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Aims and Scope

The Journal of Breast Health is the open access, scientific online-only publication organ of the Turkish Federation of Breast Diseases Societies that is published in accordance with independent, unbiased, double blind peer review principles. (The journal, which was established in 2005 under the title of Meme Sağlığı Dergisi / The Journal of Breast Health, has been published under the title of The Journal of Breast Health (J Breast Health) as an online-only publication since April 2014)

The publication language of the journal is both in Turkish and English, and it is published quarterly on January, April, July and October.

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

The editorial policies and publication process are implemented in accordance with rules set by the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), European Association of Science Editors (EASE), Committee on Publication Ethics (COPE), and the Heart Group.

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Samples

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

Chapter of a Book
Shires GT, Thal ER, Jones RC, Shires GT III, Perry MO. Trauma. In: Schwartz SI, ed. Principles of Surgery, 6th ed. New York: McGraw-Hill, 1994:175-224.

Book
Kellman RM, Marentette LJ. Atlas of Craniomaxillofacial Fixation. New York: Raven Press, 1995.

Internet Resources
Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2626828/pdf/8903148.pdf.

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The Journal of Breast Health

Contents

ENDOSCOPIC ASSISTED ONCOPLASTIC BREAST SURGERY

Minimal invasive endoscopic surgery have been widely used in many fields of surgery. Oncoplastic breast surgery is one of the rare field where the breast surgeons have not met yet the endoscopic surgery. The late meeting of the breast surgeons with endoscopic surgery may be due to the inherent low morbidity, low pain, small incisions and successful cosmetic results of the oncoplastic breast surgery techniques. It is only after Kompatscher used endoscopy for capsulotomy in breast for the first time in 1992 that the breast surgeons became interested with endoscopic techniques in breast surgery.

Endoscopic oncoplastic breast surgery represents a minimal invasive approach with the aim of both removing cancer safely and also restoring the body image. Less noticeable scar, excellent cosmetic outcomes and recently reported relatively long term safety lead to be established the technique as a routine clinical practice in some institutions of some Asian Countries such as Japan, Korea and China.

Operative techniques for both endoscopic breast conserving surgery and endoscopic nipple/areola/skin sparing mastectomy have been described in detail and being widely used. Tumor localization and marking the proposed resection margins on the skin are achieved preoperatively by injections of colored dye at several points at the tumor periphery by radiologic guidence. The purposed surgical margin is marked usually 2 cm distant from the tumor edge.

Two different working planes are used during the surgery. One of them is subcutaneous plane where the skin flap is developed, and the other one is sub-mammary plane. Skin incisions are placed usually in either periareolar region or in the axilla. Sentinel lymph node incision in the axilla is used for retromammary dissection while the periareolar incision is the route for subcutaneous dissection and for retrieving the resected specimen. Light guided specific mammary retractors are also used during subcutaneous dissection. Wound protectors are usually used to ensure adequate visualization and to protect the periareolar and axillary skin.

Endoscopic dissection between the pectoralis muscle and the posterior breast is performed with various retractors such as Ultra Retractor. Endoscopic breast retractors allow for a magnified view and extensive posterior breast dissection. Subcutaneous tunneling method is the most commonly used technique for endoscopic subcutaneous dissection. Septa between the tunnels are then dissected under endoscopic guidence. The tumescent technique in which epinephrine containing physiological saline is injected into the subcutaneous tissue provides more easy and bloodless dissection. Bipolar scissors and electrocautery are used for tissue dissection and coagulation in both subcutaneous and retromammary dissection planes. Colored dye injected at the tumor periphery or at the breast boundary determines the extent of the dissection.

To repair the defect of the excised breast tissue, usually the volume displacement technique are used. Widely dissected mammary gland and adipose tissue are mobilized to the defect and sutured by the help of light guided mammary retractors.

Endoscopic assisted breast surgery provides, in general, excellent cosmesis with minimal scar. Less noticeable scar is the most important advantage of endoscopic breast surgery. Most of the patients are satisfied with the provided cosmesis.

An average operation duration time for endoscopic assisted breast surgery has been reported as equal or 30-50 minutes longer or 20-25 minutes shorter than open breast surgery. The different results can be attributed to the different techniques used in. In general the reported longer operative durations are due to woking in a limited and small surgical dissection field.

From the Editor

Complication rates of endoscopic breast surgery are similar to open breast surgery rates. The most serious complications related with the technique are skin, muscle and nipple necrosis which are comparable to the results of the open procedures. Intraoperative blood loss is not different between endoscopic and open breast surgery.

A positive surgical margin rate in endoscopic breast surgery is between 0% to 25% and is not inferior to that open breast surgery. Local recurrens following endoscopic breast surgery is infrequently reported. Eventhough having a shorter follow-up time with an average of 24 months there was no recurrens in reported studies. On the other hand, overall survival rates following endoscopic and open breast cancer surgery are comparable with an average 20 months follow-up. Endoscopic breast surgery leads to an equivalent risk with open breast surgery for local and distant disease recurrence. Overall survival also demonstrated favorable results with endoscopic breast surgery in some studies. However the follow-up periods are too short to compare the endoscopic breast surgery with open surgery. It looks reasonable to wait for the results with longer follow-up before having a judgement about oncologic efficiency and safety of the endoscopic breast cancer surgery.

The current disadvantage of endoscopic breast surgery is the additional cost related to the use of some new devices which are not approved yet by health insurance providers for breast cancer surgery.

As a result, it looks like that endoscopic breast surgery is a new field that the breast surgeons will deal with for the forthcoming years.

Gürsel Soybir

Review

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The Role of Oncoplastic Breast Surgery in Breast Cancer Treatment

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ABSTRACT

The aim of this study is to discuss indications, advantages, disadvantages, oncologic and aesthetic results of Oncoplastic Surgery (OBS). Pubmed and Medline database were searched for articles published between 1998 and 2014 for keywords: oncoplastic breast surgery, therapeutic mammoplasty, oncoplastic breast reduction, synchrenous reconstructions. Role of OBS in breast cancer surgery, its aspects to be considered, its value and results have been interpreted. This technique has advantages by providing more extensive tumourectomy, yielding better aesthetic results compared with breast conserving surgery, allowing oncoplastic reduction in breast cancer patients with macromastia, with higher patient satisfaction and quality of life and by being inexpensive due to single session practice. As for its disadvantages are: re-excision is more difficult, risk for mastectomy is higher, it is depent on the Surgeron's experience, it has a risk for delay in adjuvant therapies and its requirement for additional imaging studies during management. Main indications are patients with small tumour / breast volume, macromastia, multifocality, procedures which can disrupt breast cosmesis such as surgeries for upper inner breas tquadrient tumours. Contraindications are positive margin problems after wide excision, diffuse malign microcalsifications, inflammatory breast cancer, history of radiotherapy and patients' preferences. Despite low evidence level, Oncoplastic Breast Surgery seems to be both reliable and acceptable in terms of oncologic and aesthetic aspects. Oncoplastic Breast Surgery increase the application rate of breast conserving surgery by obviating practical limitations and improve the results of breast conserving surgery. Correct patient and technique choice in OBS is vital for optimization of post surgical

Keywords: Breast cancer, oncoplastic breast surgery, breast conserving surgery

Introduction

Breast cancer is the most common cancer in women throughout the world (1). Breast-conserving surgery (BCS) and radiotherapy (RT) have been shown to provide similar local control and survival rates to radical procedures in the surgical treatment of early breast cancer (2). The primary aim of BCS is preservation of the breast while adhering to oncologic principles, with the secondary objective to provide breast aesthetics. In recent years, with advances in early detection and adjuvant therapy life expectancy has prolonged in breast cancer prolonged and quality of life issues have gained importance (3).

There are some problems in terms of oncologic and aesthetic perspective in BCS. Despite advances in surgical techniques, positive margin rates in breast cancer following BCS is reported as 20-30% (4,5). The rate of aesthetic problems in conservative surgery that are not amenable for surgical correction have been reported as 30% (6). In the past, breast cancer in women with macromastia was accepted as partial contraindication to BCS. There were problems related to dose distribution of RT following lumpectomy in women with large breasts (7). These shortcomings resulted in low patient satisfaction and poor quality of life (6,8). It is reported that up to 40% of women with breast cancer have large breasts (9). In a breast cancer patient with large breasts, lumpectomy with simultaneous bilateral reduction mammoplasty were performed as a solution for problems related to BCS in patients with macromastia in 1994, and oncoplastic breast surgery (OBS) was defined for the first time (10). Regarding the use of breast reconstructive techniques, simultaneous applications have been shown to provide a better quality of life than delayed procedures (11).

Currently, the concept of OBS is used to define simultaneous application of lumpectomy and reconstructive techniques in patients undergoing breast-conserving surgery for cancer. OBS helps in local control with wider excision without compromising oncologic principles, and provides esthetic closure of the formed glandular defect by plastic techniques. The debate on the role and importance of OBS application continues.

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Figure 1. An early stage breast cancer in a patient with macromastia, centrally located with nipple retraction. Grisotti flap and oncoplastic reduction was planned. Pre-operative planning and drawings

Figure 2. Clinical T2NoMo patient, sentinel lymph node sampling performed with blue dye. Incision according to planned procedure and preparation of the false nipple

The aim of our study was to evaluate the indications, contraindications, advantages, disadvantages, technical features, and oncologic and aesthetic results of OBS in breast cancer treatment together with recent data.

Material and Methods

PubMed and Medline Internet information sources were searched for 'breast cancer, oncoplastic breast surgery, therapeutic mammoplasty, oncoplastic breast reduction, simultaneous breast reconstruction, partial breast reconstruction' keywords between January 1998 and February 2104. Out of the results, 78 publications appropriate to the purpose of our study were selected. Concurrent non-BCS breast reconstructions and non-English language publications were excluded. The role, importance, and results of OBS in conserving surgery were evaluated.

Current Status and Oncologic Breast Reconstructions; Due to the positive results obtained in the surgical treatment of breast cancer, the prevalence of this technique is increasing throughout the world and our country. There was an approximately 2.3-fold increase in OBS publications over the last five years (12). The rate of OBS among general surgeons who practice breast cancer surgery in Turkey was reported as 49% (rarely 24%, sometimes 16%, often and always: 9%) (13). It was emphasized that patient preference and the technical possibilities of the institutions they are working in had an effect in the application of the technique (13).

In the majority of patients with breast cancer, BCS is applied without any oncological and aesthetic problem. In some cases, due to the size and location of the tumor, undesired esthetic results can be encountered when attempting to remove the tumor with safe borders. The main part of the esthetic problem after BCS is caused by scar contracture and glandular defects (6). Oncoplastic techniques are used for the repair of resulting glandular defects. The contralateral breast can be also included in the operation to provide breast symmetry. Oncologic breast reconstructions can be classified depending on the oncological procedure performed and the timing of breast reconstruction. There is no consensus on either the classification to be used in defects that can occur in breast cancer surgery or the ideal OBS technique to be used for correction of this problem (14,15). Although many authors have made some algorithm suggestions on this subject, most breast center use algorithms based on their own experience. The current, widely used OBS techniques are divided in two main groups as simultaneous volume displacement and breast volume replacement.

a- Breast volume displacement; This method is closure of the breast defect that resulted from tumor resection with glandular or dermoglandular flaps prepared within the breast. Although many different techniques have been defined, it basically includes defining the appropriate incision loaction, creation of a flap consisting of subcutaneous tissue, nipple and areola complex (NAC), preparation of glandular flap and reshaping the breast (15,16).

- Incision choice is important in terms of aesthetics and oncology. In certain clinical situations, skin incisions such as grisoti flap, J-mammoplasty, round block, bat-wing incision have been defined to allow easier resection of breast tumor (17-19). In the Grisotti technique, central resection and false nipple is created from breast skin for subareolar tumors or those with nipple involvement (19). Figures 1-7 demonstrate grisotti flap application in centrally located breast cancer. Round block technique is recommended for moderate breast ptosis or tumors in the periareolar areas in medium sized breasts (18). Bat-wing incision is usually defined for the excision of upper quadrant and lateral located breast tumors (17). Incisions should not be at the upper part of the breast, and should remain especially in bra field if possible.

-Glandular advancement flaps, are used to close the defect created by resection of a tumor located in any quadrant without resection of the skin of the breast usually with parenchyma (17,20). This technique is efficient in correction of small defects, especially preventing dimpling after lumpectomy.

-Radial Technique, is often used in breast tumors located laterally or medially. Skin resection can be made. The excised area is supported by glandular flap and/or subcutaneous tissue (21).

- Oncoplastic breast reduction is the first defined, and probably the most widely used OBS technique. It is used to improve oncological and functional results in women with large breasts. Lower, upper inner, upper outer pedicle flap containing NAC are prepared according to tumor location. After preparation of the flap containing NAC, significant amount of breast tissue and skin are removed with wide excision of the tumor. The similar procedure is done in the contralateral breast (22,23). This procedure provides breast symmetry that is

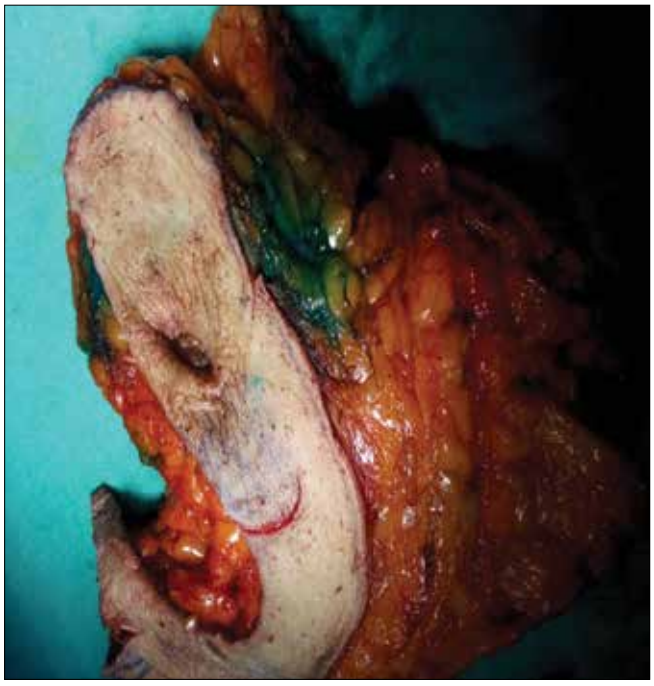

Figure 3. Wide excision of the tumor with areola, and breast reduction

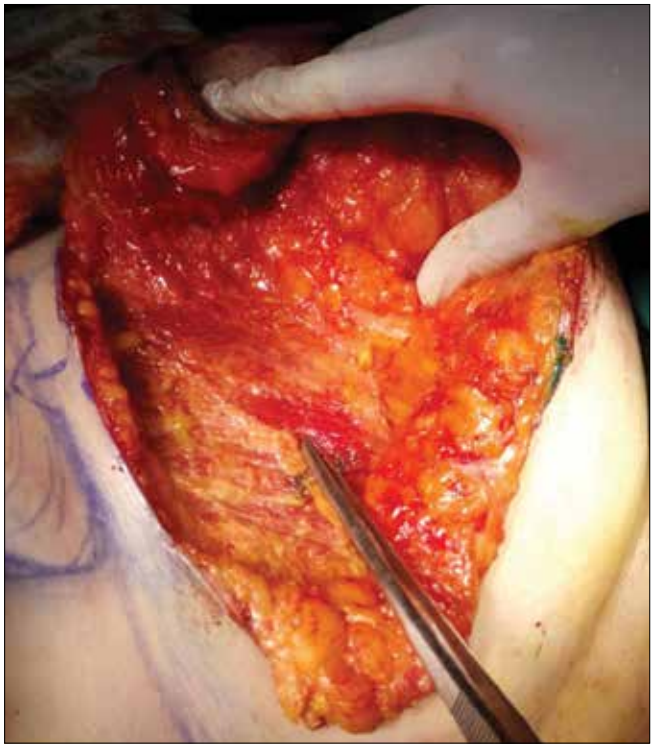

Figure 4. Clipping the tumor bed for radiotherapy

one of the most important criteria of breast aesthetics in breast cancer patients with medium and large sized breasts. During oncoplastic reduction, the breast containing the tumor is shaped 10% greater than the other breast due to shrinkage after RT (24).

-Mastopexy is used in central, upper and lower quadrant tumors in pendulous or medium-sized breast. The NAC is raised and repositioned in the midline without excision of too much breast and skin

Figure 5. Localization of the false nipple and skin closure

Figure 6. View of the breast on the 4th postoperative day

tissue. The same process is applied to the contralateral breast for breast symmetry (15,25).

b-Breast volume filling; is filling the breast defect with the patient's own tissues from areas away from the breast. It is used in patients with large tumor/breast volume ratio, those with deficient breast volume after resection, and those with significant breast defect. With this approach, myo-cutaneous, myo-subcutaneous tissue or fat tissue is transferred to the defect site.

-Latissimus Dorsi (LD) myocutaneous flap is the most common method used to fill the breast defect in women with small breasts. The LD muscle is moved along together with the skin above. The skin defect is also replaced. A similar technique, myosubcutaneous LD flap (mini LD flap) fills in the defect with LD flap, the skin is not transferred in this technique (5,26). Endoscopic LD mini flap applications are being developed with access sites from the breast and axilla (27). It is frequently used for defects in the upper, inner and lower outer quadrants.

-Subaxillary fat pad flap is used especially in closing large defects resulting from excision of tumors located in the upper and lower outer quadrant. The breast is supported laterally with subaxillary fat tissue (15,26).

-Transfer of free tissues with either a pedicle or microvascular anastomosis that aim to fill the volume from areas away from the breast for partial breast reconstruction have also been defined. Free flaps are quite popular in recent years. OBS techniques such as transverse rec-

Figure 7. View of the breast on the 17th postoperative day

tus abdominus myocutaneous (TRAM) flap, deep internal epigastric perforator flap, superficial gluteal artery perforator flap, omental flap etc. have been defined (28,29). Larger breast defects can be closed with this method.

Definition of Breast in Terms of OBS; three main issues physicians and patients are focused on after the diagnosis of breast cancer are survival, oncologic local control and quality of life. Oncoplastic techniques improve the last two main subjects. The three important factors in the decision of OBS are: breast, tumor, and technique. Preoperative assessment should include the size of the breast (small, medium, large, huge), the shape of the breast (ptotic), structure (parenchymatous breast, lipomatous breast etc.), previous operations (biopsies, previous surgery), systemic additional morbidity risks (diabetes mellitus (DM), obesity, smoking habits, etc.) and requests and preferences of the patient. The importance of measurement of breast size, planning of removed and remaining breast volume in patients with large breasts, and selection of flaps including NAC have been shown (30). Since the breast will rise on the anterior chest wall following lumpectomy and RT in ptotic breasts, the opposite breast may need to be elevated for breast symmetry. During OBS, previous biopsy scar and related parenchymal area should also be removed. Obesity, diabetes mellitus and smoking increase the rate of postoperative complications (31,32). These factors cause delay in wound healing and perfusion problems in the flap, especially in those containing NAC. Tobacco use should be discontinued 6-8 weeks prior to OBS procedures with NAC containing flap oncoplastic reduction and volume expansion. Despite oncological and aesthetic benefits, patient preference regarding simultaneous OBS varies with age, race, education and socio-economic status (33). Potential oncologic and aesthetic risks should be explained to the patient in an appropriate and unbiased manner. This approach will significantly affect post-procedure results. The size of the tumor, tumor/breast volume ratio, tumor location (upper, inner quadrant), progression rate (inflammatory carcinoma), stage of the cancer, and the size of the area to be excised with the tumor should be evaluated. The choice of oncoplastic technique according to these breast and tumor related characteristics are debated (15,16). The addition of the skills and preferences of surgeons make the decision even more complex. Preoperative decision on BCS and OBS should be planned individually for each patient.

OBS Advantages

Oncoplastic surgery provides excision of breast tumor with wider limits and in a more secure way (16). It has been shown that using this technique, especially in cases with removal of large tumors and locally advanced breast cancer, improves outcomes (34,35). The meta-analysis by Losken that compared oncoplastic applications with BCS in breast cancer, reported the average breast tissue removed as 64 gr. in BCS and as 184-249 gr. in those with oncoplastic surgery. In addition, the positive margin rate was 20.6% in the BCS group as compared to 12.3% in the OBS group (12). In addition to improving cosmetic results in breast cancer surgery, OBS reduces oncological problems associated with BCS. This status is extremely valuable in the evolution of breast cancer surgical treatment from mastectomy to BCS, and then to OBS.

Mastectomy rate is decreased and organ loss is reduced by application of OBS techniques (36,37). The implementation of these techniques avoids mastectomy and the associated wider reconstructive methods as well as additional complications related to these procedures (38). Safe oncologic and acceptable aesthetic results are provided especially in centrally located breast tumors (39,40). Previously, NAC involvement or proximity was accepted as a relative contraindication for BCS. These limitations were overcome with the development of oncoplastic techniques such as grisotti flap. Also with this method, if breast reduction is planned, it can be performed easily by the surgeon.

Breast aesthetics that identifies and complements the female body is important. OBS improves aesthetic results in the surgical treatment of breast cancer (12,18,41). BCS allows conservation of the breast in cancer surgery, while OBS that was defined to solve aesthetic problems of the protected breast reduces these problems up to 7% (42). The results of aesthetic evaluation were found to have higher rates of good and excellent results with the use of oncoplastic techniques (12).

