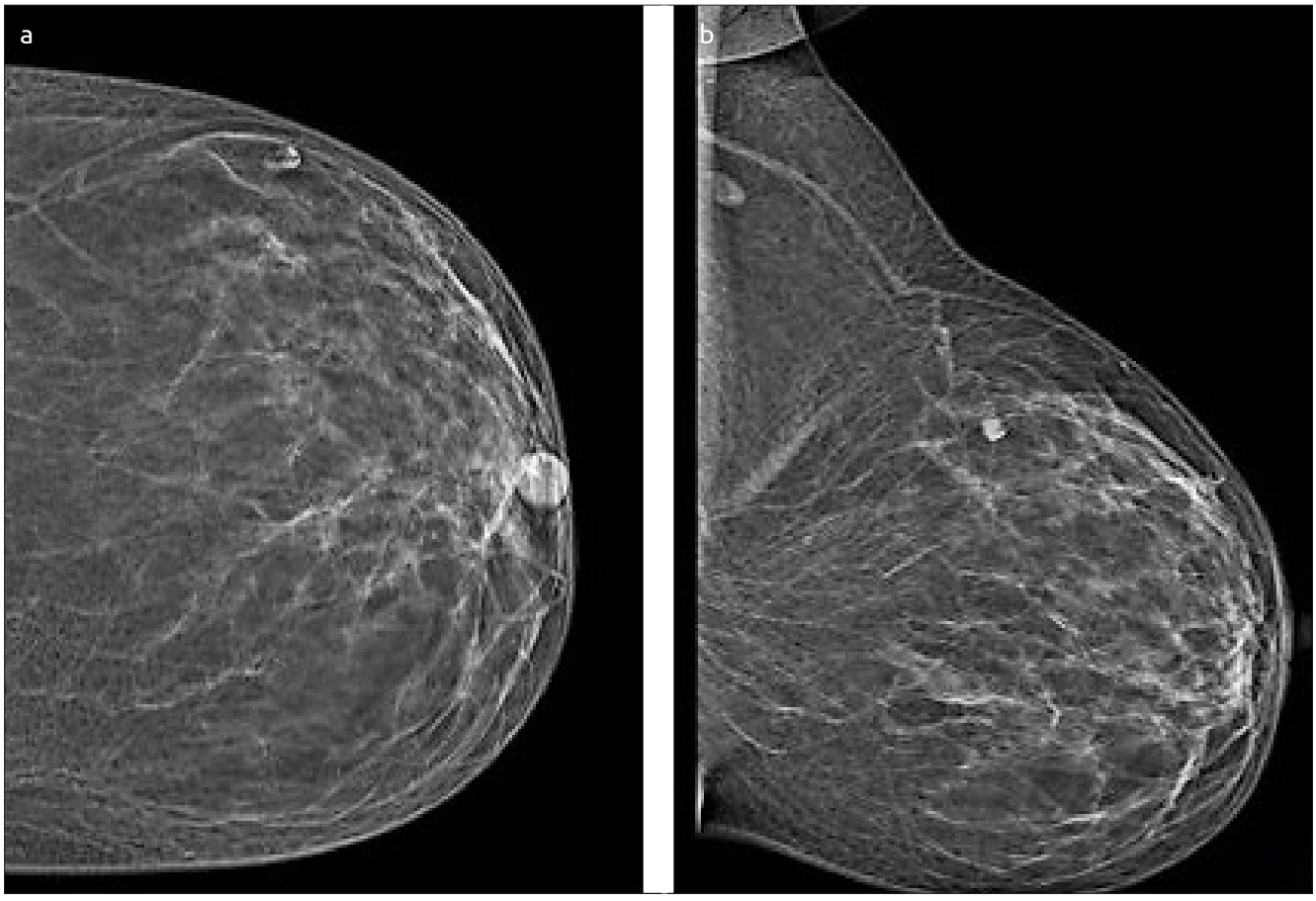

Figure 2. a, b. Left breast mammogram. Craniocaudal and mediolateral (a, b) mammogram of asymptomatic 56-year-old patient shows oval dense indistinct mass at upper outer quadrant of the left breast, no related architectural distortion nor overlying skin thickening. Oval left axillary LN with lucent center

Most of intramammary metastasis present as palpable breast swellings. Only about 14% are discovered by radiological evaluation –such as our presented case. The majority of these tumors present as solitary masses but 8-25% present as multifocal or bilateral breast masses (3) There are no specific radiologic criteria for intramammary metastasis which may be misinterpreted as benign or malignant primary breast masses on ultrasound or mammography. The most common pattern of presentation after being incidentally discovered during breast radiological evaluation is the presence of well-defined, hypoechoic oval or rounded mass with regular margins that does not show microcalcifications, speculations or posterior shadowing. (1, 3, 5)

Pathologically, there are no specific criteria for diagnosis of such cases, especially in the absence of well-known history of prior malignancy. Yet, common histologic findings could be identified such as the presence of peritumoral fibrous pseudo-capsule and the absence of in situ component (4).

Incidence of intramammary metastasis from ovarian carcinoma is very rare. It constitutes about 0.03%-0.6% of all breast tumors. It usually occurs 2 years after the primary presentation –In our patient, it was discovered 8 months after the initial presentation-. The most common histologic subtype is ovarian serous carcinoma. Those patients usually present with advanced stage with heavy peritoneal infiltration – like the case presented in this report-. Eighty-five percent of ovarian serous tumors are limited to the peritoneal cavity. The liver, lung and pleura are the most common site for metastases followed by the spleen, central nervous system, bone and skin. Yet, breast metastasis from ovarian carcinoma is associated with poorer prognosis with reported short term survival after the incidence of metastasis (1, 7-9, 11).

Accurate analysis of clinical, radiological and pathological features is required to differentiate such patients from those with primary breast carcinoma associated with Krukenburg ovarian tumors due to overlapping of pathologic features. Histopathological classification of breast secondary tumors and the differentiation from primary breast neoplasms is not an easy job and is based on the interpretation of both morphological and IHC features. The majority of intramammary metastases are characterized by the presence of papillary clusters and solid areas with slit-like spaces. Those spaces are composed of cells showing marked nuclear atypia. The adjacent breast tissue shows no pathological changes or intraductal component. IHC plays a very important role in such scenarios especially WT-1, the Wilms tumor gene product –which shows nuclear expression in about 95% of serous papillary carcinomas and only in less than 10% of breast cancers-, Gross cystic disease fluid protein (GCDFP-15), Paired-box gene 8 (PAX8) and mesothelin, which is expressed in more than 90% of ovarian serous papillary carcinoma. However, it is weakly expressed in 3 to 14% of primary breast malignancies (4, 7, 9, 11, 12)

It is to be noted that breast and epithelial ovarian cancers share some similar hereditary and risk factors which can explain the co-incidence of primary breast and ovarian cancers. That is why patients with epithelial ovarian cancer are usually subjected to thorough physical, radio-

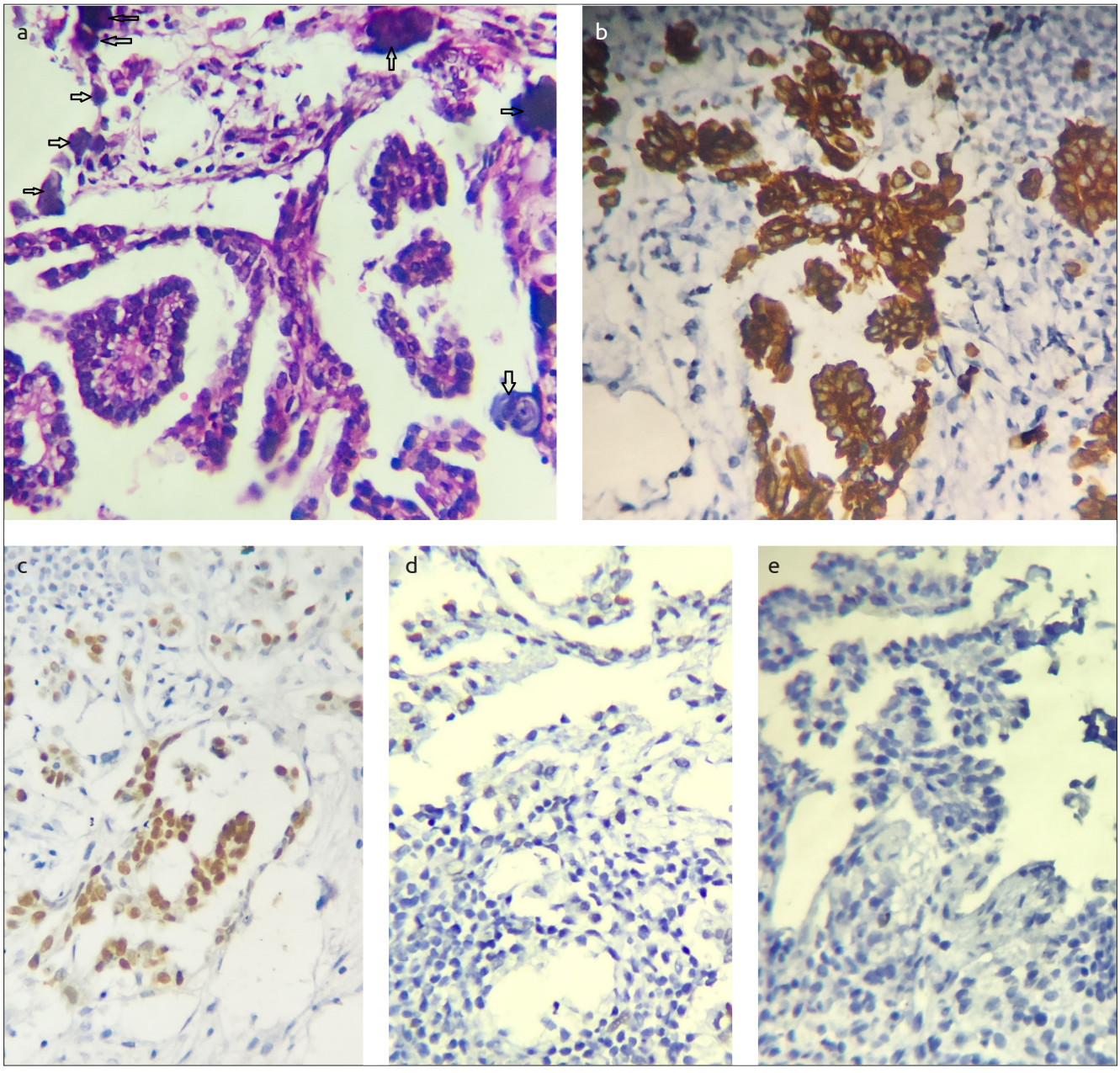

Figure 3. a-e. Microscopic examination of left breast mass core needle biopsy. Section in breast showing papillary structures lined by malignant epithelial cells, evident psammoma bodies in upper right (marked by arrows) (x400 Hx&E) (a). Cytoplasmic positivity of tumor cells in breast for ck7 (x400) (b). Nuclear staining of tumor cells for WT1 (x400) (c). Negative tumor cells for mammaglobin (x400) (d, e)

logical & serological investigations raising the possibility for detection any breast masses (8).

In conclusion, intramammary metastasis from ovarian cancer is a rare condition that carries a poor prognosis. Despite having no pathognomonic clinical or radiological characteristics, thorough analysis of clinical, radiological and pathological data is required so as not to miss the diagnosis.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.H.; Design - O.H.; Supervision - M.Z.; Resources - O.H., F.S., G.S.; Materials - O.H., F.S., G.S.; Data Collection and/or Processing - O.H., F.S., G.S.; Analysis and/or Interpretation - O.H., F.S., G.S.; Literature Search - O.H., F.S.; Writing Manuscript - O.H., F.S., G.S.; Critical Review - M.Z.

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

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Case Report

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Primary Benign Phyllodes Tumor of The Vulva: Case Report and Review of Literature

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ABSTRACT

Phyllodes tumor (PT) of the vulva is very rarely seen and has been reported in only 17 cases in English literature. It is still uncertain that proliferative mammary gland lesions including PT in the anogenital region originate from ectopic breast tissue or from local adnexal structures. We report a case of primary benign PT of the vulva in a 41-year-old female patient. Microscopic examination revealed biphasic tumoral formation with typically extensive leaf-like papillary structures growing toward slit-like spaces under the skin. In immunohistochemical examination, more than 50% of epithelial cells showed a positive reaction with ER, PR, and panCK and a focal positive reaction with GCDFP-15. Myoepithelial cells showed a positive reaction with SMA, CD10, and WT-1. In this report, we underline the clinicopathologic features of PT localized to an unusual site, and also discuss its etiology, differential diagnosis in the light of the current literature.