Wide lumpectomy with bilateral breast reduction (oncoplastic breast reduction) is applied in breast cancer patients with macromastia. Problems related to diagnosis, surgical treatment and radiotherapy applications of breast cancer in women with large breasts are well-known (7,24). The tumor field cannot be fully determined in these patients and higher doses of RT are required, which result in sharpening of breast boundaries due to extensive fibrosis and elevation of the breast mound on the chest wall, thus, breast aesthetics is impaired (43-45). That is why previously macromastia in breast cancer patients was considered as a relative contraindication to BCS. Macromastia leads to chronic shoulder, neck, back and breast pain, recurrent rash under the breast and severe restrictions in movement (46). Over time, the symptoms of macromastia are neglected by patients, and chronic problems are often overlooked. Wider resection of the tumor is possible with OBS, and the excessive breast tissue is removed. The similar procedure is applied in the opposite breast. After pathological evaluation of the contralateral breast and breast symmetry is provided. In this patient group, symptoms of macromastia are significantly decreased with oncoplastic reduction, and functional results are improved (47,48).

Worse aesthetic results and higher complication rates have been reported in OBS performed after RT as compared to simultaneous techniques (37). Simultaneous application of oncoplastic procedures

in breast cancer patients has been shown to provide better patient satisfaction than delayed applications (11). Therefore, the most appropriate correction time of breast defects is simultaneous procedures in selected patients.

Breast aesthetics, which is valuable for women's self-confidence and physical attractiveness, is protected with a single operation without increasing psychological burden due to cancer. Single-session procedures reduce the workload of surgeons, more importantly, increase the quality of life in breast cancer patients. Single-session practices are also economically advantageous. In a study, it was reported that delayed breast reconstruction was 62% more expensive as compared to simultaneous reconstruction (49). Economic advantages of OBS are also important, in a time where health financing and savings are discussed more often.

It has been shown many times that OBS can be safely used for both oncologic and aesthetic results in the surgical treatment of locally advanced breast cancer (50-52). Application of OBS can be advantageous in terms of oncologic and aesthetic results if removal of a large breast mass is considered in patients who are less responsive to neoadjuvant chemotherapy.

Disadvantages

Additional resections in patients requiring re-excision due to postoperatively identified positive margins on pathological evaluation cause a problem due to dermo-glandular flaps. Positive margin rate in OBS practices are reported as 7-12% (12,14). Risk factors for positive margins are young patients, large tumor size and presence of in situ cancer (14,34). It has been shown that mammographic and pathologic evaluation of the tissue removed during surgery decrease problems related to margins (14,53). Diligent implementation of these methods in OBS cases will help in achieving higher rates of negative surgical margins. Although re-excision can be an option in margin positivity, some cases may require mastectomy. Mastectomy risk should be shared with the patient.

Due to high survival rates in breast cancer, increased patient awareness and patient demand, there is increasing interest in aesthetics and OBS applications. Every surgeon dealing with breast surgery should be familiar these techniques and practice them. OBS technique in practice often depends on the skill and experience of the surgeon. The availability of a team of supportive health personnel who can assist in patient communication and patient care in both pre- and postoperative period will contribute positively to the process.

The aesthetic expectations of patients undergoing oncoplastic techniques have been reported to be higher than BCS (54). Poor cosmetic result rate in OBS application has been reported as 5-15% (45,47). Patients should be informed on possible problems such as scar and asymmetry, as well as the rare NAC necrosis. They should be informed about requirements for secondary breast correction surgery. It should be emphasized that the aim of OBS is not perfect breast shape but the correction of possible breast defects.

The operation time of OBS, including oncoplastic reduction and volume expansion, lasts longer than classic BCS. OBS has more complications than conventional BCS (12). The complication rate rises to 20-25% especially in oncoplastic reduction (12,24). Complication after oncoplastic reduction may cause a delay in adjuvant treatment (43,55). Clough KB et al. reported the rate of patients with delay in adjuvant treatment due to wound healing problems as 4% (56). The experience of the surgeon has a strategic importance in patient and technique selection.

During the long oncologic follow-up, breast magnetic resonance imaging (MRI) and breast biopsy may be required in addition to mammographic evaluation in patients with OBS (especially oncoplastic breast reduction) (43). Patients with oncoplastic reduction are those who require extremely careful follow-up.

Despite increased interest in recent years, the majority of the oncoplastic literature consists of case series with short follow-up, with an evidence level of 3.4. Proponents of this technique have ethical reservations about the patient group to be compared with patients who are predicted to have defects due to BCS and who will require correction (34). Almost every OBS publication emphasizes that OBS procedures should not preclude oncologic procedures (12,14,53). Absolute indications of OBS and technical algorithms have not yet been identified by consensus. Long-term oncologic and aesthetic follow-up data have not been published. The long term results are required to prove that this operation aiming at improving aesthetic results without compromising oncologic aspects actually meet these expectations. An important criticism in terms of RT can be overcome by marking the tumor bed with metal clips for irradiation of the correct area with the accurate dose. The literature generally lacks specification whether the tumor bed was clipped or not for RT (55). The question on who should perform OBS is still being debated. The approaches on this issue vary significantly. Given that the breast is an aesthetic organ, oncoplastic techniques may be required in all breast cancer operations. Currently, breast surgeons dealing with breast cancer surgery are performing most OBS. It has been demonstrated that surgeons can perform many OBS applications without the need for a plastic surgeon, by learning basic plastic techniques (57). Surgeons may correct most breast defects by learning the required techniques in plastic surgery during breast cancer surgery that they have already been doing. Advantages and disadvantages of OBS are summarized in Table 1.

Indications and Contraindications to OBS

The main indication is breast cancer patients with possible breast deformity following standard BCS. Removal of more than 20% of breast volume leads to significant deterioration in breast aesthetics (56). Patients with multi-focal tumors, macromastia, large tumor/breast volume, and are low responsive to neoadjuvant therapy are potential candidates for OBS. OBS techniques are more frequently used in central, upper and inner quadrant tumors due to aesthetic problems (17,58,59). Relief of macromastia symptoms and surgical treatment of cancer are provided in a single session in patients with symptomatic macromastia and breast cancer (60). Patient and physician preference are also indications for OBS.

Oncoplastic surgery is contraindicated in cases that require mastectomy due to margin positivity. Large T4 tumors, multicentric tumors, patients with diffuse malignant microcalcifications fall into this category (34,60,61). OBS techniques should not be applied in inflammatory breast cancer. OBS is not recommended when there is not enough remaining breast tissue after tumor resection (18). It should not be used in patients with previous history of RT, or those in whom RT cannot be administered. In patients with diabetes and heavy smoking, especially cases requiring pedicle flap, may not be eligible for OBS. Correction of these risk factors require time. In addition, preference of the patient and the surgeon's experience are also contraindications. Oncologic outcomes may deteriorate with insufficient experience in oncoplastic reduction and volume expansion methods. Surgical poor technique often causes skin scars and glandular defects.

Table 1. Advantages and disadvantages of Oncoplastic Breast Surgery as compared to Breast Conserving Surgery

Oncoplastic Breast Surgery as compared to Breast Conserving Surgery	
Advantages	**Disadvantages**
Wider tumorectomy	Difficulty in re-excision
Lower rate of margin positivity	Dependent on skills and expertise of the surgeon
Better local control	High complication rate
Better aesthetic outcome	Delay in adjuvant treatment
Lower mastectomy rate	Requirement for correction
Ease of radiotherapy in the reduced breast	Longer operation time
Obtaining breast symmetry	Requirement for additional imaging during follow-up
Single session	High risk of mastectomy in case of margin positivity
Better quality of life	
Higher patient satisfaction	
Sampling of the contralateral breast	
Cheaper than delayed reconstruction	

The implementation of OBS techniques in in situ breast cancer is controversial. It is stated that OBS should not be performed due to the diffuse pattern of in situ cancer, its multifocality, intermittent duct involvement, common micro-calcifications and the resultant oncological margin safety problems (12,53,62). It is also advocated that, with mammographic control of the removed tissue and margin control with frozen section evaluation, the resulting large defect can be replaced by OBS techniques (18,24,34). In this way, more extensive tissue can be removed while avoiding possible breast deformity. Preoperative careful clinical assessment of the patient, applying oncologic principles in the operation, and with patient consent, OBS can be applied to in situ breast cancer with expectation of breast deformity. OBS indications and contraindications are summarized in Table 2.

Oncologic and Esthetic Evaluation

Improving breast aesthetic without compromising basic oncological principles was the starting point of OBS. In their meta-analysis, Losken et al. reported the rate of margin positivity as 12.3% for OBS, 20.6% for BCS, and the local recurrence rate as 3.6-4.7% for OBS and 7% for BCS (12). In another study comparing patients with BCS and OBS, the tumor size were reported as 17mm and 24mm, surgical margins as 6 mm and 14 mm, and re-excision rates as 29% and 5.4%, respectively. It was concluded that the oncoplastic approach improved oncologic outcomes without increasing the complication rate (34). Schaverin MV et al. (62) reported that oncoplastic techniques reduce margin safety issues and provided high satisfaction in patients with multifocal and large tumors. As a result of all these efforts, OBS not only improves aesthetic and patient satisfaction outcomes, but also oncologic outcomes of breast cancer surgery, especially in patients with multifocal and large tumors. The use of oncoplastic methods provides better margin control by removal of larger tumors. Rietjens et al. reported 93% survival rate at 74 months follow-up of 148 patients (63). The 15-20 year long-term local recurrence and survival data of oncoplastic procedures in breast cancer have not been published so far. The surgical treatment of breast cancer according to molecular subtypes, and choice of OBS technique remains unclear. Luminal B / HER2 positivity, triple negative subtype and body mass index higher than 25 were shown to be risk factors for local recurrence (64). Despite all these risk factors, potential application of these techniques can be considered when required in all patients eligible for BCS.

OBS in breast cancer surgery is known to improve quality of life by improving aesthetic results (3.65). There is no consensus on methods or timing of postoperative breast aesthetic evaluation (66). Aesthetic evaluation methods by the patient, surgeon or panel consisting of 3-5 person have been described (53,66). Although the patient's perception and aesthetic evaluation are important, successful methods such as BREAST Q have been developed for objective aesthetic evaluation (67). However, most of the current literature does not consist of objective aesthetic evaluation data. Postoperative good and/or excellent results of OBS were reported as 84-89% (61). Fitoussi et al. reported the cosmetic results of patient satisfaction rate as 98% at postoperative 1 year, and as 90% at 5 years (68). Development of more fibrosis in large or heavy breasts, especially after RT, leads to breast reduction and as a result reduces esthetic appreciation rate in 5 years (69). Over time, the high aesthetic appreciation rate in the first period declines due to RT, weight gain and so on. In spite of all these, the benefits of oncoplastic reduction method in these cases are obvious.

Postoperative Approach; It has been reported that OBS does not influence the selection and timing of postoperative adjuvant therapy (41,70,71). It was demonstrated that complications in patients with oncoplastic reduction or volume expansion did not delay adjuvant treatment (70,71,72). In a similar group of patients, there are publications stating that serious complications such as flap nutritional problems resulted in a few weeks of delay in adjuvant treatment (55,73). This state may compromise oncological local control. The surgical team should be careful about possible complications particularly during the learning period.

The importance of additional RT dose to the tumor bed in local control of breast cancer is well-known (74). In patients with OBS, the position of the tumor changes due to glandular flaps, changes in NAC position, and breast elevation in the anterior chest wall. Marking the tumor bed with 4-5 pieces of metal clips is extremely strategic in RT process. Recent data suggest that the clips may be displaced in upto 50% of patients with oncoplastic methods, and thus the actual tumor bed receives insufficient RT to provide local control, or a higher dose of radiation will be required since the actual site of the tumor cannot be fully determined leading to more fibrosis and bad cosmetics

Table 2. Indications and contraindications of Oncoplastic Breast Surgery

Oncoplastic Breast Surgery	
Indications	**Contraindications**
More than 20% volume excision	Positive margin requiring mastectomy
Large tumor size	Insufficient remaining breast volume
Central, upper and inner quadrant tumors	Diffuse microcalcifications
Presence of macromastia	Multicentric tumor?
Low response to NAC in locally advanced cancer	Inflammatory breast cancer
In situ cancer presence?	Previous radiotherapy
Multifocal	Concomitant disease (Diabetes, smoking)
Patient and surgeon preference	Patient and surgeon preference

(55.75). Therefore, it is recommended that a multidisciplinary team including the radiotherapist should preoperatively evaluate patients undergoing OBS. The benefits of sharing the oncoplastic operation and location of the tumor with shared radiotherapists have been shown (55). Oncologic principles must always be primary.

OBS does not affect the selection and type of CT. The impact of CT on the aesthetic results of OBS are not clear (39).

It has been reported that glandular flaps and small-scale displacements do not pose a significant problem in follow-up of patients with breast cancer (71.76). It has been reported that mammography may be adequate for monitoring patients with oncoplastic flap, however, failure of mammography and requirement for breast MRI was emphasized in patients with oncoplastic reduction (77). Careless surgical technique and complications can add to this negative situation. Additional biopsy may be required in the diagnosis of lesions such as postoperative fat necrosis and fibrosis (78).

Conclusion

OBS, despite the low evidence level in relevant publications, is both reliable and acceptable in terms of oncology and aesthetics. This technique provides more than aesthetic correction, which was the first starting point, by reducing oncological problems. Together with its current indications and benefits, it increases the application rate of BCS. Selecting the proper patient and technique is extremely important for the optimization of postoperative period in all applications. Single-session procedure provides significant economic benefits due to ease of application. Reports on long-term results and prospective randomized trials can eliminate reservations on OBS.

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Original Article

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Problems In Determining Her2 Status In Breast Carcinoma

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ABSTRACT

Objective: Human epidermal growth factor receptor 2 (HER2) oncoprotein is overexpressed in 15-25% of breast carcinomas and associated with poor outcome. Assessment of HER2 status accurately is important to select patients who will benefit from targeted therapy.

Materials and Methods: In this study immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) were used to determine the HER2 status in 308 breast carcinoma cases of which 129 were consultation. The major problems in determining HER2 status and the reasons of discordant results between methods were discussed.

Results: HER2 expression was (-) in 124, (+) in 29, (++) in 92, (+++) in 63 cases. 25 of 76 cases consulted as (++) were evaluated as (++) and 15 of 35 cases consulted as (+++) were evaluated as (+++). HER2 amplification was found in 88 (28.6%) of 308 cases by FISH. 3 of 124 (-), 1 of 29 (+), 22 of 92 (++), 62 of 63 (+++) cases were amplified by FISH. The relation between HER2 expression and amplification was statistically significant ($p<0.001$). Centromere 17 (CEN 17) region amplification was noted in 11 cases of which 2 were (+++), 9 were (++). 6 of the 11 cases showed focal low level, 1 of them showed diffuse high level amplification.

Conclusion: The concordance rate between IHC (+++) cases and FISH was 95.4% for consultation cases, 100% for our cases. The final concordance rate for both case groups was 98.4%. The possible reasons of discrepancy were triple negativity, preanalytical and analytical procedures of consultation cases and trucut samples.

Keywords: Breast cancer, erbB genes, fluorescence in situ hybridization

Introduction

Human epidermal growth factor receptor 2 (HER2, cerbB2) gene that is located on the long arm of the 17th chromosome, encodes a transmembrane surface receptor protein by intrinsic tyrosine kinase activity (1). HER2 protein shows structural homology to epidermal growth factor receptor (EGFR), and similar to EGFR is involved in cell proliferation (2). HER2 plays a role in the oncogenesis of different cancer types. Over-expression of HER2 (increase in HER2 receptors on cell membrane) is the result of gene amplification (an increase in HER2 gene copy number) by 95%, and is detected in approximately 15-25% of breast cancer cases (3, 4). For the first time in 1987, Slamon et al (5) concluded that HER2 amplification was together with decreased overall survival and disease-free survival in breast cancer patients with lymph node metastasis. HER2 status indicates response to chemotherapeutics, hormonal agents, recombinant human anti-HER2 antibody trastuzumab (Herceptin® Genentech, California, USA) and the dual HER1 / HER2 tyrosine kinase inhibitor lapatinib (Tykerb, GlaxoSmithKline, Philadelphia, USA) that positively influences clinical progress in advanced stage patients when combined with capecitabine (6). Trastuzumab is a human monoclonal antibody that is generated against the HER2 receptor. In tumors with HER2 overexpression, it binds to the extracellular part of the receptor, inhibits HER2 mediated signals, induces antibody-mediated cellular cytotoxicity and inhibits cell proliferation.

The most common routine methods for determining HER2 status are fluorescence in situ hybridization (FISH), silver in situ hybridization (SISH), chromogenic in situ hybridization (CISH) and immunohistochemistry (IHC) methods. The most important advantage of SISH and CISH methods is that they allow evaluation by light microscope. Although the issue on which method is the gold standard is still controversial, the compatibility between SISH /CISH and FISH is very high (7).

In this study, 308 breast cancer patients including consultations were evaluated for HER2 protein expression by IHC method and for HER2 / Chromosome17 (chr 17) gene region changes by FISH method, and we investigated the causes of discrepancy between these two methods. In addition, we evaluated reasons for discrepancy between our IHC results and results of the referring unit in consulted cases, and we examined

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pre-analytical, analytical and post-analytical processes that may influence HER2 IHC results.

Materials and Methods

A total 308 cases, including 179 cases who were consulted from other centers after evaluation of HER2 protein expression levels, 76 of which were (++), and 179 cases who were diagnosed at Tepecik Training and Research Hospital between 2008-2012, 57 of which were (++), were included into the study. According to the results of first evaluation 43% of 308 patients had (++) score. This study examined the compatibility between IHC and FISH as well as factors that influence IHC/FISH results, rather than reflecting the incidence of HER2 over-expression/amplification in our department.

In order to evaluate 308 cases by IHC and FISH, two 4 microns thick sections were obtained from paraffin blocks on lysine slides. In all cases, HER2 protein expression percentage and intensity were detected by using polyclonal rabbit anti-human HER2 antibody (Clone A0485, Dako®, Glostrup, Denmark, dilution 1/300) with the Autostainer Link 48 (Dako®, Glostrup, Denmark) fully automated IHC staining device. The FISH method was applied to all 308 cases by HER2 DNA and Chr 17 centromeric PNA probe mix (DAKO, Glostrup, Denmark). The slides were left in the incubator at 58˚C for an hour, and passed through xylene-alcohol series for deparaffinization. The slides were incubated in pretreatment solution in 95˚C water bath for 15 minutes, and were treated with pepsin after washing solution at 37°C for 4 minutes. After washing and dehydration process, 10µl probmix was dropped and slides were covered with 24x24 mm slide and coverslip sealent. Denaturation was performed with hybridiser apparatus (Dako, Glostrup, Denmark) at 82°C for 5 min, and hybridizations were performed at 45°C for 12 hours. In a water bath at 65°C, following 10 minutes of posthybridisation washing and dehydration, 15 µl DAPI was dropped and kept at +4˚C for 30 min. The HER2 gene region was represented in red, and the chr 17 centromeric gene region was represented in green. The evaluations were performed with Olympus BX51 fluorescence microscope equipped with Texas Red, FITC and DAPI filter under x100 immersion objective. The American Society of Clinical Oncology and the College of American Pathologists (ASCO / CAP) 2007 criteria were used for interpretation of IHC and FISH results (Table 1, 2) (8). HER2/chr 17 centromere rate ≥5 was accepted as high-level amplification, and 2 <HER2/chr 17 <5 was accepted as low-level amplification. The IHC and FISH results, both internal and external evaluation results, as well as histological subtype, tumor grade, estrogen and progesterone receptor (ER/PR) status have been documented. The reasons for discrepancy between IHC and FISH results were also discussed.

Statistical Analysis

Statistical analysis was performed with SPSS version 15.0 (SPSS Inc, Chicago, Illinois, USA). p <0.05 was considered significant.