Keywords: Vulva, phyllodes tumor, skin, benign

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Introduction

Breast lesions can also be found in extramammary areas such as the axilla, anus, prostate, seminal vesicle, and vulva. These lesions include diagnoses such as fibrocystic disease, fibroadenoma, intraductal papilloma, hidradenoma papilliferum, lactating adenoma, and adenocarcinoma. It is still uncertain that proliferative mammary gland lesions in the anogenital region originate from ectopic breast tissue or from local adnexal structures. Phyllodes tumor (PT) accounts for less than 1% of all breast tumors and can also occur in the ectopic areas such as the vulva and axilla (1, 2). PT of the vulva is very rarely seen and has been reported in only 17 cases in English literature. The majority of cases were benign except for one borderline case, one malignant case and two low-grade malignant cases.

Case Presentation

A 41-year-old female patient (Gravida 3, Para 3) was admitted to our polyclinic due to a painless, slow-growing mass under the skin of the vulva which she first noticed 6 months ago. The mass was located between the labium majus and minus at the 5-6 o'clock position in the vulva. It was 3x4 cm in size and mobile. No redness or ulceration was observed. In the patient's history, there were no breastfeeding, breast disease, menstrual irregularity, malignancy, hormonal contraception, and pregnancy. Laboratory tests (hormone panel, gynecological and breast cancer markers) were within normal limits. The lesion was excised and sent to the pathology laboratory for histopathological examination with a preliminary diagnosis of fibroma. Macroscopic examination revealed a round, well-circumscribed, dirty-white, elastic, grooved and nodular lesion 3 cm in diameter under the skin and a 2.4x1.5 cm skin ellipse on its surface. No necrosis or hemorrhage was observed (Figure 1). Microscopic examination revealed biphasic tumoral formation with typically extensive leaf-like papillary structures growing toward slit-like spaces under the skin (Figure 2). The slit-like spaces consisted of a double layer of epithelial and myoepithelial cells (Figure 3). The stromal component consisted of monomorphic pale spindle cells and was hypocellular. Normal breast tissues were not detected in the sections prepared from the whole material. There were no stromal overgrowth, nuclear atypia, heterologous differentiation, or mitotic activity. In immunohistochemical examination, more than 50% of epithelial cells showed a positive reaction with ER, PR, panCK

This study was presented at the 1st International Congress on Sports, Anthropology, Nutrition, Anatomy and Radiology, 3-5 May 2018, Nevşehir, Turkey.

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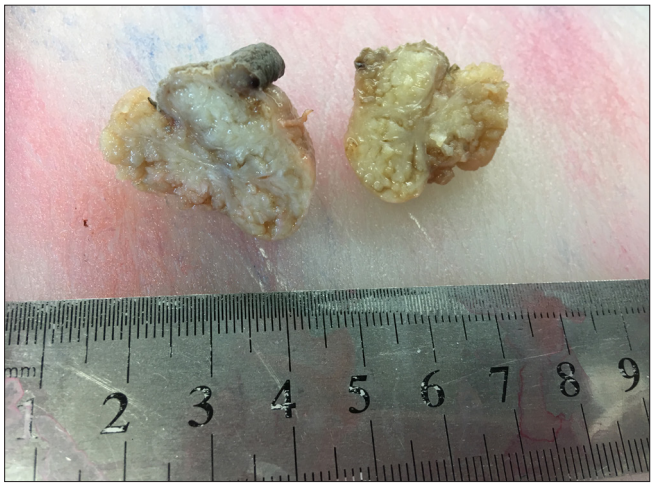

Figure 1. A round, well-circumscribed, dirty-white, elastic, grooved and nodular lesion 3 cm in diameter under the skin and a 2.4x1.5 cm skin ellipse on its surface. No necrosis or hemorrhage was observed

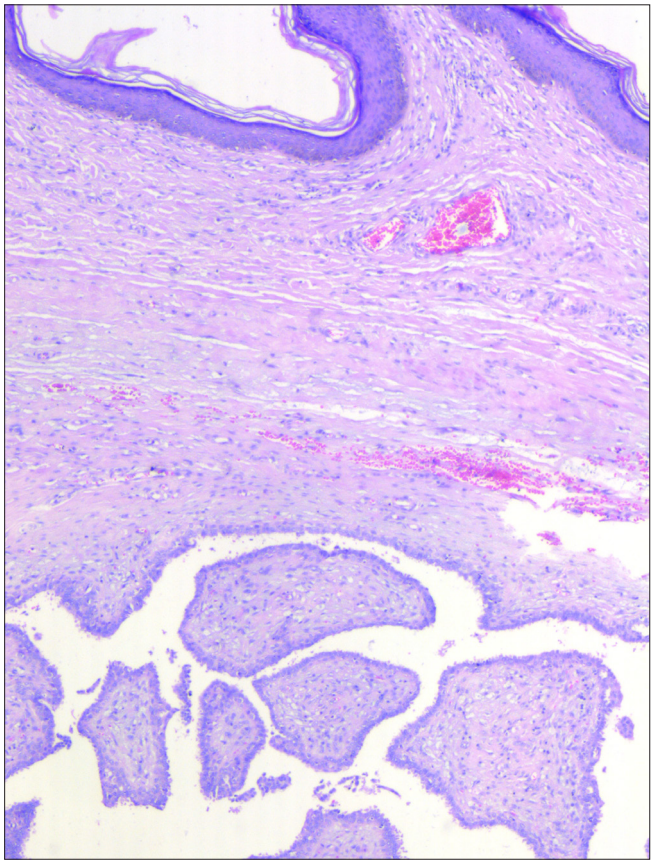

Figure 2. Typical extensive leaf-like papillary structures growing toward slit-like spaces under the skin (H&E, x50)

and CK7 and a focal positive reaction with GCDFP-15 (Figure 4a, b). Myoepithelial cells showed a positive reaction with p63, SMA, CD10, and WT-1 (Figure 4c). CK20 and CDX2 were negative. The stromal component was negatively stained with these markers. In the presence of histomorphologic and immunohistochemical findings, the patient was diagnosed with benign PT. Because a portion of the lesion showed continuity in the surgical margin, the patient was followed for the risk of recurrence. Written informed consent was obtained from patient who participated in this study.

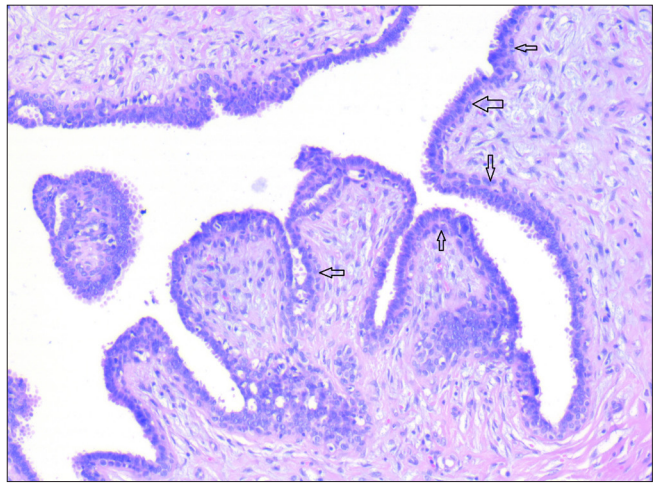

Figure 3. The slit-like spaces consisted of a double layer of epithelial and myoepithelial cells (myoepithelial cells were indicated by an arrow) (H&E, x100)

Discussion and Conclusion

Two theories have been put forward to explain the cause of PT of the vulva. The first theory is the presence of ectopic breast tissue. The second theory is the presence of regional, specific and anogenital breast-like adnexal structures. The second theory is more accepted by the authors (3).

During the 4th and 6th week of fetal development, mammary buds develop as downgrowths from mammary crests, which are thickened strips of ectoderm extending from the axilla to the inguinal region. The breast tissue continues to develop in the normal pectoral region of the milk line, with regression of the remainder of the mammary ridges. The failure of this regression leads to the formation of ectopic breast tissue that can act as normal breast tissue or cause benign and malignant tumors. The actual incidence rate is unknown. Though this tissue is present at birth, it does not become evident until affected by female sex hormones at puberty, pregnancy, or lactation (4).

Van der Putte defined a specific variant of skin glands. In normal histology, the sebaceous glands are predominantly present on the medial surface of the labia majora, regardless of the presence of hair follicles. Van der Putte called these lesions mammary-like anogenital sweat glands, which consist of apocrine and eccrine glands and express estrogen and progesterone, rather than ectopic breast tissue. Similar to mammary glands, these glands have the capacity to branch into lobuli and to form acini. The origin of various neoplastic and reactive lesions of the anogenital region (including the vulva) which mimic mammary lesions has been explained with the presence of mammary-like glands. Moreover, it has been suggested that primordia of the mammary glands do not extend from the axillary-pectoral area to the vulva in human embryos, and that the number of ridges of mammary-like glands is greater than the number of residues of mammary-like glands, and that these glands are associated directly with cloacal derived tissues rather than breast lines. These have been reported to be localized in the interlabial sulcus, the paramedian area of the perineum and around the anus (5-7).

Mariappan et al. (8) have claimed that the presence of specific breast epithelium is not a prerequisite for the development of a tumor identical to mammary gland tumor, such as PT. PTs have also been

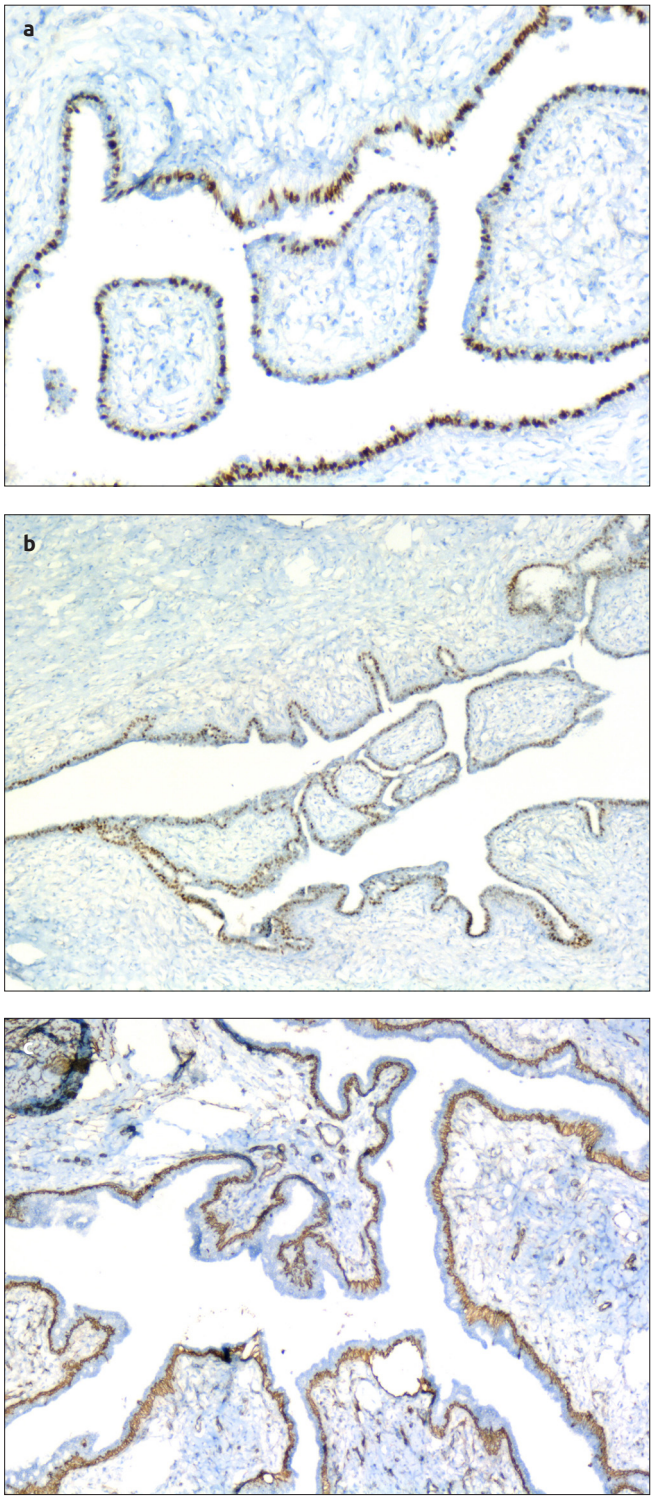

Figure 4. a-c. Immunohistochemical stains for PR, ER and SMA showed a positive reaction. A. PR x100, B. ER x50, C. SMA x50

reported in caudal regions without milk lines, such as the perianal region, prostate, and seminal vesicle. Bostwick et al. (9) reported a series of 23 cases diagnosed with PT of the prostate. They showed that the cases did not give a positive reaction with estrogen and were stained with different immunohistochemical markers such as prostate specific antigen and prostatic acid phosphatase. They demonstrated that one case was positively stained with progesterone. They suggested that two cases developed following estrogen therapy and therefore hormonal factors might be effective in the pathogenesis of the tumor (9).