Results

The mean age was 53.7 (24-91), and the mean tumor diameter 2.84 cm (0.3-13cm). A statistically significant relationship was detected between increase in age and HER2 amplification (p = 0.02) (Table 3). 279 patients (90.7%) had invasive ductal carcinoma histology (Table 4), 125 (40.6%) were grade 2, and 178 (57.8%) were assessed as grade 3. The specimens were obtained by tru-cut / incisional biopsy in 14.5%, by excision in 51.9%, and by mastectomy in 33.6% of patients. IHC evaluation for ER and PR status could not be performed in eight patients due to inability to obtain sufficient lysine slides containing tumor tissue. 84 patients were ER (-), 109 were PR (-) while

Table 1. ASCO/CAP immunohistochemical HER2 evaluation protocol (2007)

Negative (0/+)	No staining or weak interrupted membranous staining
Equivocal (++)	Weak-moderate complete membranous staining (>%10 tumor cells) or intense complete membranous staining in less than 30%
Positive (+++)	Uniform intense complete membranous staining in more than 30% tumor cell

ASCO/CAP; American Society of Clinical Oncology and the College of American Pathologists
HER2; Human epidermal growth factor receptor 2 oncoprotein

Table 2. ASCO/CAP(2007); Evaluation criteria for HER2 gene amplification

	Amplification (-)	Equivocal Amplification	Amplification (+)
HER2 gene copy number	<4	4-6	>6
HER2/CEP17 ratio	<1.8	1.8-2.2	>2.2

ASCO/CAP; American Society of Clinical Oncology and the College of American Pathologists
HER2; Human epidermal growth factor receptor 2 oncoprotein
CEP17; Chromosome 17 centromere

216 were ER (+), and 191 PR (+). There was a statistically significant correlation between decreased ER / PR expression and HER2 overexpression (p = 0.00). In addition, as the percentage of PR decreased the incidence of HER2 amplification increased (p = 0.00). IHC evaluation for HER2 expression revealed 124 (40.3%) (-) cases, 29 (9.4%) (+), 92 (29.9%) (++), and 63 (20.5%) (+++). Twenty-five out of 76 patients who were previously identified as (++) in other centers were evaluated as (++) in our center, and 15 out of 35 cases who were previously identified as (+++) in other centers were evaluated as (+++) in our center. IHC results of patients consulted from external centers and our department are compared in Table 5. Amplification by FISH analysis was detected in only 17 of 35 patients who were previously evaluated as (+++) in other centers (Table 6). Focal low-level amplification was detected by FISH analysis in 3 patients out of 124 IHC (-) patients, one consultation and 2 of our cases (Figure 1), and diffuse amplification was detected in one case, our patient, out of 29 (+) cases (Figure 2). Amplification was observed in 22 of 92 (++) patients and 62 of 63 (+++) patients (Table 7). Amplification by FISH was not detected in one patient whose tru-cut biopsy was interpreted as IHC (+++) (Figure 3). The correlation between immunohistochemical HER2 expression levels and HER2 amplification was statistically significant (p <0.001). Amplification was diffuse high-level in 67 of 88 patients, and focal low level in the remaining 21. Amplification was observed in centromeric gene region of chromosome 17 by FISH in 11 cases (Figure 4). Immunohistochemically 9 of these 11 were (++), and 2 were (+++). Diffuse HER2 amplification was noticed in one of these 11 patients, and focal amplification was detected in six patients.

Discussion and Conclusions

The ASCO / CAP guideline defined features of samples that cannot be evaluated by IHC method as specimens fixated with materials other than

Table 3. Age - HER2 amplification correlation (p=0.02)

	HER2 amplification	N	Mean	Std. Deviation	Std. Error Mean
age	positive	220	52.68	12.525	.844
	negative	88	56.51	13.108	1.397

HER2; Human epidermal growth factor receptor 2

Table 4. Histologic subtypes of tumors

Histologic subtype	Case number and percentage
Invasive ductal carcinoma	279 (90.7%)
Invasive lobular carcinoma	7 (2.4%)
Mixed carcinoma	6 (1.9%)
Invasive papillary carcinoma	5 (1.6%)
Micropapillary carcinoma	5(1.6%)
Metaplastic carcinoma	2 (0.6%)
Apocrine carcinoma	2 (0.6%)
Mucinous carcinoma	2 (0.6%)

Table 5. Comparison of HER2 IHC results of other centers with results of our center

	Tepecik HER2 result				
Consult HER2 result	-	+	++	+++	Total
-	5	1	0	0	6 (4.6%)
+	7	3	2	0	12 (9.3%)
++	36	8	25	7	76 (59%)
+++	10	2	8	15	35 (27.1%)
Total	58 (%45)	14 (%10.9)	35 (%27.1)	22 (%17)	129 (100%)

HER2; Human epidermal growth factor receptor 2 oncoprotein
IHC; Immunohistochemistry

Table 6. Comparison of HER2 IHC results from other centers with FISH results from our center

Consult IHC result	HER2 amplification by FISH		
	positive	negative	Total
-	6	0	6 (4.6%)
+	11	1	12 (9.3%)
++	65	11	76 (59%)
+++	18	17	35 (27.1%)
Total	100 (77.5%)	29 (22.5%)	129 (100%)

FISH; Fluorescent in situ hybridization
HER2; Human epidermal growth factor receptor 2 oncoprotein
IHC; Immunohistochemistry

buffered neutral formalin, excisional biopsy materials that were fixated in formalin for less than 6 hours or more than 48 hours, tru-cut biopsy materials with retraction and compression artifact, strong membrane staining in normal ductus and lobules, and control cases with unexpected results (8). The reasons for discrepancy between HER2 gene and protein product are expressed as chromosome 17 polysomy, low specifity and sensitivity of the primary antibody used in IHC, aggressive antigen retrieval methods and problems in tissue fixation-processing procedures (8).

When applying IHC, it is necessary to know the differences of HER2 antigene from the other antigens. HER2 is a thermo-labile antigen. When the lysine slides are kept in the incubator (≥60°C) overnight, drying and loss of specific staining is observed in tissues. It is recommended that the slides that will undergo HER2 IHC should be kept in an incubator overnight at 37°C or at 60˚C for one hour.

Standardization of tissue processing steps and preservation of cell morphology is very important since IHC evaluates HER2 staining on cell membrane. Assessment of membranous staining becomes very difficult in case of retraction artifact in cells. In this context, if there is a discrepancy between HER2 score and histopathological parameters at centers where standardization of the pre-analytical, analytical and post-analytical processes could not be provided, confirmation of IHC and ISH results at another center with standardization will be suitable.

Although international committees issue guidelines in order to determine HER2 accurately, there is a variety of inter-observer or inter-laboratory variables in both FISH and IHC, the compliance is low (9). In our study, IHC results from other centers and our unit were compared. The slides of patients from other centers were evaluated if their IHC slides could be obtained. HER2 score was based on pathology reports in consultation cases. Out of the 76 cases that were reported as (++) in other centers, 25 were interpreted as (++), and 44 were interpreted as (- / +) in our center. Out of the 35 (+++) cases, 15 were evaluated as (+++) and 12 as (- / +). In other centers (+++) considered amplification was observed in 18 of 35 cases. In particular, given the discrepancy between (++) / (+++) scores and FISH results, it was concluded that cytoplasmic and incomplete membranous staining was reported as complete membranous staining in other centers. Although compatibility was low in IHC (++ / +++) scores, compatibility was high between (- / +) scores from other centers and IHC and FISH results from our unit. Based on this finding, the fundamental problem appears to be linked to non-standardized pre-analytical and post-analytical processes rather than the antibodies and methods used.

Amplification was detected by FISH in one patient who had (+) IHC in our unit. On re-evaluation of hematoxylin-eosin stained tumor sections of this case, it was noticed that tumor morphology was not optimal due to pre-analytical process problems. The IHC result of the slide with fixation problems was evaluated as (+). In this case, amplification was detected by FISH technique. FISH is the least affected method by pre-analytical processes and results in the least damage to the tissue. FISH to determine HER2 status is considered the gold standard (12). Disadvantages of FISH analysis are the long technical procedures, signals fading over time, and failure to store

Table 7. Correlation of HER2 expression and amplification in consult and non-consult cases

	Immunohistochemistry		HER2 Amplification		Total
	HER2		negative	positive	
Non-consult	HER2 expression	(-)	64	2	66
		(+)	14	1	15
		(++)	42	15	57
		(+++)	0	41	41
Consult	HER2 expression	(-)	57	1	58
		(+)	14	0	14
		(++)	28	7	35
		(+++)	1	21	22
		Total	220	88	308

HER2; Human epidermal growth factor receptor 2 oncoprotein

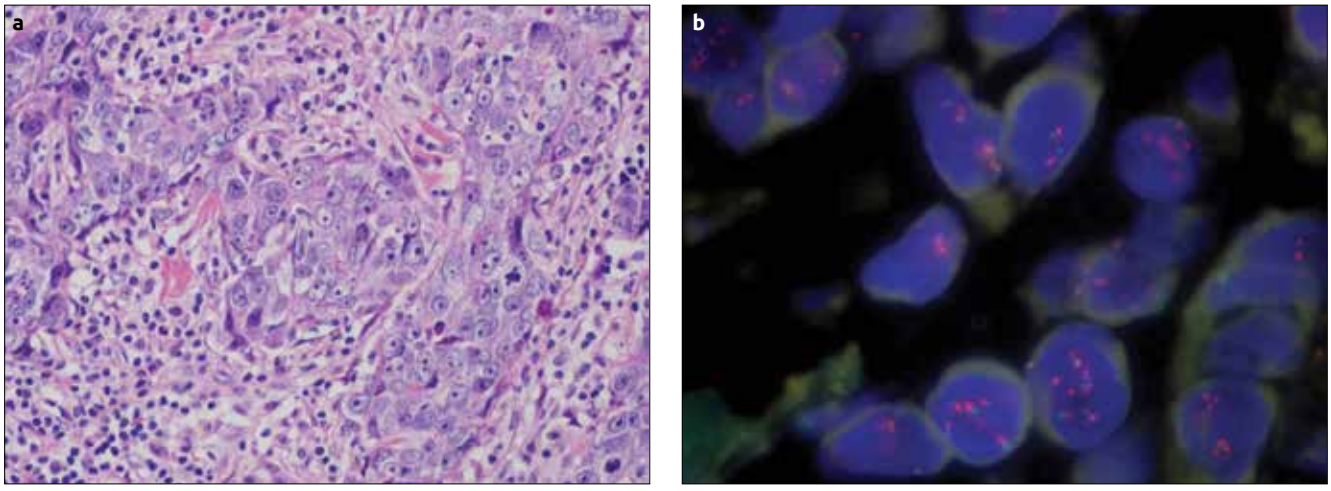

Figure 1. a, b. a) High-grade solid tumor islands containing lymphocytic infiltrate (HE, 20x), b) fluorescence in situ hybridization (FISH) amplified cells scattered between non-amplified cells (100x)

slides for a long-term, requirement of fluorescence microscopy and expertise for evaluation. It is very difficult to assess histomorphology under fluorescent microscope. Therefore, the SISH and CISH methods have been developed that enable assessment by light microscope. With these methods, it is possible to evaluate morphology and archive slides for long-term.

In the literature, the incidence of amplification in IHC (++) cases have been reported as 6-25% (10, 11). ASCO / CAP stated this rate as 23.9% (8). In our study, amplification was observed in 22 out of 92 IHC (++) (23.9%), the compatibility between IHC and FISH was calculated as 98.4%.

The prospective subgroup analyses of adjuvant randomized trastuzumab studies have shown the misinterpretation rate of HER2 protein expression level as 20% (13, 14). In this study, we also re-evaluated cases with incompatible IHC and FISH results. It was found that one case with (+++) IHC and no amplification had a tru-cut biopsy. Nowadays, tru-cut breast biopsies are commonly used for both diagnostic and therapeutic purposes. Thus, hormone receptor status and HER2 expression level can be determined in patients who will receive neoadjuvant chemotherapy. In the literature, concordance between tru-cut biopsy and excisional biopsy in terms of HER2 IHC evaluation was reported to be 87-98.8% (15, 16). Chivukula et al. (17) even stated that tru-cut biopsies are more reliable in IHC and ISH since they do not have any fixation problems. However, tru-cut needle biopsies only sample a small area of the tumor and can have false (-) results especially in heterogeneous cases. On re-evaluation of our tru-cut biopsies, it was seen that they were extremely thin and contained severe compression artifacts. Therefore, non-specific cytoplasmic and granular staining was interpreted as complete membranous positivity. Although tru-cut biopsies harbor less fixation problems interpretation of IHC score is difficult if compression artifact is present. In these cases, confirmation of IHC by any ISH method will be appropriate.

Mixed probes including the centromeric region of the chromosome are recommended for assessment of HER2 amplification. When both gene regions are amplified, the HER2 / CEP17 rate may be below the limit of amplification. How this condition affects response to treatment is still controversial. Hofmann et al. (18) reported that in 2 IHC (+++) cases with amplification in Chr centromere, FISH was negative and these patients were positive responders to trastuzumab therapy. Ultimately, it was suggested that, HER2 gene copy number might be more important than the ratio in determining the response to trastuzumab. One of the handicaps of ASCO / CAP criteria is situations when both gene regions are

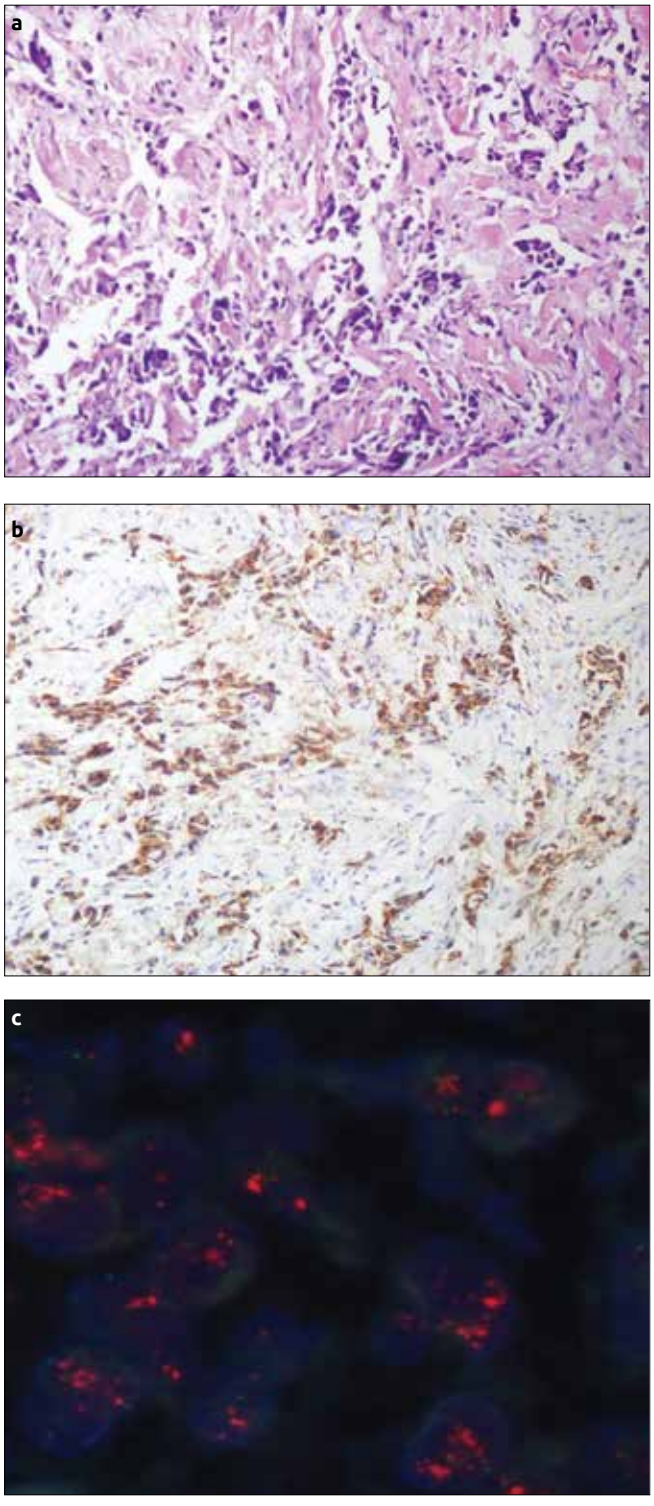

Figure 2. a-c. a) Tumor cells with pre-analytical problems (HE, 10x), b) HER2 (+) tumor cells by immunohistochemistry (DAB, 10x), c) diffuse amplification with FISH (100x)

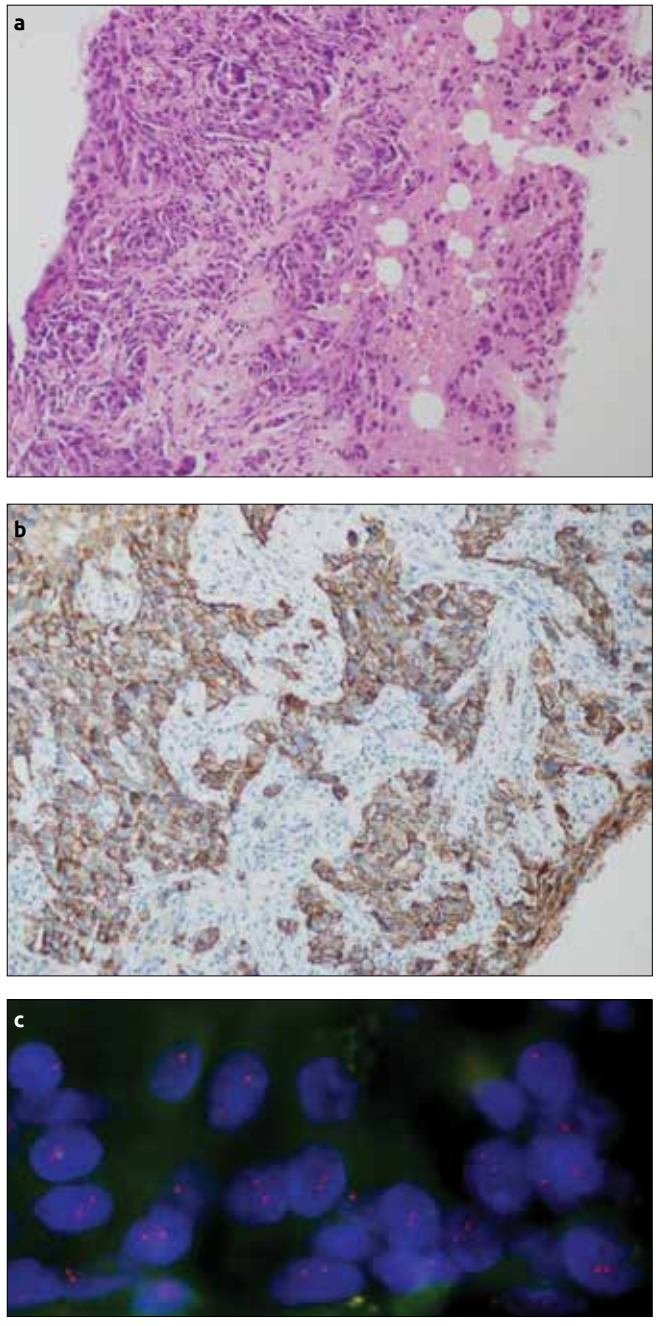

Figure 3. a-c. a) Thin tru-cut biopsy with compression artefact (HE, 10x), b) Tumor cells assessed as (+++) HER2 by IHC due to artefacts (DAB, 20x), c) Tumor cells with no HER2 amplification by FISH (100x)

amplified. Patients who would be considered as amplified based on the number of HER2 copies, remain below the amplification limit if rate is considered. Therefore, modification of ASCO / CAP criteria is proposed.

Previously centromeric gene region amplification was considered as Chr 17 polysomy. Recently many genes on Chr 17 were examined simultaneously by comperative genomic hybridization (CGH) method and it was detected that real polysomy is extremely rare (19). However, amplification is frequent in pericentromeric gene regions of HER2 (-) and (+) cases. In Chr 17 aneusomy with pericentromeric rearrangements, the aberrant patterns (clusters) observed in the centromeric region leads to misinterpretation of HER2 / Chr 17 rate (20). In this situation, the individual number of monitored signals in HER2 and centromere region should be specified. We also observed Chr 17 centromere region amplification in 11 cases. Nine cases were evaluated as (++), and two as (+++). In six of these cases focal low-level, and in one case diffuse high-level amplification was observed. In these cases, when assessing amplification individual signal number of these regions were taken into consideration as well as HER2/ Chr 17 rate.

In this study, one noteworthy aspect was detection of focal heterogeneous low-level amplification by FISH technique in three cases that

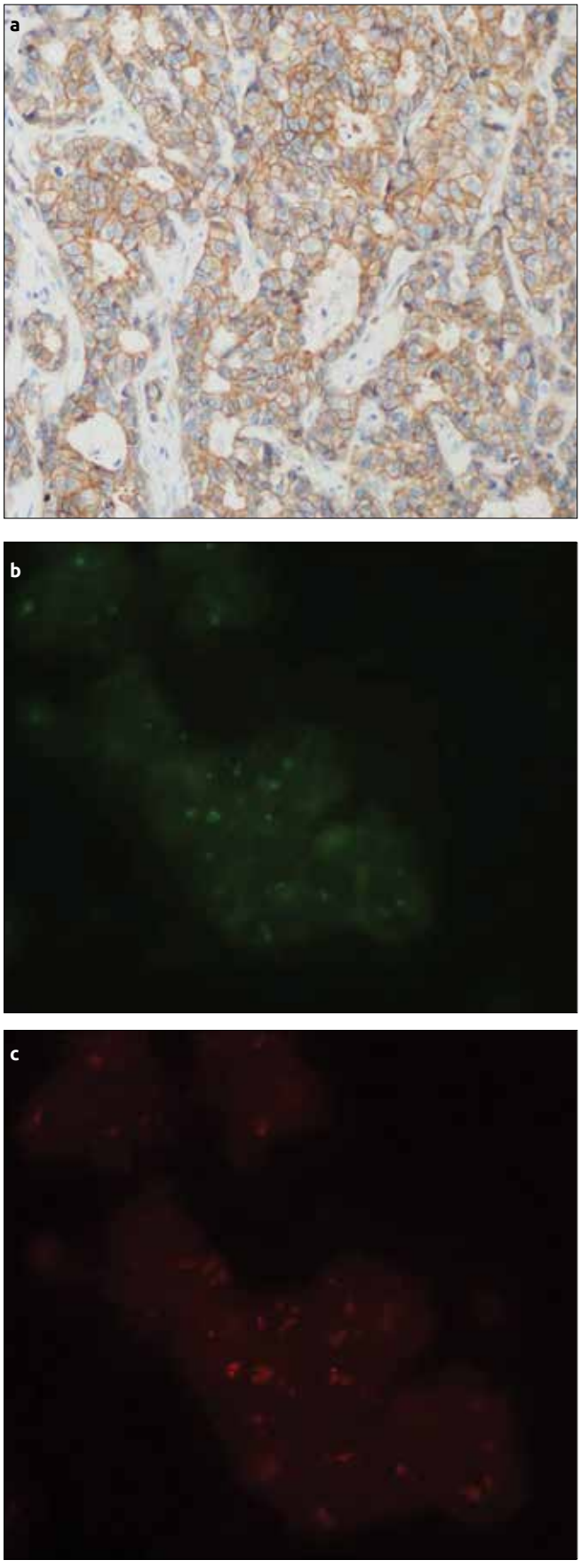

Figure 4. a-c. a) IHC HER2 (++) tumor (DAB, 20x), b) Amplification of Chromosome 17 centromere region (green filter) and c) HER2 gene region (red filter) by FISH (100x)

were triple (-) (ER, PR, cerbB2 ((-)) by IHC. Amplification was observed as small amplified clones (amplification in ≤ 5% neoplastic cells) in all cases. Bernasconi et al. (21) reported small amplified clones in 27 out of 291 cases. Two of these 27 cases were IHC negative and one was triple negative. The existence and meaning of focal low level of HER2 amplification in triple negative cases should be examined in larger series.

Recent studies indicate the presence of genetic heterogeneity in breast tumor (21). IHC may be insufficient due to compression artifacts and genetic heterogeneity in tru-cut biopsies that are increasingly being used in routine clinic practice. In these cases, the addition of an ISH method to IHC will contribute to the accurate determination of HER2 status. In addition, when reporting ISH method in any type of material distribution and number of amplified cells, the type of amplification (low-high / diffuse-focal), and whether amplification of chromosome 17 centromere region accompanies or not should be indicated. In service training on standardization of pre-analytical, analytical, and post-analytical processes should be more comprehensive.

Ethics Committee Approval: Due to the retrospective design of the study, ethics committee approval was not taken.

Peer-review: Externally peer-reviewed.

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Original Article

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The Effect of Socio-Economic-Cultural Factors on Breast Cancer

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ABSTRACT

Objective: Socioeconomic and cultural factors influence breast cancer prognosis. The effect of these factors on breast cancer was evaluated among women who live in Gaziantep and its surroundings.

Materials and Methods: female patients who were admitted to Gaziantep University Oncology Hospital with a diagnosis of breast cancer between October 2006-July 2013 were included in the study. The effects of socio-demographic characteristics on clinical-pathological features were evaluated.

Results: The mean age of 813 women was 48.8 years. The majority were premenopausal women. Advanced stage disease on diagnosis was detected more in our region. The rate of breast cancer with unfavorable prognostic features was higher among patients who were illiterate, with low economic income and residing in rural areas.

Conclusion: Socioeconomic-cultural factors influence the biology and clinical course of breast cancer among women who live in Gaziantep province.

Keywords: Breast cancer, socioeconomic status, hormone receptor status

Introduction

Breast cancer is one of the major health problems worldwide with increasing prevalence and accounts for approximately 30% of all cancers in women. The incidence of breast cancer may vary between different countries. Additionally, the incidence and prognosis of breast cancer may vary within the same society, and since a definite reason for breast cancer is yet unknown, these differences are linked to environmental factors, lifestyle and socioeconomic-cultural factors (SECF) (1).

It is estimated that the incidence of breast cancer between the eastern and western regions of our country may vary. Based on regional and SECFs, stage on diagnosis and therefore treatment may differ (2). For these reasons breast cancer prognosis may different between regions.

SECFs like patient education status, place of residence, household income level and health insurance can influence consulting a doctor and treatment options. In this study, the relationship between SECF and with clinical-pathological features of patients who reside in the city of Gaziantep and its surrounding provinces and were diagnosed with breast cancer in Gaziantep University Oncology Hospital.

Materials and Methods

A total of 813 female patients who were admitted to Gaziantep University Oncology Hospital with a diagnosis of breast cancer between October 2006-July 2013 were included in this study. Gaziantep University Ethics Committee approved the study, and verbal or written consent was obtained from all patients.

Patient age on diagnosis, place of residence (rural-urban), education level, household income level [(<500 TL), (500-1500 TL) and (>1500 TL)], and menopausal status, were obtained by one-to-one interview with the patient and were recorded by an author (AK). Patients over 40 years of age (after 40 years of age and at least 2 years before the diagnosis) were questioned whether they had a screening mammography or not, and their answers were recorded (AK). Other medical information related to histopathological diagnosis, and stages were extracted from patient files and were recorded by the authors (AK and MA).

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Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 19.0 software (IBM SPSS Statistics, New York, USA) was used for analysis. Data were analyzed using descriptive statistical methods (number, percent, mean). The impact of SECF on the clinical-pathological findings was evaluated by the chi-square test, and the effect of SECF on the time elapsed from first sign of the disease to diagnosis was analyzed using ANOVA test. p values <0.05 were considered statistically significant.

Results

The mean age at diagnosis of breast cancer patients included in the study was 48.8 (20-84) years. The majority of patients were postmenopausal as compared with premenopausal disease, 57.9% (n = 471) and 42.1% (n = 342), respectively. Demographic characteristics of the patients and tumor characteristics are shown in detail in Table 1.

Fifty-six % of patients consulted a doctor with complaints of a breast mass as the first symptom. This was followed by pain in 14%, swelling and stiffness in 13.8%, redness in 6.2%, and by other complaints in 10% of patients. The mean time elapse between first signs of disease and diagnosis was 6.5 (1-55) months. Screening mammography rate in patients over the age of 40 living in our area was quite low (5.2%).

Eighty-nine.six % of invasive breast cancers were invasive ductal carcinoma, 4.9% were invasive lobular, 1.5% were of mixed type and 4% were other subtypes. The median tumor size was 3.7 cm (0.5 to 7.2). The T stage of patients on diagnosis was T1 in 9.3% (n = 76), T2 in 54.6% (n = 444), T3 in 21% (n = 171) and T4 in 13.5% (n = 110). The rate of advanced stage disease (stage 3, 4) on diagnosis was 53%, and early stage disease (stage 1, 2) rate was 47%.

Estrogen receptor (ER) positive tumor rate was 71%, progesterone receptor (PR) positive tumors accounted for 71.3%, and Human epidermal growth factor receptor-2 (HER2) positive tumor rate was 31.9%. Histological grade 2 and 3 tumors had a higher rate; 42.9% and 44.3%, respectively.

Eighty.six % of patients (n = 655) were living in urban (city / county) areas, while 19.4% (n = 158) lived in rural (village / town) areas. Approximately half of the patients were illiterate (47.7%) and the proportion of household income under 500 TL was 22.9% (n = 186).

Although screening mammography rate was quite low in our study among women older than forty years of age, it was found that SECF may affect these rates. Screening mammography rates increased with a higher level of education (college graduates) and a higher economic income level (> 1500 TL). The rate of screening mammography was 2.5% in illiterate patients, was 10% in junior high graduates, and was 15% in university graduates (p <0.001). This rate was 2% in patients with a low economic income (< 500 TL), while this rate was found as 8% in patients with high income (>1500 TL) (p = 0.02). The effect of residence area on the rate of mammography imaging was close to statistical significance. This rate was 0, 5% among those living in urban areas, while it was found as 0.2% for those in rural areas (p = 0.09).

When time elapsed between the date of first disease symptom and diagnosis was evaluated in terms of residence area, economic income and educational status; patients living in rural areas in about 6 months, while this period was 9 months for patients living in urban areas (p

Table 1. Sociodemographic and clinical properties of patients

Variable	Patient n (%)
Age at diagnosis	
20–39	196 (24.1)
40–49	258 (31.7)
50–64	255 (31.4)
65 ve üzeri	104 (12.8)
Menopausal status	
Premenapausal	471 (57.9)
Postmenapausal	342 (42.1)
Histopathology	
Invasive ductal	729 (89.6)
Invasive lobular	40 (4.9)
Mucinous	12 (1.5)
Mixed type	12 (1.5)
Other	20 (2.5)
Histologic Grade	
I	43 (5.3)
II	349 (42.9)
III	360 (44.3)
Unknown	61 (7.5)
Disease stage	
I	32 (3.9)
II	350 (43.1)
III	362 (44.5)
IV	69 (8.5)
ER status	
ER+	577 (71)
ER–	227 (27.9)
Unknown	9 (1.1)
PR status	
PR+	580 (71.3)
PR–	221 (27.2)
Unknown	12 (1.5)
HER2 status	
HER2+	259 (31.9)
HER2–	544 (66.9)
Unknown	10 (1.2)
Education level	
None	388 (47.7)
Primary school	268 (33)
Junior-high school	48 (5.9)
High school	63 (7.7)
University	46 (5.7)
Residence	
Urban	655 (80.6)
Rural	158 (19.4)
Economy[a]	
<500 TL	186 (22.9)
500–1500 TL	309 (38)
>1500 TL	318 (39.1)
Treatment type	
Surgery	731 (89.7)
Chemotherapy	695 (85.4)
Radiotherapy	535 (65.8)
Hormonotherapy	516 (63.4)

[a]Monthly family income level
ER: Estrogene receptor, PR: Progesteron receptor
HER2: Human epidermal growth factor receptor-2
n: Patient number

Table 2. Effect of sociodemographic properties on HRS, tumor size, stage and tumor grade

		Education level, n (%)					Economic Income (TL), n (%)			Place of Residence,n (%)		
		None	Primary	Junior high	High school	Univesity	<500	500–1500	>1500	Urban	Rural	P*
Hormone receptor status	ER+	259 (67.6)	202 (76.2)	30 (63.8)	49 (77.7)	37 (80.4)	123 (66.5)	204 (67.5)	250 (78.9)	478 (73.5)	99 (64.2)	<0.03
	ER-	124 (32.4)	63 (23.8)	17 (36.2)	14 (22.3)	9 (19.6)	62 (33.5)	98 (32.5)	67 (21.1)	172 (26.5)	55 (35.8)	
	PR+	258 (67.5)	211 (80)	32 (68)	44 (71)	35 (76)	120 (64.8)	220 (73)	240 (76.2)	479 (73.9)	101 (66)	<0.04
	PR-	124 (32.5)	53 (20)	15 (32)	18 (29)	11 (24)	65 (35.2)	81 (27)	75 (23.8)	169 (26.1)	52 (34)	
	HER2+	128 (33.3)	87 (33)	15 (31.9)	22 (34.9)	7 (15.2)	65 (35.1)	97 (31)	97 (30.9)	201 (31)	58 (37.4)	>0.1
	HER2-	256 (66.7)	176 (67)	32 (68.1)	41 (65.1)	39 (84.8)	120 (64.9)	207 (69)	217 (69.1)	447 (69)	97 (62.6)	
Tumor size	<2 cm	21 (5.5)	29 (10.9)	4 (8.7)	13 (20.9)	9 (19.6)	9 (4.8)	20 (6.6)	47 (15)	66 (10.2)	10 (6.5)	<0.003[a]
	2–5 cm	206 (54)	147 (55.5)	30 (65.2)	36 (58.2)	25 (54.3)	81 (44.1)	186 (61.2)	177 (56.6)	361 (55.9)	83 (53.5)	
	>5 cm	155 (40.5)	89 (33.6)	12 (26.1)	13 (20.9)	12 (26.1)	94 (51.1)	98 (32.2)	89 (28.4)	219 (33.9)	62 (40)	
Disease stage	1	8 (2)	13 (4.9)	1 (2.1)	6 (9.5)	4 (8.7)	2 (1.1)	10 (3.2)	20 (6.3)	26 (4)	6 (3.9)	<0.02
	2	155 (39.9)	120 (44.7)	24 (50)	32 (50.8)	19 (41.3)	56 (30.1)	147 (47.6)	147 (46.3)	288 (44)	62 (39.2)	
	3	177 (45.6)	120 (44.7)	21 (43.8)	22 (34.9)	22 (47.8)	112 (60.2)	130 (42.1)	120 (37.7)	295 (45)	67 (42.4)	
	4	48 (12.5)	15 (5.7)	2 (4.1)	3 (4.8)	1 (2.2)	16 (8.6)	22 (7.1)	31 (9.7)	46 (7)	23 (14.5)	
Tumor grade	1	17 (4.8)	17 (6.8)	4 (8.7)	1 (1.6)	4 (9.3)	10 (5.7)	17 (5.9)	16 (5.6)	39 (6.4)	4 (2.8)	>0.2
	2	174 (49.2)	113 (45.4)	22 (47.8)	19 (31.7)	21 (48.9)	72 (41.1)	130 (44.7)	147 (51.4)	279 (45.9)	70 (48.6)	
	3	163 (46)	119 (47.8)	20 (43.5)	40 (66.7)	18 (41.8)	93 (53.2)	144 (49.4)	123 (43)	290 (47.7)	70 (48.6)	

[a]There was no statistically significant correlation between place of residence and tumor size (p:0,1), n: Patient number
HRS: Hormone receptor status, ER: Estrogene receptor, PR: Progesteron receptor, HER2: Human epidermal growth factor receptor–2
* Chi-square

<0.02). The elapse was 4.3 months in high economic income level (> 1500 TL) (p <0.001), and 3.7 months in university graduates (p = 0.01).

The effects of socio-demographic characteristics on histopathologic properties are shown in detail in Table 2. When tumor size and disease stage was evaluated in terms of residence area, economic income and educational status; advanced stage disease (stage 3, 4) was significantly higher in those with low economic income, who are illiterate and living in rural areas (p <0.003). There was no relationship between tumor size and residence area, while there was a relationship between economic status and education level (Table 2).

When hormone receptor status (HRS; ER, PR) and HER2 status were evaluated in terms of educational level, economic income and residence area; patients with low-education and low economic income had significantly higher rates of ER-negative and/or PR-negative tumors (p = 0.001). However, no difference was found between HER2 rates. In addition, residents in rural areas had a greater proportion of HR-negative tumors (p <0.004, Table 2).

Discussion and Conclusion

The incidence and prognosis of breast cancer can vary among different geographic regions of the same society. Despite advances in diagnosis and treatment of breast cancer, these differences remain constant (3, 4). Ethnicity, environmental and socioeconomic factors, lifestyle, treatment compliance and differences in treatment response are implicated as reasons for these differences (5-7). It is estimated that incidence and prognosis of breast cancer vary between eastern and western regions of our country due to different lifestyles, educational status and breast cancer awareness (2). The effect of such factors on breast cancer is well

known in western society; however, there is no known study in our country regarding this issue. In this study, it was found that SECF of patients diagnosed with breast cancer in Gaziantep province may be associated with clinic and pathological features of breast cancer, and that it may be associated with negative prognostic features in women with disadvantages.

Criteria determining socioeconomic-cultural factors may vary among countries. Generally, household income level, education level, health insurance status and residence area are indicated among SECF. Ethnicity is also an important parameter for determining SECF in western studies. However, this factor was not considered in our study due to insufficient data regarding ethnicity of the patients.

Socioeconomic-cultural factors that may have either positive or negative effects on breast cancer clinic and biology is a complex process. The incidence of breast cancer is low among women with low SECF, while their prognosis is worse (8). Studies have found that women with low SECF have more unfavorable prognostic features, and their prognosis was therefore adversely affected (9-13). For example, lifestyle habits such as smoking, alcohol use and physical activity may affect HRS that is an important prognostic factor. Smoking and alcohol use is reported to be associated with HR-negative breast cancer (14-15). Personal habits such as physical activity and dietary intake of fiber have been shown to reduce HR-negative breast cancer rate, and this situation has been associated with SECF (16-20). Increasing awareness on breast cancer is also associated with SECF, and participation in mammography screening programs has been reported to affect HRS. It was stated that slow progressive ER-positive breast cancer can be detected in higher rates in women with higher SECF, possibly due to higher compliance with screening mammography (21-23). Therefore, the rate of HR-negative tumors can be higher in women with low SECF. Since participation in screening programs is significantly lower among these individuals, they are diagnosed at more advanced stages and their chances of accessibility to standard treatment is limited (24). In addition, women with low SECF are more likely to be exposed to organochlorine that is used in agriculture fields and has been reported to be associated with ER-negative breast cancer (25-27). Disadvantaged women are diagnosed with disease at an earlier age, and prognosis is worse in this patient group (3). In addition, serious problems are observed among disadvantaged women in both access to treatment and treatment compliance (6, 28). As a result, the prognosis of breast cancer in these patients is worse as compared to patients with high SECF.

Ethnicity is accepted as an important SECF parameter for breast cancer in western studies, and African-American women usually represent lower SECF. In patients with low SECF, larger tumor diameter, more nodal metastases and ultimately more advanced stage disease are detected on diagnosis. McBride and colleagues (29) reported larger tumor size and more nodal spread in African-Americans as compared to Caucasians. In accordance with the literature, although ethnicity was not taken into account, larger tumor size and more advanced stage disease was detected on diagnosis in patients with low SECF in our study.

Twelves and colleagues (30), and Thomson and colleagues (31) evaluated the relationship between SECF and tumor histological grade and HRS among Caucasian European women with breast cancer, in two separate studies. They both reported a significantly higher rate of negative prognostic factors, ER-negative tumors and high-grade tumors, in women with lower SECF. Gapstur and colleagues (32) detected higher incidence of ER-negative and grade 3 tumors in African-American women as compared to Caucasian women. Recently, in a study conducted by Bhoomi-Pathy et al in Southeast Asia (Malaysia and Singapore) (33), it was stated that a higher rate of ER-negative and undifferentiated tumors were detected in Malaysian women with lower SECF than those with higher SECF. Similarly, in our study, the rate of ER-negative and/or PR-negative tumors was found higher in patients with SECF disadvantages. However, there was no difference in tumor grade.

In western studies, access to and compliance with treatment are also closely related to SECF. When patients were standardized according to tumor characteristics and age at diagnosis, African-American women with lower SCF had significantly lower chance of obtaining systemic and topical treatments as compared to Hispanic-American women (34). However, in our study, there was no difference between compliance and access to treatment among patients. Western studies indicate regional differences and religious factors to play a role, whereas in our study these factors did not have an impact.

In conclusion, more premenopausal and advanced stage disease was detected on diagnosis of breast cancer at our region. It was determined that SECF influences breast cancer clinics and biology. Further studies are required in this regard, and programs should be developed to increase the awareness of breast cancer in the society.

Ethis Committee Approval: The study is approved by Gaziantep Üniversity Local Ethical Committees.

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

Peer-review: Externally peer-reviewed.

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Original Article

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Evaluation of Breast Cancer Cases Diagnosed In the Breast Cancer Screening Program In the Near East University Hospital of North Cyprus

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ABSTRACT

Objective: This study is about determination and eveluation of the breast cancer cases which were diagnosed during the early diagnosis and screening programs covering a three years of digital mammography images at the Near East University Hospital.

Materials and Methods: This study covers 2136 women patients who applied to the early diagnosis and screening program of the Near East University Hospital between July 2010 and July 2013. The mamographic images were re evaluated retrospectively according to ACR's (The American College of Radiology) BİRADS (Breast Imaging Reporting and Data System). The mamographic results as required were correlated with breast ultrasound (US) and compared with the pathologic results of materials obtained by surgery or biopsy. The results were analyzed statistically in comparison with the literature data.

Results: The women who were screened aged between 34-73 years with a median of 53.5 (SD = 27.5). Suspected malignancy were evaluated in 54 patients, which 42 of them were diagnosed BIRADS 4 and 12 patients BIRADS 5 and 21 patients were correleted breast cancer based on histopathologic examination. 17 patients had the breast-conserving surgery and 4 patients were treated with mastectomy.

Conclusion: Breast cancers that are detected at early stages by breast cancer screening tests are more likely to be smaller and still confined to the breast resulting in more simple operations and more succesfull treatment. Promoting the breast cancer screening and registration programs in our country will help to control the desease at our region.

Keywords: Mammography, breast cancer, screening program

Introduction

Breast cancer is the most common primary cancer in women, and the second leading cause of death in women after lung cancer (1). Treatment is more successful when diagnosed in early stages by screening methods. Epidemiological studies have shown that advanced age, history of breast cancer in first degree relatives, early menarche, late menopause, late term pregnancy , lack of breast-feeding , obesity, hormone replacement therapy after menaupose are important risk factors for the development of breast cancer. In addition, BRCA 1,2 mutations in familial cases have also been demonstrated (2).

Determining the exact frequency of breast cancer in a country is difficult when there is no regular breast cancer screening and monitoring program, despite individual breast cancer screening practices in various institutions. This study aimed to retrospectively evaluate 2136 women's mammography images, that were obtained over a three year period as part of a breast cancer screening program implemented on 2010, together with additional imaging tests performed if required.