The presence of normal breast tissue or mammary-like glands around the lesion can give some clues about histogenesis (4). In our case, normal breast tissue or mammary-like glands were not observed within or around the lesion. However, the tumor was located between the labium majus and minus, and therefore it is likely to originate from the anogenital glands.

Patient with PT of the vulva are usually admitted with a one-sided, painless and solid mass. The labia majora, labia minora, and interlabial cleft are the most frequent sites of presentation. It involves both sides of the vulva in some cases admitted with itching, irritation, and dyspareunia (7). It is seen in the age range 17 to 69 years and commonly manifests in the 3rd and 4th decades of life in women. The average age at the time of admission was 35.14 years. The largest tumor diameter varies from 0.7 to 6.6 cm. The average tumor diameter is 3.47 cm. The growth rate is variable. While some cases show rapid growth in the near future, other cases remain the same size for years and are incidentally detected. Macroscopically, it is dirty-white, homogeneous, solid and well-circumscribed, pushes surgical boundaries and has papillary projections or polypoid appearance (2, 3).

Phyllodes tumor of the vulva exhibits identical microscopic signs with its counterpart in the breast thanks to its biphasic pattern and leaf-like configuration. Hyperplastic epithelium and pseudostratification can be observed. The stroma may show cellularity ranging from low to high. Significant nuclear pleomorphism is rare. There is no mitosis or lower. Immunohistochemically, secretory epithelial cells are positively stained with estrogen and progesterone, and myoepithelial cells are positively stained with p63, SMA and S100. The stroma is negatively stained with estrogen, progesterone, WT1, and CD10 and is positively stained with CD34, vimentin, and SMA. The Ki-67 proliferation rate can range from 1 to 15% (3).

Fibroadenoma is mainly considered in the differential diagnosis of PT of the vulva. The overlapping properties can be seen, and the separation of these entities from each other may be problematic. The characteristic leaf-like projections of PT are rarely described in fibroadenoma. Similar to PT of the breast, the tendency to become cystic, increased cellularity, cellular heterogeneity and stroma with cytological atypia may be more common in PT of the vulva (7). Papillary hidradenoma may show a complex papillary growth pattern such as PT but does not have a marked stromal component. Moreover, papillary structures are surrounded by double epithelial layer and have focal apocrine protrusions. Chondroid syringomas have cartilaginous islands within fibromyxoid stroma. In contrast to PTs, chondroid syringomas may have areas of squamous and sebaceous differentiation. Mullerian adenosarcoma of the cervix that secondarily involves the vulva may imitate a PT due to the formation of polypoid mass, a similar leaf-like architecture, and biphasic pattern. However, periglandular stromal condensation, increased stromal cellularity, and mitosis are more frequent (10).

Benign PT of the vulva is rarely seen in this localization and has homologous features with the breast histopathologically and immunohistochemically. However, its histogenesis has not yet been fully understood. In our case, we could not reveal histomorphologic findings that would definitely support one of the theories suggested in the pathogenesis. However, we think that the lesion can originate from anogenital mammary-like glands because it was located between the

labium majus and minus and that a possible hormonal etiology may also play a role. Recurrence is rare with total resection of the tumor.

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Case Report

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Unexpected Finding on Mammography and MRI due to Accumulation of Iron Oxide Particles Used for Sentinel Lymph Node Detection

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ABSTRACT

We present a case with imaging artefacts on mammography and Magnetic Resonance Imaging (MRI) caused by iron oxide particles. After being diagnosed with the medullary cancer of the breast, the female patient had a breast conserving surgery on right breast. Iron oxide particles were used for the detection of the sentinel lymph node during operation. On follow ups, a de novo density on mammography, which was initially thought to be a new tumour, was found. MR images proved that the lesion is an artefact caused by iron oxide accumulation. Our aim in this case study is to underline and discuss the imaging artefacts caused by these particles and raise awareness.

Keywords: Breast, iron oxide, mammography, MRI

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Introduction

A sentinel lymph node biopsy (SLNB) is a procedure during which the sentinel lymph node, which is the main drainage pathway, is identified, excised, and evaluated histopathologically to detect cancer cells. A negative SLNB result suggests that cancer cells have not developed the ability to spread to nearby lymph nodes or other organs. Sentinel lymph node biopsy (SLNB) is a feasible and reliable method for staging the axilla before breast cancer surgery (1-6). The conventional method is with radiotracer ^{99m}tc using blue dye. In the latest years a new method for detecting sentinel node called iron oxide particle technique ("SentiMag® technique"), has been developed as an alternative to the radiotracer. In this new method a liquid which contains iron oxide particles is injected subareolarly. The liquid dissolves in the breast towards the axilla by manual massage. Later, a probe is used to detect iron oxide particles with ferromagnetic effect. Prospective clinical studies like "The Central-European SentiMag study" and meta analyses of earlier studies showed that magnetic SLNB method can be performed easily, safely and is a promising alternative to the radioactive method. (7-10). By time these iron oxide particles disseminate and are cleared through the lymphatics. However, we know that in some cases they might stay in the breast tissue for years and reduce imaging quality and sensitivity by causing artefacts (7, 8). Our aim in this case study is to discuss those imaging artefacts and help radiologists be aware of them.