Materials and Methods

In this study, digital mammography images of 2136 cases obtained between 20.07. 2010- 20.07.2013 as part of a screening program (GE Healthcare Senographe Essential Stereotaxy) were evaluated retrospectively. Patients with a mammography from other centers, those who were referred for diagnosis rather than screening, and those who had previous operation due to breast cancer were excluded.

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Table 1. Number of women according to check-up and screening dates. Number of patients diagnosed by radiologic evaluation, BIRADS and histopathologic diagnosis

Parameters	20.07.2010- 20.07.2011 (Case number (n))	20.07 2011- 20.07.2012 (Case number (n))	20.07.2012- 20.07.2013 (Case number (n))
Women applying to check-up and screening programs	1134	581	421
Radiologic Mammography	11	8	13
Patients with suspicious malignancy findings onbilateral breast ultrasonography and mammography	7	9	6
BIRADS-4	13	14	15
BIRADS-5	5	3	4
Histopathology			
Invasive ductal	4	3	4
Invasive lobular	1	-	1
Mucinous carcinoma	1		
DCIS			
Other carcinoma	3	1	3

BIRADS: Breast Imaging Reporting and Data System
DCIS: Ductal Carcinoma in situ
USG: Ultrasonography

An ethical approval was obtained from Near East University Hospital medical research ethics committee, and informed consent was obtained from all participants. All data were coded numerically. Arithmetic mean, standard deviation, number, and percentage calculations were used for analysis. The MMG and USG evaluations were performed according to The American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) (3).

Statistical Analysis

The World Health Organization (WHO) International Agency on Research on Cancer (IARC) calculated 460,000 deaths from breast cancer in 182 countries in 2008 (4). Breast cancer incidence shows serious geographical differences. The incidence of 102 / 100,000 in the Northern European countries is decreased to 70 / 100,000 in the south, and to 47 / 100,000 in the east. The breast cancer incidence in countries such as Netherlands, Denmark, Finland and the UK, countries with older female population, less women giving birth and decreased number of births, is very high (92, 86, 78 and 75 in a thousand, respectively), while in some Mediterranean countries with more conservative fertility characteristics and eating habits as compared to other European countries (48 in one hundred thousand in Greece and Spain), the incidence is lower. The 50% reduction in mortality in the United States, which occurred in the last 25 years, is attributed to early diagnosis with screening and effective treatment (5,6).

Results

The age range in our study was 34-73, with a median age of 53.5 years (SD = 27.5). Three women under the age of 40 years underwent mammography due to a family history of breast cancer. Bi-directional (MLO, CC) bilateral MMG images were obtained during routine screening. Additional views were obtained in 143 cases (spot and spot compression magnification) , in addition to bilateral breast and axillary ultrasound in 502 cases.

Seven hundred eighty four women (36%) were premenopausal, while 1352 (64%) were post-menopausal. Eighty percent of women had given birth at least once, and 52.3% of those breastfed their children for at least 6 months.

It was found that 37% of women regularly performed BSE (breast self-exam), 59% did not know how to perform the examination or did not perform, and 4% was reluctant to examine their selves. In our study, 31.8% had family history of malignancy other than breast and 16.4% had family history of breast cancer.

A total of 54 patients (2.5%) (32 MMG and 22 bilateral breast USG) had suspicious findings that may be related to breast malignancy. The age range of these patients was 40-72, with a median age of 56 years (SD = 2.6). Suspicious lesions were as spiculated masses, spiculated masses in 15 out of 32 patients, spiculated mass and microcalcification cluster in 9, only pathological microcalcifications in 3, and radial scar in 5 cases. Eighty six percent of patients with suspicious of malignancy had these findings on mammographic imaging only and 14.3% had suggestive findings on both mammography and bilateral breast ultrasound. Forty-two out of 54 patients with breast lesions were evaluated as BI-RADS 4, and 12 as BIRADS 5, and tissue diagnosis was recommended for these patients. Eighteen BI-RADS 4 cases did not accept any further tests, and were lost to follow-up. Four patients with suspicious findings in terms of malignancy who refused biopsy had stable lesions that are being followed-up. Twenty BI-RADS 4 patients and 12 BI-RADS 5 patients accepted tissue diagnosis.

Ultrasound guided tru-cut biopsy was applied in15 out of 32 cases with a palpable mass on physical examination. There were 17 non-palpable lesions, 14 patients had USG guide-wire insertion, and 3 had MMG guided insertion, followed by excision. All non-palpable lesions that were excised with guide-wire were confirmed by specimen x-ray 8USG or MMG) after excision. Nine BI-RADS 4 patients out of 20 (45%) with tissue diagnosis, and all 12 BI-RADS 5 patients (100%)

were diagnosed with breast cancer on pathologic examination (Table 1). Four patients underwent mastectomy and 17 had breast-conserving surgery. The pathologic evaluation revealed ductal carcinoma in situ in 7 cases, invasive ductal carcinoma in 11, invasive lobular carcinoma in 2, and mucinous carcinoma in 1 case. The rate of breast cancer diagnosed with screening was found to be 0.98%.

Discussion and Conclusion

Mammography and clinical breast examination facilitates the early detection and treatment of breast cancer, and are reliable methods to reduce the mortality rate. Their main advantage is detection of breast cancer before it can be detected as a palpable lesion (7). Mammography was used for the first time in 1913 in order to show the spread of the tumor to the axilla, the importance of accurate positioning and compression could only be understood in the 1950s (8). The use of mammography as a screening method reduced breast cancer mortality rate by at least 25% (9). The American Cancer Society recommends a baseline mammography between ages 35-39, followed by annual repetitions after 40-years (10). Detection of microcalcifications in 20-25% of all cancer cases emphasizes the importance of mammography for early diagnosis. Microcalcifications are the major finding in mammography (11,12). In our study, 59.2% of patients suspected for malignancy were diagnosed with mammography, and the incidence of pathological microcalcifications was found as 25.9%. In addition, the radiation dose was 0.1 -0.2 rad, which is within safety limits (13). There are no studies showing the contribution of screening with USG on breast cancer mortality. However, various studies focused on the affect of USG on breast cancer diagnosis, especially in women with mammographic dense breast tissue. These studies reported that USG can detect lesions undetectable by MMG in women with dense breast tissue, and the sensitivity of mammography was found as 78%, while this rate was 91% when MG and USG were used in combination (14). However, the specificity of ultrasonography is reported to be low with high false positivity rates, leading to unnecessary biopsies (14).

Screening methods are useful only when applied regularly. Cancers occurring in-between two scans are called interval cancers. It is more commonly seen in young women, and the prognosis of interval cancers is worse. Therefore, application of screening methods at appropriate intervals and frequency is important for early diagnosis (15).

The lifelong of breast cancer incidence of a 50-year-old woman during her remaining life is approximately 10% (16). In our study, the median age of women diagnosed with breast cancer was 56 years (SD = 22.6). It is stated that breast cancer is nowadays being detected at an earlier age. Breast cancer is rare under the age of twenty years. The incidence steadily increases after 20 years of age, and reaches a plateau between 45-55 years. A rapid rise in incidence is observed after 55 years (17). It is most common in developed countries, and least common in underdeveloped countries in Asia and Africa. When standardized by age, the rate in North America is 99 / 100,000, while this rate in Central Africa is 17 / 100,000. Breast cancer incidence in the world shows a 0.5% increase annually since 1990. The annual increase rate in China is about 3-4%. 15 years ago, cervical cancer was the most common cancer in India, whereas currently breast cancer has become the most common female cancer (18). In the current study, breast cancer rate diagnosed with screening was found to be 0.98% only in a certain area of Cyprus.

Breast cancer is the most common malignancy in the female population in Europe and North America, an estimated 1 out of 9 women are at risk of developing the disease (19). More than 10% of breast cancer in Western countries indicate genetic predisposition. Although there are no regular studies on breast cancer incidence in Northern Cyprus, according to data from a Southern Cyprus (Republic of Cyprus) study on the etiology of 1109 histopathologically diagnosed breast cancer, nulliparity, lack of breast-feeding, and family history of breast cancer were shown to be main disease-related risk factors in Cyprus population (19). In our study, the presence of family history of malignancy other than the breast in 32%, and family history of breast cancer in 16% in our patients with breast cancer was found to be interesting.

Early diagnosis is important in the treatment of breast cancer, and the positive contribution of breast cancer screening programs in morbidity and mortality has been shown in many studies. Although it has some disadvantages and therefore, some opposing views, MG is a screening method with proven efficacy. However, 5-10% of breast cancers are detected by physical examination without mammographic findings. Therefore, clinical breast examination should be performed in conjunction with screening mammography. The development of screening and recording programs for early diagnosis of breast cancer, which is a very important issue throughout the world as well as Northern Cyprus, and the development of recording programs, and implementation of standardized, modern treatment and follow-up programs with quality control not only in certain institutions but nationwide is extremely important.

Ethis Committee Approval: Ethics committee approval was received for this study from the ethics committee of Near East University Hospital.

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

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Original Article

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Barriers on Breast Cancer Early Detection Methods

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ABSTRACT

Objective: Breast cancer is the most common type of cancer in women throughout the world. It is the second leading cause of cancer related deaths, after lung cancer. Breast cancer is the most common cancer in women in Turkey with a rate of 23,4%. One out of every four women has breast cancer. This study was conducted to determine the barriers on methods of early diagnosis of breast cancer.

Materials and Methods: The research population consisted of women over the age of 40 years who live in the neighborhood of Doğanlar (N=2404). The sample size was determined (n=251) with Epi İnfo Statcalc account program with 95% confidence interval, with the incidence of breast cancer accepted as 24%. Women over the age of 40 years who agreed to participate were included in the study. In order to collect the necessary data, a 27-item questionnaire including socio-demographic characteristics and methods of early diagnosis was created according to the literature. This study was conducted between March-October 2012 in Doğanlar neighborhood.

Results: Two-hundred-fifty-four women participated in the study, with a mean age of 54,27±1, and an average monthly income of 895,0197 TL (min=0 TL, max=7000 TL). 79,1% were married, 89,8% were housewives, 56,7% were literate, and 83,1% had health insurance. The status of performing regular Breast Self Examination (BSE) was significantly higher in women who had knowledge about BSE, (p=0.000). Married (p=0.015) women and those who had a social security system (p=0.048) had significantly higher rates of mammography. Women who were informed on mammography (p=0.000) had significantly higher rates of mammography. When reasons for not getting mammography was addressed, it was observed that 99,2% was due to lack of information and education. Women who had regular BSE had significantly higher Clinical Breast Examination (CBE) (p=0.024). Women's sociodemographic characteristics did not affect the status of performing regular BSE and CBE significantly.

Conclusion: Barriers against implementation of breast cancer screening methods in women were related to level of education and lack of adequate information about breast cancer screening, and symptoms of breast cancer. Women's lack of information about signs, symptoms and treatment in the early stages of breast cancer needs to be eliminated. Health care providers may have a key role in increasing breast cancer early detection rates.

Keywords: Breast cancer, early detection, barriers

Introduction

Breast cancer is the most common type of cancer seen among women in the world. It is the second leading cause of cancer death in women, after lung cancer (1, 2). Breast cancer ranks first among cancers seen in women in Turkey with a rate of 23.4%. One in every four women has breast cancer (3).

World Health Organization and International Agency for Research on Cancer report that, at least, 1/4 of all cancers can be prevented and 3/4 can be treated with existing knowledge, technology, and interventions based on screening in the next 20 years (4-6).

While some cancers seen in under-developed countries (liver, stomach, esophagus), offer poor prognosis, some cancers, seen in developed countries (prostate, breast, colorectal) have high survival rates in spite of high incidence rates (1, 6, 7). This result is related to early diagnosis and screening programs in developed countries (2, 4, 6).

Some type of cancers such as breast cancer can be diagnosed with a basic scan and be treated in a short time. Systematic screening programs are effective in the early diagnosis of breast cancer, in reducing the burden of disease in the community and in reducing the mortality (1, 3).

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The early diagnosis practices in breast cancer such as mammography, clinical breast examination (CBE) and breast self-examination (BSE) are vital in reducing cancer related death by providing early detection of breast cancer (1, 8).

American Cancer Society and the American Cancer Institute encourage women who show no signs to get a mammography each year at 40 years old and above, every three years at 20 to 40 years old, and then to get CBE once a year after 40 years old to be implemented by health-care workers trained in this regard. They also suggest that women should perform BSE starting from the age of 20, after being trained by health professionals (9, 10).

Early detection and screening is vital but there are some obstacles such as economic, cultural and personal factors. Identification of women's obstacles to the implementation of early diagnostic methods of breast cancer will give an opportunity to health care planning and create a resource to other areas. This research was conducted to determine the obstacles of breast cancer early detection methods.

Materials and Methods

This study is a cross-sectional field research, applied to women over 40 years old, living in a neighborhood of Izmir, between March and October 2012.

The study population consists of women over the age of 40 (N = 2404) years living in this neighborhood. Using Epi Info Statcalc calculator program (Epi Info, Atlanta, USA), the sample size was calculated as n = 251 with a breast cancer incidence rate of 24%, and with 95% confidence interval. 254 women over 40 years old were included into the study, after receiving their verbal informed consent. A 27-item questionnaire, prepared according to the literature, containing socio-demographic characteristics and breast cancer screening methods, was used to collect the required data.

The questionnaires were applied to 30 people apart from the research group, as a preliminary-application, and incomprehensible statements were corrected. The researchers were out to the area at 10:00 hours on certain days of the week, and filled-in the questionnaire with one-to-one interviews at homes. Participation is on a voluntary basis and verbal consent was obtained from patients who agreed to participate in this research study. Those women who could not be found at home and those who did not accept to participate in the study were excluded. The required permissions to collect data in the study region were obtained from Non-Invasive Clinical Research Board, İzmir Tepecik Training and Research Hospital, Ministry of Health of Turkey, and Directorate of Health Affairs, Bornova Municipality, that is responsible for the region.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 (SPSS Inc. Chicago, Illinois, USA) software package, the correlation between socio-demographic data and regular BSE, CBE and mammography were evaluated using chi-square analysis.

Results

The mean age of 254 women participating in the study was 54.27 ± 1, and the average monthly income was 895.02 Turkish Lira (TL) (min = 0 TL, max = 7000 TL). Seventy-nine percent of them were married, 89.8% were housewives, and 56.7% were literate only, and 83.1% had health insurance.

Socio-demographic characteristics of women did not affect significantly their status of exercising regular BSE and status of getting CBE. Status of getting mammography is significantly high in women who were married (p = 0,015) and had social security system (p = 0, 048) (Table 1). Fifty-three percent of women had information about BSE. When reasons for not getting mammography were addressed, it has been shown that 99.2% resulted from lack of information and education.

Status of practicing BSE regularly was significantly higher in those with information about BSE (p = 0,000). Women younger than or equal to 49 years of age were found to have significantly higher BSE information status as compared to those who were older than or equal to 50 years old (p = 0,020). A significant difference was found when women's level of education was compared to their status of BSE information (Table 2).

The status of getting mammography was significantly higher in women with information on mammography (p = 0,000) (Table 3). The status of getting CBE was found to be significantly higher in women who practiced regular BSE (p = 0.024) (Table 4).

Discussion and Conclusion

Four out of five women who participated in the study (83.1%) had health insurance. The levels of getting mammography of those who had health insurance were found to be high. The level of getting mammography was significantly higher in women who were married and had health insurance. Marital status of women or not having health insurance may interfere with status of getting mammography. Schootman et al. (11) found that status of health insurance affected the access to health care. Achat et al. (12) stated in their study that the rate of getting mammography was higher in women who were married or in a relationship (77.2%) than those who were single or divorced.

Women's descriptive characteristics did not significantly affect their status of practicing regular BSE and getting CBE. The status of practicing regular BSE, getting CBE and mammography were all significantly higher in women who were informed about these methods. Knowledge on breast cancer early diagnosis methods leads to application of these methods by women. 31.9% of women who participated in the study practiced BSE regularly. These findings are supported by similar studies (13, 14). 53.1% of women who participated in our study had knowledge about BSE while 86.4% of women who participated in study conducted by Ozen et al. (15) had knowledge about BSE. Forty-four percent of women had CBE at least once throughout their lifetime. However, Yavan et al. (16) reported that 33.0% of women (16) had CBE. Forty-seven percent of women who participated in our study did not have any information about mammography. Sixty-one percent of them did not get any mammography. Mammography rate in similar studies were also found to be low in parallel with our study (13, 14).

The most important barriers against obtaining screening mammography were lack of information about breast cancer and low level of education in 99.2% of women. Rızalar and Altay (17), and Meissner et al. (18) also stated in their studies that lack of knowledge on breast cancer was the main reason of not to obtain mammography.

The status of BSE knowledge in the group of women who were 49 years old and younger was significantly higher than those who

Table 1. Demographic cahracteristics, Regular BSE, CBE and Mammography Performance Status

	Had Regular BSE (n:)		Did not have regular BSE (n:)		Had CBE (n:)		Did not have CBE (n:)		Had Mammography (n:)		Did not have mammography (n:)	
Properties	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Age group	χ^2=0.088, p=0.767				χ^2=0.029, p=0.865				χ^2=0.321, p=0.571			
49 and below	11	12.6	76	87.4	39	44.8	48	55.2	36	41.4	51	58.6
50 and above	19	11.4	148	88.6	73	43.7	94	56.3	63	37.7	104	62.3
Family type	χ^2=0.273, p=0.601				χ^2=0.802, p=0.371				χ^2=1.772, p=0.183			
Core family	21	12.6	146	87.4	77	46.1	90	53.9	70	41.9	97	58.1
Other	9	10.3	78	89.7	35	40.2	52	59.8	29	33.3	58	66.7
Education status	χ^2=2.483, p=0.289				χ^2=0.854, p=0.652				χ^2=4.490, p=0.106			
Illiterate	13	9.0	131	91.0	60	41.7	84	58.3	48	33.3	96	66.7
Primary/Junior high gradutae	16	15.5	87	84.5	49	47.6	54	52.4	48	46.6	55	53.4
High school and ↑	1	14.3	6	85.7	3	42.9	4	57.1	3	42.9	4	57.1
Marrital status	χ^2=1.169, p=0.346				χ^2=2.789, p=0.095				χ^2=5.878, p=0.015			
Married	26	12.9	175	87.1	94	46.8	107	53.2	86	42.8	115	57.2
Single (Widowed/Divorced)	4	7.5	49	92.5	18	34.0	35	66.0	13	24.5	40	75.5
Occupation status	χ^2=0.355, p=0.524				χ^2=0.373, p=0.541				χ^2=0.003, p=0.955			
House-wife	26	11.4	202	88.6	102	44.7	126	55.3	89	39.0	139	61.0
Other (Working)	4	15.4	22	84.6	10	38.5	16	61.5	10	38.5	16	61.5
Social security	χ^2=1.161, p=0.436				χ^2=0.105, p=0.746				χ^2=3.905, p=0.048			
Had social security	27	12.8	184	87.2	94	44.5	117	55.1	88	41.7	123	58.3
Did not have social security	3	7.0	40	93.0	18	41.9	25	58.1	11	25.6	32	74.4

BSE: Breast Self Examination
CBE: Clinical Breast Examination

Table 2. Demographic characteristics and BSE performance status according to knowledge on BSE

	BSE knowledge					
	Yes		No		Total	
Properties	**No**	**%**	**No**	**%**	**No**	**%**
Regular BSE Performance status	χ^2=29.986, p=0.000					
Performed (n:)	30	22.2	0	0.0	30	11.8
Did not perform (n:)	105	77.8	119	100.0	224	88.2
Age group	χ^2=5.387, p=0.020					
49 and below	55	40.7	32	26.9	87	34.3
50 and above	80	59.3	87	73.1	167	65.7
Education status	χ^2=22.866, p=0.000					
Illiterate	58	43	86	72.3	144	56.7
Primary/Junior high graduate	71	52.6	32	26.9	103	40.6
High school ↑	6	4.4	1	0.8	7	2.8

BSE: Breast Self Examination

Table 3. Influence of awareness of mammography on obtaining mammography

Properties	Had mammography (n:)		Did not have mammography (n:)		Total	
	No	%	No	%	No	%
Mammography knowledge status	χ^2=1.138, p=0.000					
Yes	94	69.6	41	30.4	135	53.1
No	5	4.2	114	95.8	119	46.9

Table 4. Influence of performing regular BSE on obtaining CBE

Properties	Had CBE (n:)		Did not have CBE (n:)		Total	
	No	%	No	%	No	%
Regular BSE	χ^2=5.108, p=0.024					
Yes	19	63.3	11	36.7	30	31.9
No	93	41.5	131	58.5	224	68.1

KKMM: Kendi Kendine Meme Muayenesi
KMM: Klinik Meme Muayenesi

were 50 years old and above. This condition was associated with the women's level of education. There are significant differences among BSE knowledge, age, education and marital status in many studies (12, 15, 19, 20, 21).

This study showed that barriers against implementation of breast cancer screening methods in women were related to lack of knowledge about these methods. The level of education and lack of adequate information about breast cancer screening, and symptoms of breast cancer may result in late diagnosis. Health care providers may have a key role in increasing breast cancer early detection rates.

Ethis Committee Approval: To put the research in practise permission is taken from Turkish Republic Ministry of Health İzmir Tepecik education and research hospital non- interventional (invasive) clinical research ethic council and Municipality of Bornova to whom the district is related.

Informed Consent: Participation is on a voluntary basis and verbal consent was obtained from patients who agreed to participate in this research study.

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Determination of Knowledge and Behavior of Women Working at a Hospital on Breast Cancer Early Detection Methods, and Investigation of Efficiency of Planned Education

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ABSTRACT

Objective: This study aimed to evaluate knowledge and attitude of women working in the hospital on breast cancer, their behaviors related to early diagnostic methods, and to determine the effectiveness of training in order to increase awareness on breast cancer.

Materials and Methods: The study group consisted of women working in the Dokuz Eylül University Hospital. The data of this cross-sectional study were collected by a questionnaire. Within the scope of this study, a training program on breast cancer was organized. The effectiveness of this training was evaluated by a preliminary survey and a final survey. Data were expressed as number and percentage, and paired t test and chi-square test were used for comparison.

Results: 161 women participated in the study with a mean age of 35 ± 8. It was determined that 81.4% of women knew early diagnosis and screening methods for breast cancer. 49.1% of women stated that they perform breast self-examination, but only 6.2% practiced it once a month. 32.9% of women had clinical breast examination, 22.4% had a breast ultrasound, and 22.3% had mammography. Most of the women did not perform any of these methods. The average knowledge level of women was significantly increased after completion of the planned training as compared to pre-training levels ($p < 0.001$).

Conclusion: It was determined that the majority of women were informed on breast cancer early diagnosis and screening methods, but did not practice these methods on themselves. Information and awareness of women against breast cancer have increased with the use of planned training programs on breast cancer, early detection and screening methods.

Keywords: Breast cancer, early diagnosis, screening, training program

Introduction

Breast cancer is the most common cancer and the leading cause of death in women around the world and in our country (1-3). Breast cancer starts with uncontrolled proliferation of cells and structures in breast tissue. The most important factor that determines the prognosis of the disease is early diagnosis. Although breast cancer is common in women, with early detection, it can be treated with quite successful results and cancer mortality can be reduced. The diagnosis of breast cancer can be easily made by early detection and screening methods and treatment can be initiated early (4-6).

It is well-known that with regular use of early diagnosis and screening methods, and with timely and effective treatment options breast cancer survival rates have increased in developed countries (5,7). Early diagnosis and screening methods of breast cancer include breast self-examination (BSE), clinical breast examination (CBE) and mammography (4,7-9). The most important method that reduces breast cancer mortality is screening mammography. Early diagnosis by screening mammography resulted in up-to a 30% decrease in mortality (9). However, mammography is an expensive method that requires experienced personnel. Therefore, it is not widely applied in our country. BSE and CBE are known to be useful in increasing awareness of breast cancer in women (4,7,10).

The American Cancer Society and the American Cancer Institute recommend mammography in women older than 40 years as a method of breast cancer screening, even though there are no symptoms (4,6). CBE is recommended in every three years for 20-40 years of age, and once a year above 40 years of age by a trained health personnel, and after the age of 20 particularly in countries where screening programs are inadequate, regular monthly BSE is recommended after explanation of its benefits and limitations by medical personnel (4,6,7). BSE is a recommended method to increase women's awareness, although, its effect on reducing cancer mortality is debated. In the literature, it

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is reported that approximately 80% of breast lumps are initially determined by women themselves (10). Therefore, regular BSE is important so that women can recognize their breast and notice potential changes early, thus leading to early admission to medical institutions.

The Ministry of Health indicated that women should undergo mammography once every two years starting at age 40 (11). In our country, the incidence of breast cancer varies between regions. Western regions have a higher incidence of breast cancer than the east. Western lifestyle and availability to health services is thought to influence this higher incidence. According to the national breast cancer registry program, although varying between regions, about two-thirds of breast cancer cases in our country are under the age of 40 (12,13). While educating women about breast cancer, these information should be kept in mind and early detection methods and their timing and frequency of administration should be explained.

Increasing awareness of the society about breast cancer, and increasing the level of knowledge through planned training programs may provide regular application of early screening and diagnosis methods. Training on breast cancer, causes, symptoms, screening, prevention and early detection issues can increase awareness in the society against breast cancer and may provide early clinical admission in women with or without clinical signs. Therefore, by presenting early diagnosis and appropriate treatment options, the burden of breast cancer on the community can be reduced.

This study aimed to evaluate knowledge and attitude of women working in a university hospital on breast cancer, to detect their behaviors on early diagnostic methods, and to determine the effectiveness of training provided in order to increase awareness against breast cancer.

Materials and Methods

The study group included women who work as supportive staff and secretary (non-health care workers) at the Dokuz Eylul University Hospital. Written permission was obtained from the Dokuz Eylul University School of Medicine Clinical and Laboratory Studies Ethics Committee. The data of this cross-sectional study were collected by a questionnaire between February-December 2011, after obtaining verbal informed consent from the participants.

The study survey form, pre-training and post-training questionnaires that were generated by the authors based on literature information was used to collect data. Within this research, a planned training program was organized in order to increase breast cancer awareness on breast cancer symptoms, risks, early detection and screening methods, and prevention. In this training program, interactive education and presentation techniques were used as well as breast models and visual materials. In order to evaluate the effectiveness of this training, a pre-survey questionnaire consisting of 10 questions relevant to the educational content and a final questionnaire that included the same questions were prepared and filled-in by the participants. The training sessions lasted for 30 minutes, and twenty women were invited to each session.

The survey questionnaire was filled in by the researchers, on a different day from the day of training, by face-to-face interviews with the participants. The study survey form consisted of questions regarding socio-demographic characteristics of women, information on breast self-examination, clinical breast examination, breast ultrasound and mammography, their status and influencing factors on the application/not application of these methods.

Statistical Analysis

SPSS 15.0 (SPSS inc. Chicago, Illinois, USA) statistical software package was used for analysis. For statistical analysis; number, percentage, mean, standard deviation, paired t test, chi-square test, and Mantel-Haenszel chi-square tests were used. p-value less than 0.05 were considered as significant.

Results

The youngest women who participated in the study was 20 years old, and the oldest was 59 years, with a mean age of 35.3 ± 8.9. The analysis of socio-demographic characteristics of women revealed that 32.9% of women were in the 20-29 age range, 37.3% in the 30-39 age range, 22.4% in the 40-49 age range, and 7.5% in the 50-59 year range. 24.2% of the participants were educated at primary school, 53.4% at high school, 22.4% were college graduates, and 75.8% were married (Table 1). The majority of women (82.6%) did not have any chronic illness. 9.9% had a family history of breast cancer (Table 2).

It was determined that 81.4% of women knew at least one breast cancer early detection and screening method. 70.2% stated that they had knowledge on BSE, 44.1% on CBE, 46.0% on breast ultrasound, and 64.0% on mammography (Table 3). Women obtained information on breast cancer early detection and screening methods mainly from midwives, nurses or doctors (35.4%) (Table 4). The status of women in early diagnosis and screening methods are presented in table 5. It was detected that only 4.3% of women had CBE, 13.1% had CBE and breast ultrasound, 6.8% had mammography, 6.2% had CBE and mammography, and 9.3% had CBE together with breast ultrasound and mammography. The majority of women (60.2%) did not perform any of the methods indicated (Table 5).

When women who did not perform BSE were asked the reasons for not applying BSE, 52.5% stated that they were unaware, and 43.8% that they neglected the examination. 46.2% of women who did not perform mammography or breast ultrasound stated that they did not know that it should be done, 31.7% that they neglected these methods, and 12.5% that they did not believe in the requirement of these methods (Table 6).

Table 1. Patient sociodemographic characteristics (n=161)

Variable	Number	%
Age group		
20-29	53	32.9
30-39	60	37.3
40-49	36	22.4
50-59	12	7.5
Education status		
Primary school and less	39	24.2
Junior-high school	86	53.4
University and more	36	22.4
Marital status		
Married	122	75.8
Single	20	12.4
Divorced	19	11.8

As depicted in Table 7, 50.9% of women did not perform BSE at all, and only 6.2% performed BSE once a month regularly. 30.2% of those who had CBE had an examination during the past year, while 37.7% stated that more than three years elapsed since their last CBE. The most recent mammogram or breast ultrasound was obtained within the past year in 26.3% of women, between one to two years in 28.1%, within two-to three-years in 15.8%, and more than three years ago in 29.8%. The majority of women received these services from the institutions they work at (Table 7). The mammography or breast ultrasound results were reported as normal in 68.4%, with only very few (3.5%) women requiring breast biopsy (Table 8).

Table 9 presents the average knowledge level of women on breast cancer, in the pre-and post-training period. Women's knowledge on breast cancer was significantly increased after training as compared to pre-training levels ($p < 0.001$).

Analysis of BSE performance status according to socio-demographic characteristics and family history did not detect significant difference in BSE performance between women over 40 years and those under 40 years of age, between high school and higher education level and those with lower education, between single and married women, and between women with and without family history of breast cancer ($p > 0.05$). CBE rates were significantly higher in women over the age of 40 than those under 40 years of age ($p < 0.01$). However, there was no significant difference in CBE performance in terms of education level, marital status or family history ($p > 0.05$). Analysis of undergoing mammography or breast ultrasound in terms of socio-demographic characteristics showed that women over 40 years of age had a significantly higher rate ($p < 0.01$). There was no statistically significant difference in undergoing mammography or breast ultrasound, in terms of education level, marital status and family history ($p > 0.05$) (Table 10). Age was determined as the main independent variable in CBE, mammography or breast ultrasound status. Analysis of family history as a confounding factor showed that family history was not a confounding factor ($p > 0.05$).

Discussion and Conclusion

Breast cancer is the most common type of cancer in women. Diagnosis at an early stage and appropriate treatment options can be life-saving (4,8). Therefore, in order to detect breast cancer at an early stage both national and international authorities recommend regular BSE after 20 years of age, CBE by specialized physicians, and regular mammography after 40 years of age (1,4,6,9-11).

It was determined that the majority of women who participated in the study (81.4%) knew at least one breast cancer early detection and screening method. A study conducted in Izmir reported 93% awareness on breast cancer early detection and screening methods among women with intermediate socioeconomic level, living in urban areas (14). Since all participants of this study were working in a university hospital, higher rates of awareness were expected on breast cancer early detection and screening methods, due to their ability to obtain information from health care personnel in this regard. Those who were unaware of such methods were younger women and the 50-59 age group with a low level of education. 32.9% of the study group was young adults in the 20-29 age group, and 24.2% were educated at primary school and lower levels, which may have an effect on information regarding breast cancer early detection and screening methods.

The analysis on where/whom did women learn breast cancer early detection and screening methods from showed the highest rate (35.4%)

Table 2. Presence of comorbidites and family history (n=161)

Variables	Number	%
Comorbidity*		
Yes	28	17.4
No	133	82.6
Family history of breast cancer		
Yes	16	9.9
No	145	90.1

*Co-morbidites were accepted as hypertension, diabetes, hypercholesterolemia, asthma, rheumatoid and autoimmune diseases

Table 3. Knowledge on breast cancer early diagnosis and screening methods (n=161)

Properties	Number	%
Knowledge on breast cancer early diagnosis and screening methods		
No	30	18.6
Yes	131	81.4
Knowledge status on breast cancer early diagnosis and screening methods		
Information on BSE		
No	48	29.8
Yes	113	70.2
Information on CBE		
No	90	55.9
Yes	71	44.1
Information on breast US		
No	87	54.0
Yes	74	46.0
Information on mammography		
No	58	36.0
Yes	103	64.0

BSE: Breast self examination
CBE: clinical breast examination
US: Ultrasonography

Table 4. Source of information on breast cancer early diagnosis and screening methods

Source of information on breast cancer early diagnosis and screening methods (n=131)	Number	%
Television-radio	20	12.4
Magazines -hand-outs	18	11.2
Midwives-nurse-doctors	57	35.4
Friend-neighbor	31	19.3
Conference-seminar	5	3.1

Table 5. Utilization of breast cancer early diagnosis and screening methods

Properties	Number	%
None	97	60.2
CBE	7	4.3
CBE+US	21	13.1
Mammography	11	6.8
CBE+mammography	10	6.2
CBE+US+mammography	15	9.3

CBE: Clinical breast examination
US: Ultrasonography

Table 6. Reasons for not performing early diagnosis methods

Non-performance reasons	Number	%
BSE		
Lack of knowledge	42	52.5
Neglect	35	43.8
Disbelieving in its necessity	5	7.3
Mammography / US		
Lack of knowledge	48	46.2
Neglect	33	31.7
Disbelieving in its necessity	13	12.5
Fear of detecting a mass	2	1.9
Not knowing where to get the test	8	7.7

BSE: Breast self examination
US: Ultrasonography

in midwives, nurses or doctors, and in decreasing order from friends and neighbors (19.3%), magazine-newspaper-brochures (11.2%), television-radio (12.4%), and conference-seminars (3.1%). In different studies, the rate of obtaining information on breast cancer and early detection methods from health personnel ranged between 21.5% and 47.7%, and was mostly ranked within the top three sources of information (14-20). Koç and colleagues (19) found the highest rate of information on BSE to be obtained from the health care team. In two different studies from Istanbul, it was detected that television was the primary source of information followed by newspapers, and magazines, while obtaining information from health care personnel ranked third and fourth (15,20). Dişçigil and colleagues (18) found that majority of women obtained information on breast health from the television, followed by doctors and finally printable media. The finding in our study that health personnel were the main source of information may be due to the participants occupation at a hospital. Being informed by health personnel who are competent to providing accurate information on breast cancer and early detection methods may increase sensitivity of women on this issue. The Ministry of Health aims to increase breast cancer early detection and screening facilities, in reproductive health programs as well as cancer prevention efforts, and primary care. Cancer Early Diagnosis, Screening and Training Center staff are being trained in these matters (11).

Table 7. Frequency and circumstances of performing early diagnosis and treatment methods

Properties	Number	%
Regular BSE performance		
None	82	50.9
Irregularly	57	35.4
During every shower	12	7.5
Monthly	10	6.2
Last CBE timing (n=53)		
Within the last year	16	30.2
1-2 years	13	24.5
2-3 years	4	7.6
3 years and more	20	37.7
Last mammography/US timing (n=57)		
Within the last year	15	26.3
1-2 years	16	28.1
2-3 years	9	15.8
3 years and more	17	29.8
Location of last mammography/US		
University hospital	51	89.4
Private Clinics	3	5.3
State Hospital	3	5.3

BSE: Breast self-examination
CBE: Clinical breast examination
US: Ultrasonography

Table 8. Result of last mammography/US

Result	Number	%
Normal follow-up in 1 year	39	68.4
Normal follow-up in less than 1 year	3	5.3
Fibrocystic breast	4	7.0
Benign tumor	9	15.8
Biopsy suggestion	2	3.5

US: Ultrasonography

Breast self-examination is a simple, economical and easily applicable method in the early diagnosis of breast cancer. More than two-thirds of women who participated in the study had information on BSE. This finding was higher than the results from studies conducted in Ordu, İstanbul and Kütahya (15, 16, 20-22,), and was lower than the results reported from İzmir (14).

Approximately half of the women who participated in our survey stated that they perform BSE. In studies conducted with communities outside health professionals in Turkey, this ratio was reported between 13.8% and 84.1% (14-17,21-25). The high rate of BSE performance in the study by Özaydın et al (15) as compared to others may be due to the study design that only included the 40-69 year age group. The awareness of this group may be increased due to their being the at-risk age group for breast cancer. In our study, it was detected that the

majority of those who perform BSE, did the examination whenever they remembered to. Regular monthly BSE performance rate was very low (6.2%). In studies conducted in our country, the rate of those performing regular monthly BSE ranged from 4.3% to 38.8% (14-16,21,24,25). Regular BSE performance rates are also quite different in other countries; in South Korea this rate (2.9%) was lower than our rates, in Nigeria a similar rate (7.3%) was reported, whereas in African Americans this was higher (32%) than our rate (26-28).

Fifty-one percent of our study group stated that they never performed BSE. Reasons for lack of BSE were expressed as being unaware (52.5%), followed by neglect and disbelief in its requirement. In a study from İstanbul in women aged 40-69, it was detected that more than two-thirds of women applied BSE (20). The higher rate of BSE performance in the study by Demir Yıldırım and colleagues (20) as compared to our results may be due to the different distribution of age groups in the two studies. Nahcivan and colleagues (29) stated the rate of disbelief in BSE to be higher than our results. In the study by Nahcivan and colleagues (29) the participants filled in the survey whereas in our study the researchers filled in the questionnaires, which may have led to abstaining by participants. Biçen Yılmaz et al (17) reported the reasons for lack of BSE as negligence, not having breast related complaints, lack of information, the fear of detecting a mass and not believing in its requirement. The finding that in our study, lack of information and negligence were the main causes of not applying BSE suggested that lack of knowledge can be overcome and these habits are likely to be acquired with planned training.

In our study, age, education and socio-demographic characteristics such as marital status did not have an effect on BSE application. Nahcivan and colleagues (29) reported that the level of education did not affect BSE performance, while those under 40 years of age and those who are married applied BSE significantly more. In another study, it was stated that married women and those over 35 years perform BSE more (22), and in another study women over the age of 40, with high level of education and those who are married applied BSE significantly more (24). In a study on African-American women, women in the 40-59 years age group applied BSE significantly more than those who were either younger or older (26). According to national and international resources, women over the age of twenty should perform BSE regularly (5,6,9,11,13,30). Instructing women on the importance and the technique of BSE can provide regular application of BSE.

Forty-four percent of women who participated in the study had knowledge on BSE, 46.0% on breast ultrasound, and 64.0% on mammography. These findings are higher than the results studies from Istanbul and Kütahya (15,16). When practice of these methods were evaluated, 32.9% of women had BSE, 22.4% had breast ultrasound, and 22.3% had mammography. These rates are quite low when compared with women's knowledge level. Although women were informed about methods of early diagnosis, the application of these methods were inadequate. 30.2% of those who had CBE, had the exam in the past year, while 37.7% stated that there was a more than three years elapse. Studies from different countries reported similar rates of regular CBE to our findings (26,27). Analysis of CBE status in terms of socio-demographic characteristics showed that women over 40 years had significantly more CBE as compared to those less than 40 years; however, no statistically significant difference was found in terms of education level and marital status. Dişçigil et al (18) detected the high-

Table 9. Average knowledge level before and after training

	Number	Mean	SD	t	p
Pre-test	122	17.6	3.8	30.1	<0.001
Last-test	122	27.5	2.2		

SD: Standard deviation

Table 10. Early diagnostic method performance status according to sociodemographic properties

	BSE			CBE		Mammography/US	
	None n (%)	Once a month n (%)	Irregular n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Age group							
20-39	62 (54.9)	7 (6.2)	44 (38.9)	25 (22.1)†	88 (77.9)	18 (15.9)†	95 (84.1)
≥40	20 (41.7)	3 (6.3)	25 (52.1)	25 (52.1)	23 (47.9)	33 (68.8)	15 (31.3)
Education level							
Junior high-below	63 (51.6)	7 (5.7)	52 (42.6)	41 (33.6)	81 (66.4)	43 (35.2)	79 (64.8)
High school-above	19 (48.7)	3 (7.7)	17 (43.6)	9 (23.1)	30 (76.9)	8 (20.5)	31 (79.5)
Marital status							
Married	63 (51.6)	7 (5.7)	52 (42.6)	41 (33.6)	81 (66.4)	43 (35.2)	79 (64.8)
Not married	19 (48.7)	3 (7.7)	17 (43.6)	9 (23.1)	30 (76.9)	8 (20.5)	31 (79.5)
Family history of breast cancer							
Yes	6 (37.5)	2 (12.5)	8 (50.5)	4 (25.0)	12 (75.0)	7 (43.8)	9 (56.3)
No	76 (52.4)	8 (5.5)	61 (42.1)	46 (31.7)	99 (68.3)	44 (30.3)	101 (69.7)

†Chi square p<0.01
BSE: Breast self-examination
CBE: Clinical breast examination
US: Ultrasonography

est CBE application rate in the 40-59 age group and in women with more than 12 years of education. A study from Izmir found that about half of women had CBE alone or in combination with other methods (14). In another study, the majority of the study group was found to lack CBE (17). The consensus on CBE by institutes and institutions is that breast examination should be performed every 2 years after the age of 20, and annually after 40 years (4,6,9,11). It is expected that educating women about CBE may have a positive influence on the application of this method.

In our study, one in five women had breast ultrasound, and one in five women had mammography. These findings were lower than the results of studies on the frequency of breast ultrasound in our country (14,15,17,20). In terms of frequency of mammography, our results were higher than (16,19,31), similar to (32), or lower than several studies on the frequency of mammography in our country (14,15,17,18,20,29). The higher prevalence in studies on the frequency of mammography than in our study (14,15,18,29) may be related to the advanced age group and mean age of participants. The mean age of the women who participated in our study was lower than these studies. In our study, the majority of women who had a mammography stated that they were reported as 'normal', while only a few women (3.5%) stated that a biopsy was recommended. Şen and colleagues (16) determined a similar rate of women who underwent breast biopsy in their study in the city of Kütahya.