Case Presentation

We present a 41-year-old female patient who had breast conserving surgery for biopsy proven medullary cancer a year ago. Informed consent was taken from the patient. She had a 7x3 mm sized palpable right breast mass. Although being palpable, it was occult on mammography (Figure 1a). The lesion was detected by sonography. On sonography a hypoechoic lesion with well-defined borders was found and classified as category 3 by Breast Imaging Reporting and Data System (BI-RADS) (Figure 1b). However, the patient insisted on biopsy and histopathological diagnosis revealed the medullary cancer. A breast conserving surgery was performed on right breast. 12 months later the patient was referred to mammography unit for routine follow up. On mammography, a spiculated de novo lesion that was denser than the radiographically dense breast parenchyma was identified on right upper breast (Figure 2a). The lesion was first thought to be compatible with recurrence. A new primary was also considered since the previous lesion was occult on mammography. We could not identify the new lesion on sonography. Magnetic Resonance images were obtained to delineate the whole breast. On MRI, a marked magnetic

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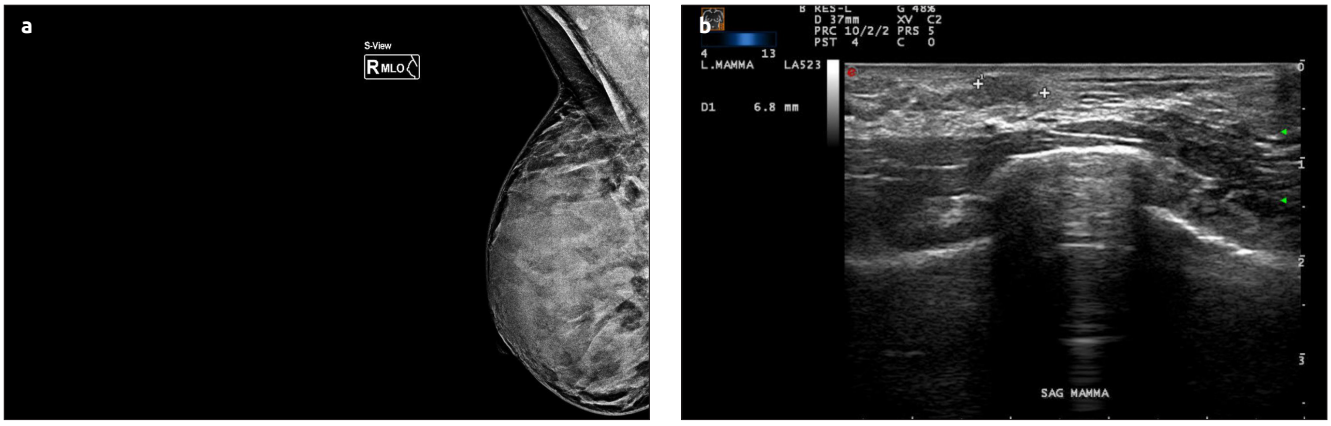

Figure 1. a, b. Right MLO Mammography images. No mass is seen (a). A hypoechoic lesion with well-defined borders is seen on sonography compatible with BI-RADS 3 lesion (b)

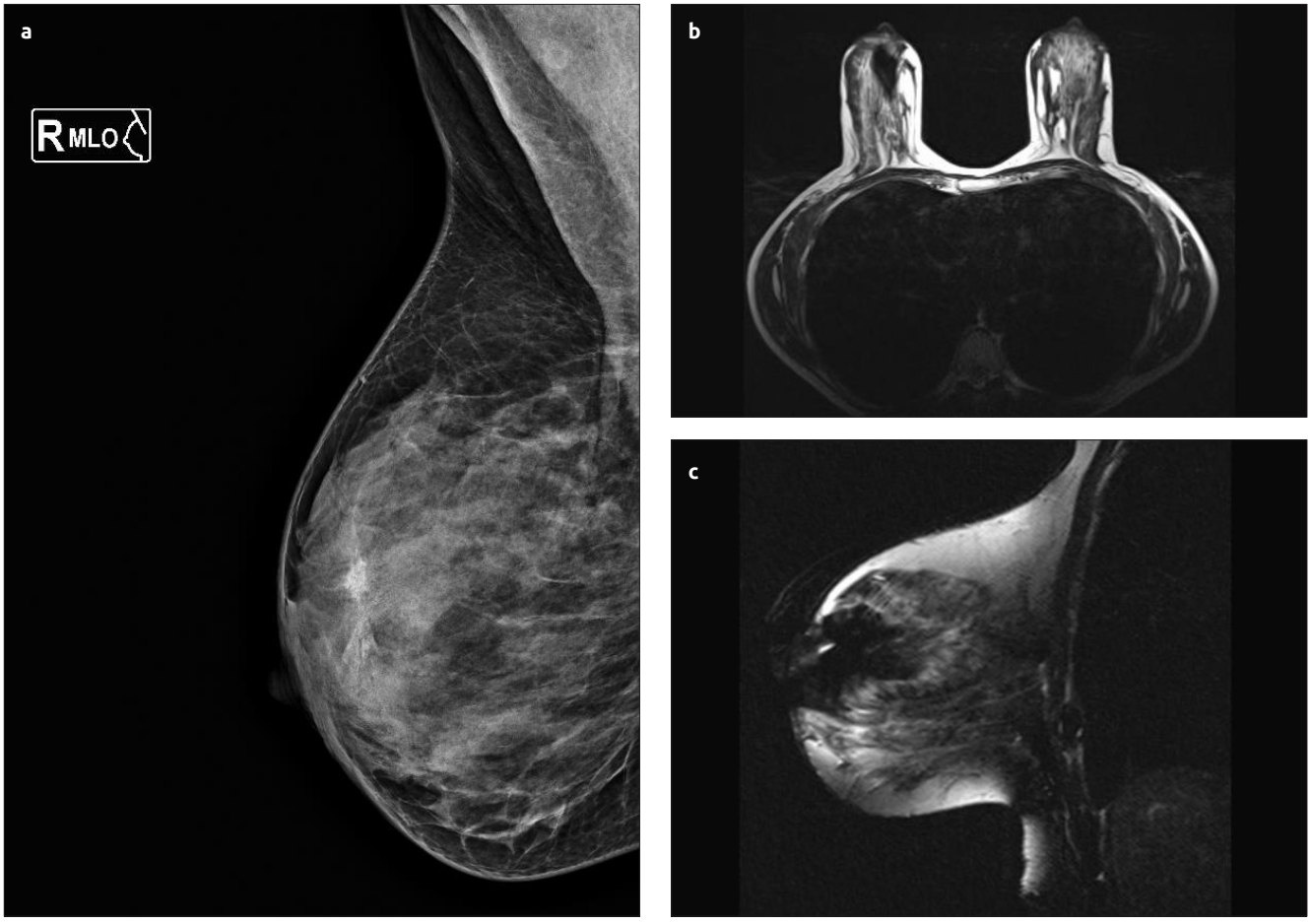

Figure 2. a-c. Postop mammography. Right MLO images. A spiculated density is seen on the right upper breast (a). Postop MRI. Axial and sagittal T2 weighted TSE, non-fat saturated image. A prominent susceptibility artefact is obscuring the right breast (b, c)

susceptibility artefact obscuring the central part of the breast was seen. These areas were attributed to previous iron oxide particles which were injected for SLN detection (Figure 2b, c) (SentiMag® technique).

Discussion and Conclusion

Iron oxide technique is a new, promising safe and effective method used as an alternative to radiotracer method for sentinel lymph node detection (1-6). Large metanalyses such as Nordic SentiMag trial and The Central-European SentiMag study have shown their efficacy and safety (7-8). The Central-European SentiMag study found that more pathologically positive SLNs were found with the SentiMag technique compared to the radiotracer method (7). However, the artefact caused by iron oxide particles and its effect on the quality of follow up imaging have not been discussed in these trials. Although a couple of previous studies (11-13) have shown the susceptibility artefacts caused by iron oxide particles on MRI, the appearance of these particles on mammography which is the first line modality used during the follow ups after breast conserving surgery have not been previously discussed. To

our knowledge, this is the first case study to demonstrate the iron oxide particles on mammography. Knowing the appearance of iron deposits on MRI and especially mammography is essential. In our case, the iron deposits were highly dense and denser than the breast parenchyma on mammography but interestingly occult on sonography. The density depends on the amount of particles accumulated; hence it might not be so dramatic in all cases. Iron oxide particles cause significant magnetic susceptibility as they are paramagnetic. On MRI, susceptibility artefact is seen as loss of signal which is called as "signal void" and they cause spatial distortion. The area effected by artefact is usually much larger than the size of the object causing the artefact so even a tiny amount of ferromagnetic material occult on x-ray or sonography can lower image quality on MRI. In the case study by Karakatsanis et al. (13), a patient with a history of iron oxide injection was discussed. In their case, unlike ours, no artefact was seen on the follow up mammogram. However, susceptibility artefacts were observed on the follow up MRI. On post contrast MR images, a new tumour was seen adjacent to artefacts. In our case the artefact on MRI was so evident in all sequences that it was impossible to detect a new lesion. Besides artefacts, staining the skin on the injected area (14) which is usually temporary is another limitation of these particles. Interestingly no staining was observed in our case.

We believe lowering the doses of these particles might be a solution for these undesirable side effects. An ongoing trial (Senti-Dose, https://doi.org/10.1186/ISRCTN11156955) is currently investigating the effect of lower doses.

In conclusion, the artefacts caused by iron deposits might be a problem in the long run. Reducing the amount of the injected material or changing the technique of massage for dissolving the particles might be a solution. As radiologists, we have to be alert for these kind of side artefacts. When we deal with a new density on follow ups of breast cancer on mammography, we have to question the method used for SLNB to avoid unnecessary biopsies and more importantly, to reduce the patient's anxiety. Knowing the patient's history and the method used for SLN detection guide us to consider this differential diagnosis.

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Peer-review: Externally peer-reviewed.

Author Contributions: Concept - L.Ç.; Design - G.A.; Supervision - L.Ç.; Data Collection and/or Processing - G.A.; Analysis and/or Interpretation - L.Ç., GA.; Literature Search - G.A.; Writing Manuscript - G.A.; Critical Review - L.Ç.

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

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Letter to the Editor

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Treatment of Capsular Contracture After Radiotherapy in Breast Reconstruction

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Dear Editor,

Breast prostheses are made for cosmetic reasons and in order to reduce defective body perception and psychosocial trauma caused by the absence of breast tissue. Silicone breast prostheses are frequently used in breast reconstruction after breast augmentation or mastectomy. Safety and efficacy criteria are considered when applying silicone breast prostheses. Non-toxic, immunogenic, teratogenic, carcinogenic, and lack of potential effect on mammography determine its reliability; development of capsular contracture, deflation, palpation and the possibility of folding in the anatomical pouch is determined by its effectiveness. The fillers and implant options used in consideration of these criteria are also limited in time and the ideal ones are introduced in medicine (1-4).

The most common complication after reconstruction or augmentation with silicone implant is the formation of constrictive fibrous capsules around the implant. This causes fibrous tissue capsule contraction. The contraction is caused by pain in the breast, hardening, and asymmetry in the breast. It has been reported that between 1.3% and 30% of the patients with implant have developed capsular contractures. Approximately 92 percent of contracture occur within the first 12 months after surgery. The longer the implants settle, the higher the risk of contracture occurring cumulatively. Although bacterial colonization, implant surface characteristics, hematoma formation and radiation are found to be associated with etiopathogenesis, the cause and pathogenesis is still not known. In order to prevent the formation of capsule contracture, various methods the prosthesis pouch with various substances, using fibrin glue, preventing hematoma, using silicone outer surfaces in different tissues and placing the prosthesis in different anatomical locations were tried. However, the exact treatment is not available at present (3-8).

Nowadays, mastectomy is applied to the patients concurrently with surgery, 2 weeks after mastectomy or in patients who will receive RT after 3 months. In breast cancer cases, subcutaneous mastectomy with simultaneous expander and implant and breast reconstruction are common methods. It is not clear yet which of these three applications is a more reliable method. When radiotherapy (RT) is applied in breast cancer patients with silicone prosthesis, it is very important for the treatment of prosthesis in the treatment area and the complications that may occur. It has been reported that silicone breast prostheses have no negative effect on photon and electron dose distribution. In addition, it was determined that the silicone elastomer used in breast prostheses did not reduce the radiation transmission (9). There is not enough information in the literature regarding the prevention / treatment of complications in prostheses after RT. In studies performed, it was shown that complications of complications such as capsular contracture (1.3-15%) and worse cosmetic results and reconstruction after radiotherapy treatment have increased in patients with breast reconstruction with silicone implant (2, 3, 6-8). However, most of the current studies are retrospective cohort studies and there is no prospective study. The effects of radiation on the formation of capsules are tried to be explained. Recent studies have shown that the transforming growth factor-β (TGF-β1) is an important factor in the formation of fibrosis and radiation-induced capsule formation. Positive results have been reported in studies to prevent these effects by inhibition of TGF-β signal transduction (3). Evans et al. (4) performed breast reconstruction with implants and compared the contracture stage, pain and extrusion in patients with RT without RT. They reported that radiotherapy increased the capsular contracture stage (Baker III, IV) and had significant negative consequences for the clinical appearance and patient satisfaction. Azzi et al. (5) reported that radiotherapy accelerated the process of capsular contracture around the silicone implant in a study of 105 patients.