The most recent mammogram or breast ultrasound was obtained within the past year in 26.3% of women, between one to two years in 28.1%, within two-to three-years in 15.8%, and in more than three years ago in 29.8%. In studies from different countries, the rate of mammography within two years ranged from 43% to 78% (26-28,33,34). Studies in Turkey focused on whether mammography was obtained or not, rather than the timing of mammography (16,17,19,20,29,32,). Very few studies investigated timing of mammography (12,14,15,18,31). In a population-based study by Ozmen and colleagues (12), the rate of mammography within the last two years was found to be 41.6%. It was stated that mammography within the last two years was more common among women with high level of education, who comply with regular gynecological follow-up and with regular BSE (12).

Dişçigil and colleagues (18) conducted a study on women living in urban and semi-urban areas of the Aegean Region, and they reported that 40.6% of women older than 40 years had a mammography, and the frequency of mammography within the last two years was 48.9% among women older than 50 years. In our study, both findings were detected at a lower rate. In our study, although the finding that 68.8% of women over the age of 40 had mammography is optimistic, it must be kept in mind that thirty percent of our participants were over forty years of age. Our study group consisted of women employed in hospital cleaning and supportive services. The study group of Dişçigil and colleagues (18) included women who participated in six consecutive health workshops or in meetings of civil society organizations. It can be expected that these group of women are more sensitive for their well-being, and therefore, had a higher rate of mammography. Another factor may be the age range of the participants. 70% of women in our study were under 40 years of age, whereas in the study by Dişçigil and colleagues (18) this rate was 38.3%. The frequency of mammography was lower in the community-sampled study by Dündar and colleagues (31) from Manisa than in our study. The rate of mammography and breast ultrasound within the last two years was higher in the 2009 community-based cross-sectional study by Özaydın and colleagues (15) on women aged 40-69 years than in our study.

Analysis of mammography or breast ultrasound status in terms of socio-demographic characteristics revealed that women over 40 years had significantly more mammography or breast ultrasound as compared to those less than 40 years, however, no statistically significant difference was found in terms of education level and marital status. In a study by Seçginli and colleagues (32) that was conducted in women living in Istanbul, level of education and marital status did not affect mammography status. Dündar et al (31) conducted a study among women who reside in rural areas of Manisa reported that educational level, marital status or increasing age did not effect mammography. In a survey from Istanbul, it was observed that marital status had no effect on mammography, but women with higher level of education, with high income and social security had more mammography than those with lower education, lower income and without social security (20).

The majority of the women who participated in the survey (60.2%) stated that they did not perform any breast cancer early diagnosis and screening method. Reasons for this behavior were stated as unawareness in 46.2%, negligence in 31.7%, disbelief in their requirement in 12.5%, not knowing where to get these tests from in 7.7%, and the fear of detecting a mass in 1.9%. In the study by Koç et al. reasons for not having CBE and mammography were reported as lack of knowledge (73.8%), followed by shame, fear of detecting a mass, lack of time, fear of radiation exposure, high cost and fear of discomfort (19). In one study, it was detected that 55% of women did not undergo mammography at all, and the main reasons were stated as negligence (55.1%), not knowing that it was required (33.9%), not knowing where it was performed (26.3%), fear of being diagnosed with breast cancer (10.2%), being afraid of undergoing mammography (8.5%), not having social security (6.8%), and being ashamed of having mammography (5.1%) (14). The higher rate of women who were unaware of early detection methods in our study may be due to the younger age group than the previous study (14).

A training program aiming to increase awareness on breast cancer symptoms, risks, early detection and screening methods, and protection methods was implemented as part of this study. Breast models and visual materials were used during this program. In order to evaluate the effectiveness of this training program, women's average knowledge level on breast cancer was determined both prior to and after the training. Women's average level of knowledge on breast cancer was significantly increased after the training as compared to pre-training levels. Güçlü et al. carried out a study in Kütahya, on women in the 15-49 age group, and they reported that knowledge score of women was significantly increased after education on breast cancer (22). Koç and colleagues (19) observed that women's knowledge level on breast cancer, early detection and screening methods, and screening frequency was increased after training among women who admitted to the hospital in Sinop. These findings can be considered normal due to the newly obtained information after training. However, transformation of this information into practice, and creation of a permanent change in behavior are more valuable. Training is known to be an important factor on breast cancer awareness and implementation of early detection methods. The participants in this study were employed within the hospital, therefore, it is planned to follow-up their knowledge level and if these information were translated into practice in the coming years.

In conclusion, it was detected that 81.4% of women knew at least one of the breast cancer early detection and screening methods, and that this information was mainly learned from health personnel. It was determined that 70.2% of women were informed on BSE, 44.1% on

CBE, 46.0% on breast ultrasound, and 64.0% on mammography. It was observed that women's application of early detection methods was lower than their knowledge level. 49.1% of women had BSE, 32.9% had CBE, 22.4% had breast ultrasound, and 22.3% had mammography. The frequencies of application of these methods were lower than the recommended frequency. Being older than 40 years of age influenced CBE, breast ultrasound and mammography rates, whereas educational level and marital status did not have an effect. It was observed that average knowledge level of women participating in this study was significantly increased after training on breast cancer as compared to pre-training levels. Practical training on breast models is thought to particularly contribute to this increase.

It is important to educate women in order to increase awareness on breast cancer. Sensitivity of health personnel in this regard, and informing women admitted to health organizations at every opportunity, may contribute to raising awareness. Regular public education on breast cancer by public health and health care professionals, early detection and screening methods may lead women to applying early diagnosis and screening methods according to their age group. Distribution of leaflets in hospitals in a language that can be clearly understood by the community about breast cancer, and display of appropriate visual materials can contribute to raising awareness both within corporate employees and among women admitted to the hospital. Providing women with accurate information on breast cancer may also lead to spread of correct information to the community.

Ethis Committee Approval: Dokuz Eylül University School of Medicine Clinical and Laboratory Studies Ethics Committee (2009/203).

Informed Consent: Informed consent was obtained from the participants.

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Case Report

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Pseudoangiomatous Stromal Hyperplasia of The Breast Presenting As A Giant Breast Tumor: A Case Report

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ABSTRACT

Pseudoangiomatous stromal hyperplasia (PASH) of the breast is a benign proliferative lesion of mammary stroma. It is identified as stromal cleavage surrounded by spindle-shaped stromal cells histomorphologicaly. Generally, it is determined in premenopausal women incidentally during breast biopsy. Clinically, it is rarely emerges as a palpable mass. PASH may be confused with low-grade angiosarcoma, hamartomas and phyllodes tumors in histopathological examination. Here, we report a giant left breast lesion that caused breast asymmetry and pain, and treated by total excision of the mass. The patient was a 39 years old women. Histopathologic examination of the specimen was evaluated as PASH. No additional medical treatment and clinical follow-up was recommended to patient. Within four months of the patient fallow-up, no problem occured.

Keywords: Pseudoangiomatous stromal hyperplasia, breast, benign neoplasms, breast diseases

Introduction

Pseudoangiomatous stromal hyperplasia of the breast (PASH) is a benign breast disease due to excessive proliferation of mammary stroma. They are usually discovered incidentally in breast biopsies of premenopausal women (1). They are rarely encountered as palpable masses in clinical practice. They may be histopathologically misdiagnosed as low-grade angiosarcomas and hamartomas, thus it is important to diagnose this entity.

In this report, a PASH case that presented as breast asymmetry and pain and was treated with excision was presented.

Case Presentation

A 39-year-old female patient admitted to our clinic with a large palpable mass in the left breast and pain. She had noticed a small lump in her left breast about 1.5 years ago during breastfeeding. The mass enlarged in time leading to breast asymmetry, and caused pain since the last two months. Ultrasonography revealed a 95x50 mm in size, hypoechogenic, partially homogeneous lesion with cystic tubular components and regular borders in the left breast (Figure 1). On mammography, the breast parenchyma was assessed as ACR type 3 pattern. An approximately 15x11 cm in size, regular bordered opacification was reported in the left breast parenchyma with no microcalcifications in both breasts (Figure 2). On physical examination, a mobile mass measuring 10 x10 cm and having an elastic consistency was palpated in the upper outer quadrant of the left breast. Preoperative biopsy was not considered necessary due to the very large and lipomatous characteristics of the lesion on preoperative tests and physical examination due to the patient's preference. The entire lesion was excised under general anesthesia (Figure 3). Frozen section evaluation was not performed during the operation due to the benign appearance of the lesion (encapsulated and regular bordered). Histopathology of the excised lesion showed small slit like vessels within hypocellular stroma, showing hyalinization, spindle like cells lining these clefts and lobules consisting of epithelial lining without atypia (Figure 4). Positive immunohistochemical staining with CD34 and Desmin, and negative staining with CD31 and Pancytokeratin was observed (Figure 5). A diagnosis of PASH was made based on marked stromal hypercellularity, and absence of atypical endothelium and mitosis, as well as immunohistochemical findings. No additional medical treatment was recommended to the patient and clinical follow-up was recommended. There was no problem during four-months of follow-up.

Discussion and Conclusions

Vuitch et al. (2) first described PASH in 1986 histomorphologically as stromal cleavages surrounded by spindle stromal cells. It has been reported to be incidentally detected in breast biopsy at a rate of 0.4% - 23 (1, 3). They are rarely encountered as a palpable mass in clinical

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Figure 1. Ultrasonographic view of the mass

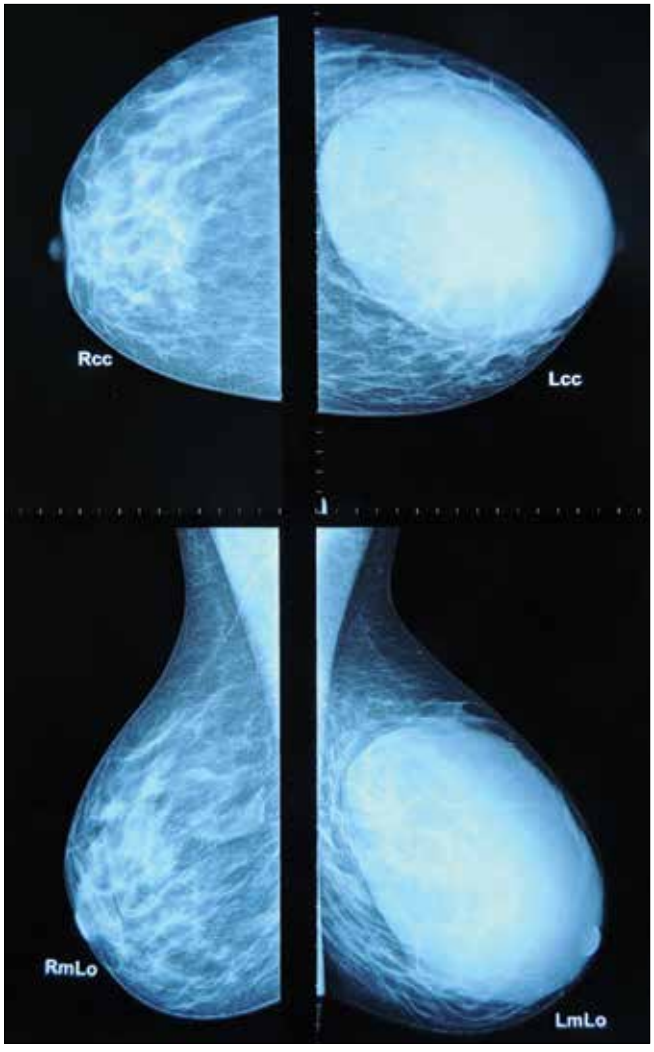

Figure 2. Mammographic view of the mass

practice. In our case, it presented as a giant mass 11x11x6 cm in size, weighing 455 g (Figure 3).

In our case, another radiologically benign or malignant pathological lesion accompanying this mass was not detected. It was described as regular bordered opacification on mammography, and the ultrasound revealed a hypoechoic lesion with cystic tubular areas (Figure 1, 2). These tumors cannot be distinguished from fibroadenomas by mammography and ultrasonography. Most lesions do not have any mammographic findings; however, the most common mammographic findings were reported as sharply demarcated mass and focal asymmetric density. They are encountered as regular bordered, hypoechoic or isoechoic mass on ultrasonography (4). On ductoscopy, ducts with increased vascularity without further intraductal pathology are observed (5). These findings suggest a radiologically benign mass, and additional tests are generally not required. It has been reported that PASH can be accompanied b y breast cancer in 4-25% of patients (4, 6). This high ratio is thought to be related to the patient's only being followed-up without a biopsy or excision due to the benign appearance of lesions without concomitant radiological imaging of malignant or suspicious findings. In most of the studies, microcalcifications were detected on mammography in almost all patients with malignancy that is accompanying PASH (4, 7). Malignant neoplasms infiltrating the lesion have rarely been reported (8). On the other hand, a study intended to determine the relationship between PASH and breast cancer risk in women, concluded that the risk of breast cancer was not increased in women with PASH as compared to women without PASH (7).

Figure 3. Macroscopic view of the mass. (455 g in weight 11x11x6 cm in size)

Histopathologically, it is important to differentiate PASH from angiosarcoma due to differences in prognosis and treatment (2). In our case, blood cells, atypia or mitotic activity were not seen within cleavages on pathological evaluation, and were distinguished from angiosarcoma (Figure 4, 5)

The treatment of PASH varies depending on the clinical presentation of the disease. In case of incidental diagnosis on a biopsy performed for other pathologies, additional treatment is not required. Excision may be required for persistent pain and cosmetic reasons. Recurrence rate after excision has been reported between 0-22 % (4). A 12-year-old patient who underwent bilateral mastectomy due to recurrent excisions has been reported in the literature (9). Clinical follow-up can be an

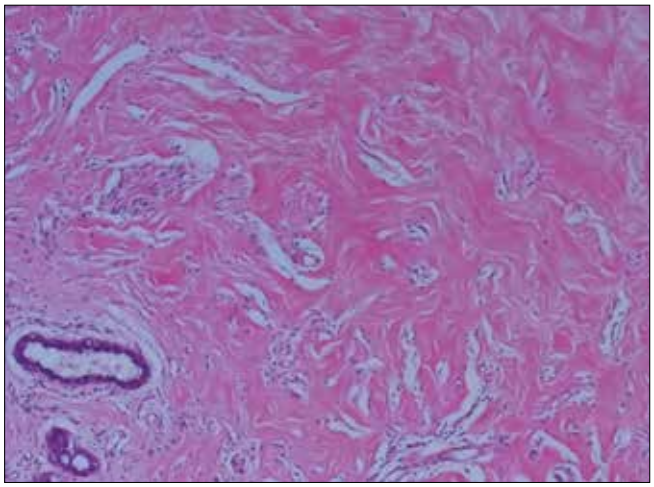

Figure 4. Microscopic view of the mass: Slit-like spaces paved with spindle cell in dense collagenous stroma. (HEX100)

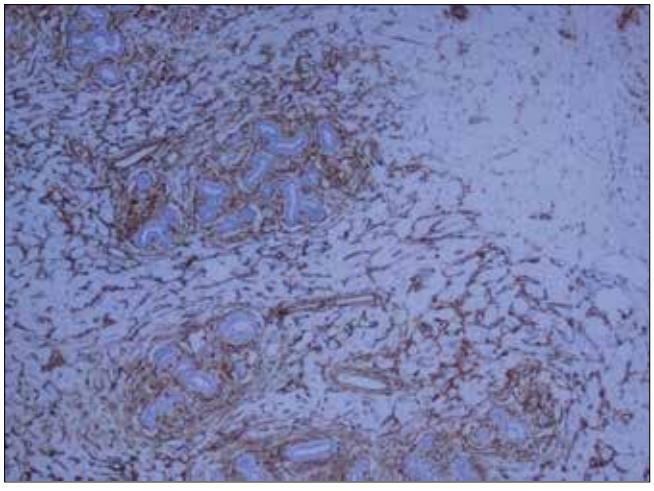

Figure 5. Positive immunohistochemical staining with CD34 in spindle cells. (x100)

alternative in selected cases with pathological and radiological benign findings. There is not enough data in the literature relating to medical treatment. Pruthi et al. (10) reported a 39-year-old patient with bilateral progressively growing PASH that was treated with tamoxifen, and stated that the mass disappeared at 6 months. However, this is a limited report of only one patient and larger series are required.

In conclusion, PASH is an extremely rare tumor of the breast, and it may rarely present as a giant mass. In these patients, excision should be considered as first line treatment due to the associated malignant potential and similarity to hamartoma and sarcoma.

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

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Case Report

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Possible Synchronous Lung Metastasis of Breast Mass Detected Using Breast Ultrasonography: A Report of Two Cases

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ABSTRACT

Ultrasonography (US), which is used for the diagnosis of breast cancer and the evaluation of its local metastasis, has proven its worth as a diagnostic method. In breast ultrasonographic examination peripherally localized metastatic lesions at the posterior of the screened breast tissue can also be detected. In this case report, two female patients whose breast ultrasonography showed lumps. Their peripheral lung metastases were screened ultrasonographically, and the patients were diagnosed in a timely manner. Ultrasonographic examination at a patient's first appointment – and especially during routine check-ups after the primary treatment – can allow an early diagnosis of peripherally localized lung metastasis at the posterior of the screened breast tissue and make a vital contribution to the patient's prognosis.

Keywords: Breast cancer, lung metastasis, breast ultrasound

Introduction

Despite significant developments in its diagnosis and treatment, breast cancer is still the second most common cause of death in women (1). Although mammography is the most widely used screening method in the general population, the clinical use of ultrasonography (US) and its contribution to the detection of breast cancer has been increasing daily (1). The size of a tumor determined through ultrasonographic examination can have significant effects on lymph node metastasis, and on the planning and prognosis of distant metastasis treatment (2). There is no information in the literature about the use of US in the detection of lung, or distant, metastasis although this has the potential to completely change the treatment schedule. This case report details how ultrasonography can also be used to detect peripheral lung metastasis of breast cancer, which is localized at the posterior of the screened breast tissue.

Case Presentation

Case 1

A 38-year-old female patient came to our breast screening unit with a complaint of swelling in the breast. On physical examination, a palpable painless mass detected on the right upper quadrant of the breast. The ultrasonographic examination, performed using a Toshiba Aplio XG SSA-790A ultrasonography device (Toshiba Medical Systems Corporation, Otawara, Japan) and a 7.5-Mhz high-frequency linear probe, detected a 3-cm hypoechoic malignant-appearing mass lesion with an irregular contour and infiltrative pattern on the upper outer quadrant of the right breast. There were metastatic lymphadenopathies in the right axillary region. The images showed a large number of nodular mass lesions in the peripheral region of the right lung (Figure 1a). Chest X-ray showed a large number of nodular lesions in the both lung (Figure 1b). Thus, after written consent was obtained from the patient, an ultrasound-guided Tru-Cut biopsy was performed on the patient's breast lump and lung mass lesion. The breast lump was invasive ductal carcinoma, and the lung lesions were breast carcinoma metastases.

Case 2

A 43-year-old female patient came to our breast screening unit with a complaint of swelling in the breast. On physical examination, a painless palpable immobile mass lesion detected on the left breast's lower mid quadrant. The ultrasonographic examination, performed using a Toshiba Aplio XG SSA-790A ultrasonography device (Toshiba Medical Systems Corporation, Otawara, Japan) and a 7.5-Mhz high-frequency linear probe, detected a 23x17-mm hypoechoic malignant-appearing mass lesion with an irregular contour on the lower mid quadrant of the left breast. Ultrasonographic examination showed a mobile hypoechoic lesion, which was compatible with mobile hypoechoic lump metastasis, on the peripheral region of the left lung and adjacent to the pleura (Figure 2a). Because the lump in the lung was mobile during respiration, it was interpreted as having not invaded the parietal pleura. The patient, who was thought to have lung

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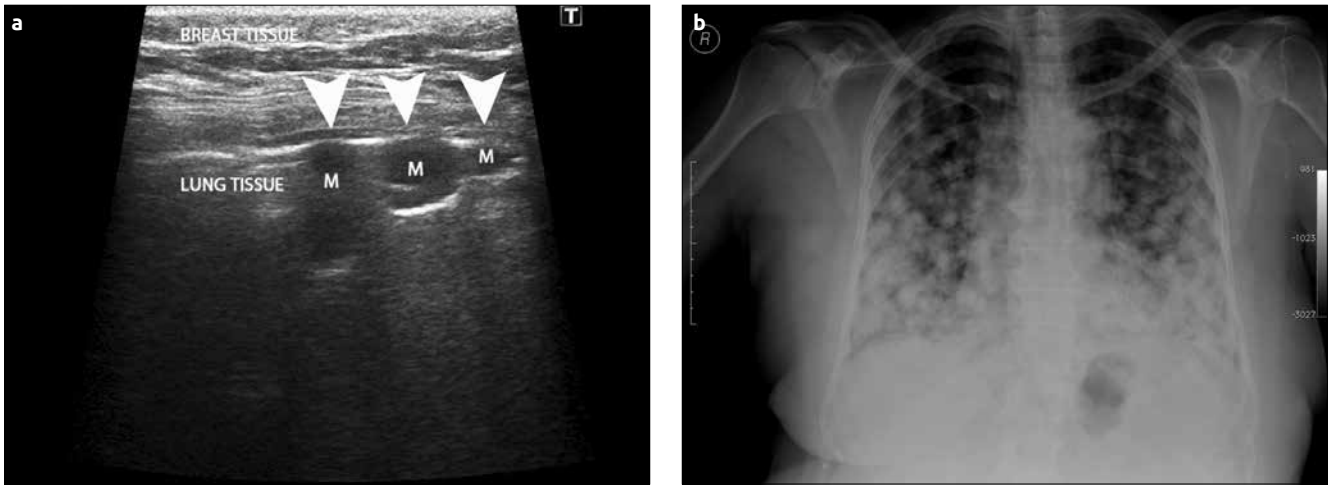

Figure 1. a, b. a) Ultrasonographic examination detected mass lesions compatible with nodular metastasis, which were peripherally localized, adjacent to the visceral pleura and mobile during respiration in the lung parenchymal under the breast tissue (arrowheads). b) Chest X-ray shows a large number of nodular lesions in the both lung.