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Nowadays, the increase in the studies on the use of implants has led to an increase in the studies to investigate the agents for prevention of implant complications. Chung and colleagues reported that simvastatin was effective in reducing radiation-induced capsular fibrosis around silicone implants in rats (6). Cook and his colleagues treated mastectomy with adjuvant radiation-induced breast prosthesis for 30 days with Trental and Vitamin E for 180 days. Three patients underwent implant revision. In 2 cases developed contracture. In conclusion, it was reported that combination of Trental and Vitamin E could prevent serious contractures and implant losses (8). In the recent meta-analysis, the use of biological cellular dermal and synthetic matrices in combination with a tissue expander or an implant has been reported to slow the progression of capsule formation and fibrosis (6).

In the literature, it was observed that patients who received RT after breast reconstruction were not informed about the risks of connective tissue disease, autoimmune disease, or tumor development, and that no laboratory or clinical evaluation was performed to determine possible systemic disease development. In addition, there is no data to evaluate the risk of cancer recurrence, delayed adjuvant therapy, and health-related quality of life in this group of patients.

As a result, there is no agent to prevent the complications of prosthesis in patients who will undergo postoperative radiotherapy after oncologic surgery and in implant and breast operations. Breast cancer patients who have breast prostheses should be followed for a long time in terms of cancer recurrence, connective tissue disease, autoimmune disease, or tumor development risks. Patients with signs and symptoms of systemic disease should be identified and laboratory investigations and clinical evaluation should be performed. Studies on this subject are needed.

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Letter to the Editor

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Lapatinib? or Radiotherapy? In Cranial Metastasis of Breast Cancer

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Dear Editor,

During the last two decades, significant advances in molecular oncology have led to the introduction of targeted therapies into clinical use. Many drugs that are being used in targeted therapy interfere with the proliferation of tumor cells by interacting with cell receptors and intracellular signaling molecules. Monoclonal antibodies and oral small molecule kinase inhibitors, which have recently been used in cancer treatment, are molecular agents that have been developed with the understanding of specific signaling pathways (1-3).

Lapatinib ditosylate (Tykerb ®, GW 572016) is a tyrosine kinase inhibitor that acts reversibly to human epidermal growth factor receptor 1 (EGFR/HER1) and human epidermal growth factor receptor 2 (HER2/ErbB2) tyrosine kinase by inhibiting the phosphorylation and activation of the receptor. Inhibition of phosphorylation and activation of the receptor results in inhibition of the PI3K/Akt and MAPK pathways activated by HER2, thereby stopping cellular growth and proliferation, resulting in increased apoptosis. Lapatinib's activity against several types of tumors were investigated in phase trials and their effect was tested especially in breast cancer. It has been approved for use in patients with HER2-positive metastatic breast cancer after progressive, regimens including taxanes, anthracyclines and trastuzumab. With the introduction of this drug, it has been possible to prolong survival in the treatment of metastases in HER2 positive breast cancer and in adjuvant therapy. Although it was moderately effective as monotherapy in first-line treatment in metastatic breast cancer, its main effect was obtained by its combination with cytotoxic agents. Lapatinib is generally well tolerated and most of its side effects are mild (grade 1 or 2). Diarrhea, nausea, vomiting and cutaneous toxicity are frequently observed in the early stages of treatment (1-6).

Lapatinib crosses the blood-brain barrier due to its small molecule structure. Lapatinib has been shown to prevent the development of brain metastases in breast cancer when combined or alone. Cameron et al. (1) reported a lower incidence of brain metastasis in the lapatinib group in the phase III study in which lapatinib-capecitabine was compared with the combination of lapatinib-capecitabine in HER2 (+) metastatic breast cancer (2% in lapatinib-capecitabine arm, 6% in capecitabine arm, p=0.045). Lin et al. (3) looked at the efficacy of monotherapy lapatinib in patients who had previously been treated with trastuzumab and developed brain metastasis. A 20% response to brain metastases has been reported. Metro et al. (4) reported a 31.8% partial response with a combination of lapatinib - capecitabine and a stabilization of 27.3% in HER2 (+), metastatic breast cancer patients who had been treated with brain metastasis under the treatment of trastuzumab. The overall survival was 27.9 months in patients treated with lapatinib - capecitabine and 16.7 months in patients who were treated with trastuzumab alone (p=0.01) (4). These results led to the demonstration of the efficacy of lapatinib in breast cancer brain metastases and led scientists to compare other treatment options applied. Miller et al. (6) looked at the response in radiotherapy in patients with HER2/epidermal growth factor receptor tyrosine kinase inhibitor (TKI) and untreated breast cancer brain metastasis. The incidence of 12-month cumulative poor response decreased from 15.1% to 5.7% in patients with concurrent TKI with stereotactic radiosurgery (p<.001). In conclusion, in the HER2 positive patient group, radiosurgery with TKIs was suggested to prevent neurocognitive disorder and all brain radiotherapy should be considered in salvage treatment (6). Studies have shown that lapatinib treatment after whole brain radiation therapy can improve survival in patients with HER2-positive breast cancer with multiple brain metastasis with significant neurological symptoms (7). In another study, it has been suggested that lapatinib as a consecutive treatment because of the limited

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effect of cranial radiotherapy in patients with HER2 positive cranial metastases (8). In the phase II study of patients with brain metastasis, the efficacy of lapatinib monotherapy was evaluated in patients who had previously received local treatments such as trastuzumab or cranial radiotherapy. The partial response in 8% of the patients and the stable response in 16% of the patients indicated that the treatment alternative seemed to be an important option in a very limited group of patients. However, it has been reported that it can prolong survival by preventing the development of brain metastasis (5).

As a result, lapatinib is a double-acting selective inhibitor that inhibits signal transduction by inhibiting EGFR/HER1 and HER2/ErbB2 tyrosine kinase. In addition, the results of the treatment of brain metastases, which is an important problem in HER2 overexpressing breast cancers, are promising because of the first small molecule TKI that crosses the blood brain barrier. However, in order to achieve better control of cranial metastasis and a longer overall survival, new treatment strategies should be developed with radiotherapy. Studies on this subject are needed.

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