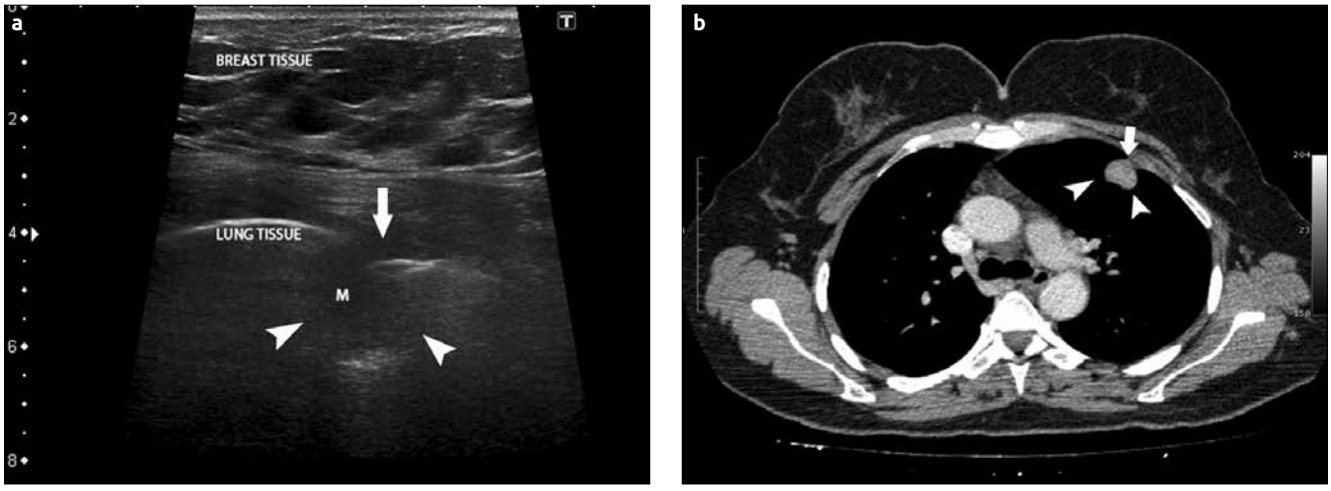

Figure 2. a, b. a) Ultrasonographic examination detected metastatic mass lesions compatible with nodular metastasis, which were peripherally localized, adjacent to the visceral pleura under the breast tissue (arrowheads). The fact that the lump was mobile during respiration was seen to indicate that it was not a parietal pleura invasion (arrow). b) The lung CT to check for metastasis detected a nodular mass lesion adjacent to the pleura under the breast tissue on the left lung (arrowheads, arrow).

metastasis, had a lung CT, and two metastatic nodular lump lesions were found on different lobes of the left lung (Figure 2b). After written consent was obtained from the patient, an ultrasound-guided Tru-Cut biopsy was performed on the breast lump, and histopathological analysis revealed that the diagnosis was invasive ductal carcinoma.

Discussion and Conclusion

In US, breast cancer is typically seen as a hypoechoic mass lesion with an infiltrative pattern, which causes acoustic shadowing on the posterior (2). With ultrasonographic breast examination, the lump size, multifocality, multicentricity, axillary metastasis, and the presence of distant metastasis can be evaluated. Ultrasonographic local staging is widely used as it helps to determine the surgical treatment required (3). Axillary lymph node metastasis, which is an important indicator of a patient's prognosis, can be evaluated in detail with US. Research has shown that it decreases false-negative rates in the detection of sentinel lymph nodes (1). Moreover, ultrasound-guided biopsies can be performed on suspicious lymph nodes that are seen during ultrasonographic examination, while ultrasonographic preoperative staging helps to determine the kind and schedule of the treatment. In the case of the presence of breast cancer's distant metastasis, the whole treatment schedule changes, and early diagnosis is therefore important. When a lump is found in the breast during ultrasonographic examination at a patient's first appointment, peripheral lung metastasis behind the breast tissue can be detected. In our cases, peripheral lung metastases were detected in good time, and synchronously with breast cancer lump using ultrasonography during the first US screening of the patients. Especially during the follow-up of patients who have had operations for breast cancer, the operated breast can be evaluated with ultrasound and potential peripheral lung metastasis can be detected. Ultrasonographic examination is superior to mammography since it can also evaluate axillary, and adjacent lung tissues as well as breast tissue. Moreover, since US enables dynamic screening, the invasion of lung metastasis to the pleura can also be examined. Lumps that are immobile during respiration are considered to have invaded the parietal pleura (4). In our second case, the movements of the lump were followed in real time during respiration, and it was possible to say that it had not invaded the parietal pleura. Although it is rarely seen, breast metastasis of primary lung cancer can imitate breast cancer and breast cancer's lung metastasis (5, 6). Thus, the US-guided Tru-Cut biopsy can diagnose the tissue.

In general, patients who have had breast cancer operations have follow-ups with mammography and US. Breast cancer can present as a local recurrence, bone metastasis, and lung metastasis during the postoperative period (7). Especially in this group of patients, since additional screening modalities are not used during follow-ups, through an ultrasonographic examination, peripheral lung metastasis, which can appear years after primary treatment, can be detected early (7). Research shows that surgical metastasectomy makes a positive contribution to the prognosis in cases where lung metastases are detected early (7).

This case series emphasizes that, ultrasonography, which is successfully and safely used in the detection of breast cancer and the evaluation of its local metastasis, can also be used to detect peripheral breast cancer lung metastasis localized at the posterior of the screened breast tissue.

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

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Case Report

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Intracystic Carcinoma of the Breast: Report of Two Cases

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ABSTRACT

Intracystic papillary carcinoma of the breast (IPC) is usually seen in postmenopausal elderly women. Its prognosis is much better than other type of breast tumors, and usually do not contain invasive components. Surgical excision with negative margins and axillary sentinel lymph node sampling is the recommended treatment. Two cases of intracystic papillary carcinoma of the breast that was treated at our clinic are herein presented. Both cases were postmenopausal, were both positive for estrogen and progesterone receptors and negative for HER 2. They underwent breast-conserving surgery. One patient had an invasive focus, therefore axillary lymph node sampling was performed, and the sentinel lymph node was not metastatic. This patient received hormonal therapy as well as radiotherapy. In the other case, there was no invasive focus and the surgical margins were negative, therefore, additional surgery was not performed. The patient is receiving hormonal therapy. Intracystic carcinoma of the breast should be kept in mind especially in elderly patients with breast cysts, with clinically or radiologically suspicious features, and biopsy and local excision should be considered. Although there is not any standard approach for patients with IPC, each patient must be evaluated for surgery and should be individually assessed in terms of adjuvant therapy

Key words: Cystic breast cancer, intra-cystic papillary carcinoma, breast cancer

Introduction

Intracystic papillary carcinoma (IPC) is an extremely rare tumor that constitutes 0.5-2% of all breast cancers (1). Although rare, this type of breast cancer is known to have very good prognosis (2). Its diagnosis is very difficult as compared to other types of breast carcinomas, since the criteria for diagnosis and treatment have not been yet defined (3). They usually present as a large cystic mass. The tumor is often retroareolar, and is well-circumscribed. In some cases, nipple discharge may be the first sign (4). On ultrasonography (US) it may appear cystic, semi solid or solid (5). Microcalcifications may accompany the lesion on mammograms (4). There are no specific clinical or radiologic signs. Magnetic resonance imaging (MRI) may be useful in differentiating benign tumors from invasive tumors (3). The diagnosis of this tumor can be made by either fine needle aspiration biopsy or core-biopsy. Excisional biopsy is required if these methods are inconclusive (3). Surgical excision of the cyst is recommended in the presence of atypia on biopsy, a high-risk lesion, the presence of malignancy or radiologic-histologic discordance. If the US or mammography are suspicious for IPC then excisional biopsy should be performed as the first approach (5).

IPC is characterized by papillary growth within macrocysts. They usually do not exhibit invasive growth over the cyst wall, so they are often treated as ductal carcinoma in situ (DCIS). Although treatment methods are still controversial, surgery remains the treatment of choice (3). Endocrine therapy and radiation therapy are used in most medical centers but the evidence indicating that this method improves prognosis is still insufficient (5). Two patients with IPC who were treated at our clinic are presented together with the relevant literature.

Case Presentation

Case 1

A 56-year-old postmenopausal women underwent cyst excision from her right breast at another center, and was diagnosed with ''intracystic papillary carcinoma of the breast'' upon pathologic evaluation. The surgical margins were negative, and she was referred to our clinic. The existing pathology blocks were re-evaluated at our hospital's pathology department and were interpreted as ''intracystic papil-

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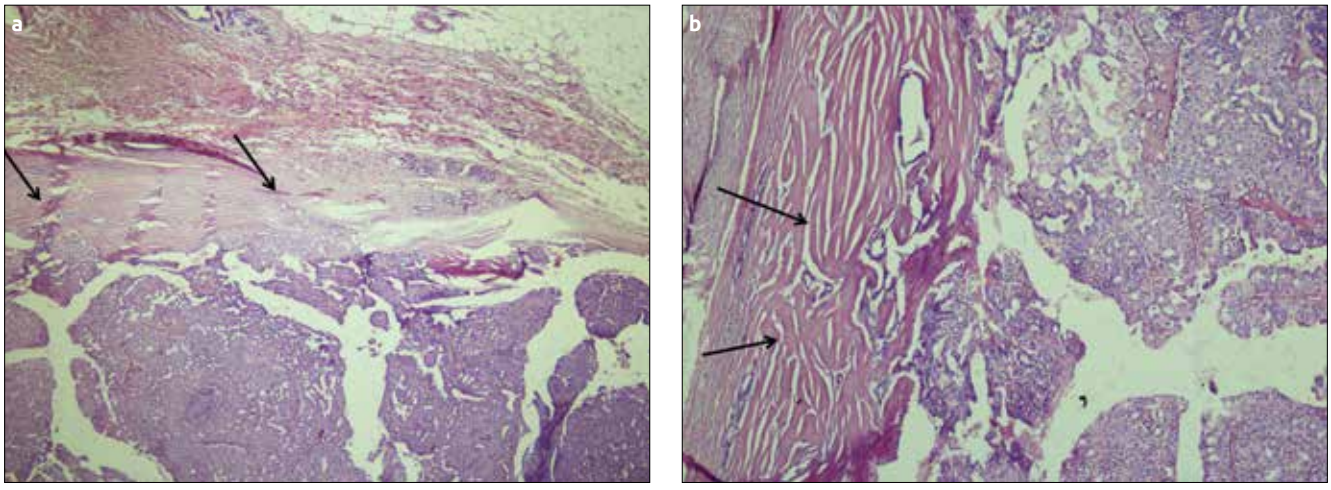

Figure 1. a, b. a) Invasive tumor area, extending beyond the capsule within the tumor that shows intracystic papillary growth. HEx40 b) Invasive tumor area, extending beyond the capsule within the tumor that shows intracystic papillary growth. HEx40

lary carcinoma of the breast with microinvasion" (Figure 1a, b). The estrogen receptor (ER) and progesterone receptors (PR) were positive. On US and MRI, secondary changes due to the previous operation on the right breast, and reactive lymphadenopathy on the right axilla were detected. The previous mammography was classified as BIRADS 0. Sentinel lymph node sampling was performed and no metastasis was detected. There were no pathologic findings on systemic screening. The patient is receiving hormonotherapy after radiotherapy.

Case 2

A 50-year-old postmenopausal woman was admitted due to a palpable mass in her right breast. Her US showed a 3.5-cm hypoechoic mass containing hypoechoic debris and hyperechoic septa at 11 o'clock position in the right breast. On MRI and mammography, a 3.5 cm mass was observed in the same region that was suspicious for complicated hemorrhagic cyst, hemorrhagic solid lesion or sarcoma phyllodes. The patient underwent excisional biopsy, and the histopathology evaluation revealed ''intracystic papillary carcinoma of the breast that did not contain an invasive focus" (Figure 2). The surgical margins were negative, and ER and PR were positive. Screening for distant metastases did not show any additional pathology. Since there was no invasive focus within the tumor, a sentinel lymph node sampling was not applied. The patient is still receiving hormonotherapy.

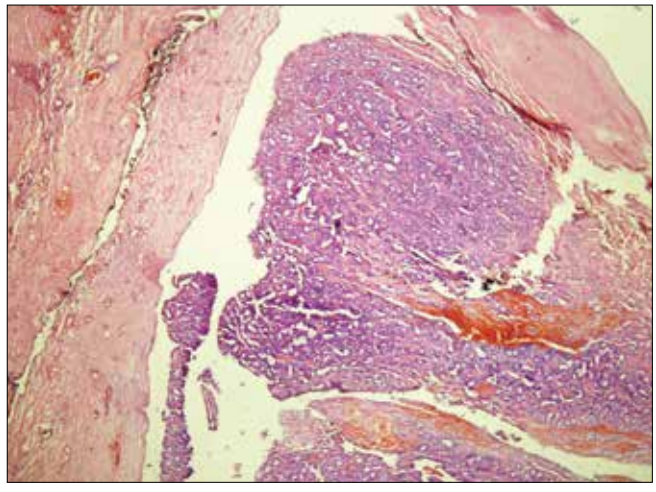

Figure 2. The tumor that shows intracystic papillary growth without invasion. HEx40

Discussion and Conclusions

IPC is a rare entity constituting approximately 1 to 2% of all breast cancers (6). It may rarely be seen in men, accounting for nearly 5 to 7.5% of all male breast carcinomas (7). Until recently, the distinction between these types of cancer was not clear and IPC was thought to have a poor prognosis. Currently, it is known that they have a better prognosis than DCIS (4). Patients usually present with a palpable mass in the breast, bloody nipple discharge, or radiographic abnormalities. Both of our cases presented with a breast mass.

The tumor histologically contains a nodule with papillary carcinoma, which is surrounded by a dilated tubule coated with fibrovascular stroma within a thick fibrous capsule (8). Although it may be seen in any age, it is usually detected in post-menopausal women and at a higher age than the mean age for breast cancer. The mean age is reported as 65 years in the literature (3, 8). Although both of our cases were postmenopausal, their age was younger.

The classification of IPC varies in the literature (9). Generally, it is accepted as a non-invasive breast cancer and as a low-grade DCIS subtype, however, there are classifications where it is regarded as invasive breast carcinoma (2). The presence of myoepithelial cells around papillary carcinoma is considered as a sign of invasive focus rather than in situ tumor (8). However, recent studies where myoepithelial cells were not detected around papillary carcinoma with DCIS created doubts on the presence of another type of IPC between in situ and invasive forms (8, 9). The rate of invasive focus is reported as 40% in many series, although it may vary (2, 8, 10). The rate of lymph node metastases range between 0-36%, and is much lower than that in normal breast cancer (3). Some studies reported simultaneous liver metastasis at the time of diagnosis of invasive IPC (3, 11). Although it is known to have a very good prognosis, this paradoxical situation should not be ignored both in diagnosis and in treatment (6). One of our cases had an invasive focus. Distant metastasis was not detected in both cases.

Fine-needle aspiration biopsy and core biopsy are often performed for its diagnosis. However, cytological false negative rate is quite high (12). Tomonori et al. (3) stated that its preoperative diagnosis was very difficult, and suggested excisional biopsy for the diagnosis of these lesions, since it cannot be diagnosed with either fine-needle or core-biopsy.

There is no agreement on its treatment, because it is a rare type of breast cancer with only case reports or series in the literature. In general, the treatment includes breast conserving surgery with wide local excision or mastectomy, followed by sentinel lymph node biopsy in its invasive forms and axillary lymph node dissection according to the pathological result, followed by adjuvant therapy. In terms of adjuvant therapy, if ER/PR is positive and HER 2 is negative, the choice of treatment is tamoxifen (1, 6, 13). Although the focus is on tamoxifen as choice of endocrine therapy, there is no conclusive evidence for the indication of endocrine treatment (9). Both of our patients were ER/PR strong positive and HER 2 negative, consistent with literature. Due to the invasive focus on one of the cases, breast-conserving surgery was followed by radiotherapy and hormonotherapy, while breast-conserving surgery followed by hormonotherapy was used in the other patient who did not have an invasive component.

Grabowski et al. (8) published the largest series in the literature with 917 patients, and stated that classification of IPC as in situ or invasive did not have a clinical significance, with excellent prognoses in both types. In addition, they advocated the treatment of all IPCs as DCIS. However, Solorzano et al. (1) emphasized that radiotherapy affected neither recurrence nor survival. On the other hand, Fayanju et al. (13) reported that adjuvant radiotherapy and hormonotherapy would reduce the risk of local recurrence in patients with DCIS under the age of 50 or those with microinvasion. Many studies have shown that tumor recurrence or mortality rate due to cancer was not increased in patients with breast conserving surgery (1, 8).

Lefkowitz et al. (2) emphasized that the growth pattern of IPC is quite slow. In addition, they reported the mean 10-year survival and disease-free survival rates as 100% and 91%, respectively. Obviously, the prognosis of this disease is very good and there is not any adjuvant treatment regimen shown to improve disease-free survival. That is why, concerns on the potential risks of adjuvant therapy is emphasized (1). Despite all general treatment recommendations and principles, the treatment of IPC remains to be controversial (6).

In conclusion, IPC of the breast should be kept in mind especially in post menopausal patients with clinically or radiologically suspicious breast cysts, and biopsy and local excision should be considered. Although there is not any standard approach for patients with this diagnosis, each patient must be evaluated for surgery and should be individually assessed in terms of adjuvant therapy.

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Case Report

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Long-term Survival after Lapatinib Rechallenge in Isolated Brain Metastasis of HER2-positive Breast Cancer

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ABSTRACT

Lapatinib is an effective drug in HER2-positive breast cancer. We present a case with successful treatment of lapatinib in brain metastasis of HER2+ breast cancer. Forty-eight years old woman was admitted our clinic with early breast cancer. In third years after adjuvant chemotherapy and trastuzumab, isolated and multiple brain metastasis were detected. After whole brain RT, lapatinib (with capecitabine for 10 months and with letrozole for 3 months) has been used. Volumetric reduction of lesions was achieved and symptoms disappeared. When lapatinib discontinued, brain metastasis relapses. Lapatinib plus capecitabine reinduction has been started. Totally, longer survival than 45 months was achieved after first brain metastasis detection. Because both combinations of lapatinib with capecitabine and letrozole were effective and reinduction treatment was successful, presented case has strongly supported activity of lapatinib treatment in brain metastasis of HER2+ breast cancer.

Key words: Lapatinib rechallenge, isolated brain metastasis, HER2

Introduction

Metastasis to the central nervous system (CNS) is significant clinical situation of breast cancer. It is documented to occur in approximately 10%-16% of cases, and tend to occur in patients with larger tumors, aggressive histological subtypes, triple negative or HER2- positive tumors (1).

Brain metastasis of breast cancer is managed with local therapy, systemic therapy, and supportive therapy. Three local treatments are basically used, namely surgical resection, stereotactic radiotherapy (RT), and whole brain RT. The surgical resection is principle therapy. The stereotactic RT and/or whole brain RT may be replaced or added to surgery. Symptom control is important. It includes corticosteroid treatment of peritumoral edema and increased intracranial pressure, treatment and prevention of seizures and of venous thromboembolism.

The systemic therapy of breast cancer contains chemotherapy, hormonal therapy, and targeted therapy. Trastuzumab and lapatinib have been used for a long time in HER2+ breast cancer systemic treatment. Trastuzumab is very effective, but it cannot cross the blood-brain barrier. CNS metastases have been reported in 25%-50% in patients undergoing chemotherapy and trastuzumab (2). Lapatinib has been considered as effective treatment option in brain metastases from HER2-positive breast cancer (3, 4). We would like to also present a case strongly supported efficacy of lapatinib in brain metastasis of HER2+ breast cancer.

Case Presentation

Forty-eight years old woman was admitted our clinic with early breast cancer. Estrogen receptor was negative, progesterone receptor and HER2 were positive (>%90 and (+++) respectively). Perimenopausal patient received adjuvant TAC (docetaxel, doxorubicin and cyclophosphamide) chemotherapy, adjuvant trastuzumab, adjuvan radiotherapy (RT) and tamoxifen. After 3 years, isolated and multiple brain metastasis were detected. T2-weighted MR images show dural metastases adjacent to the left frontal lobe and surrounding edema caused midline shift effect. Contrast-enhanced T1- weighted MR images showed homogenously enhancing dural-based masses (Figure 1).

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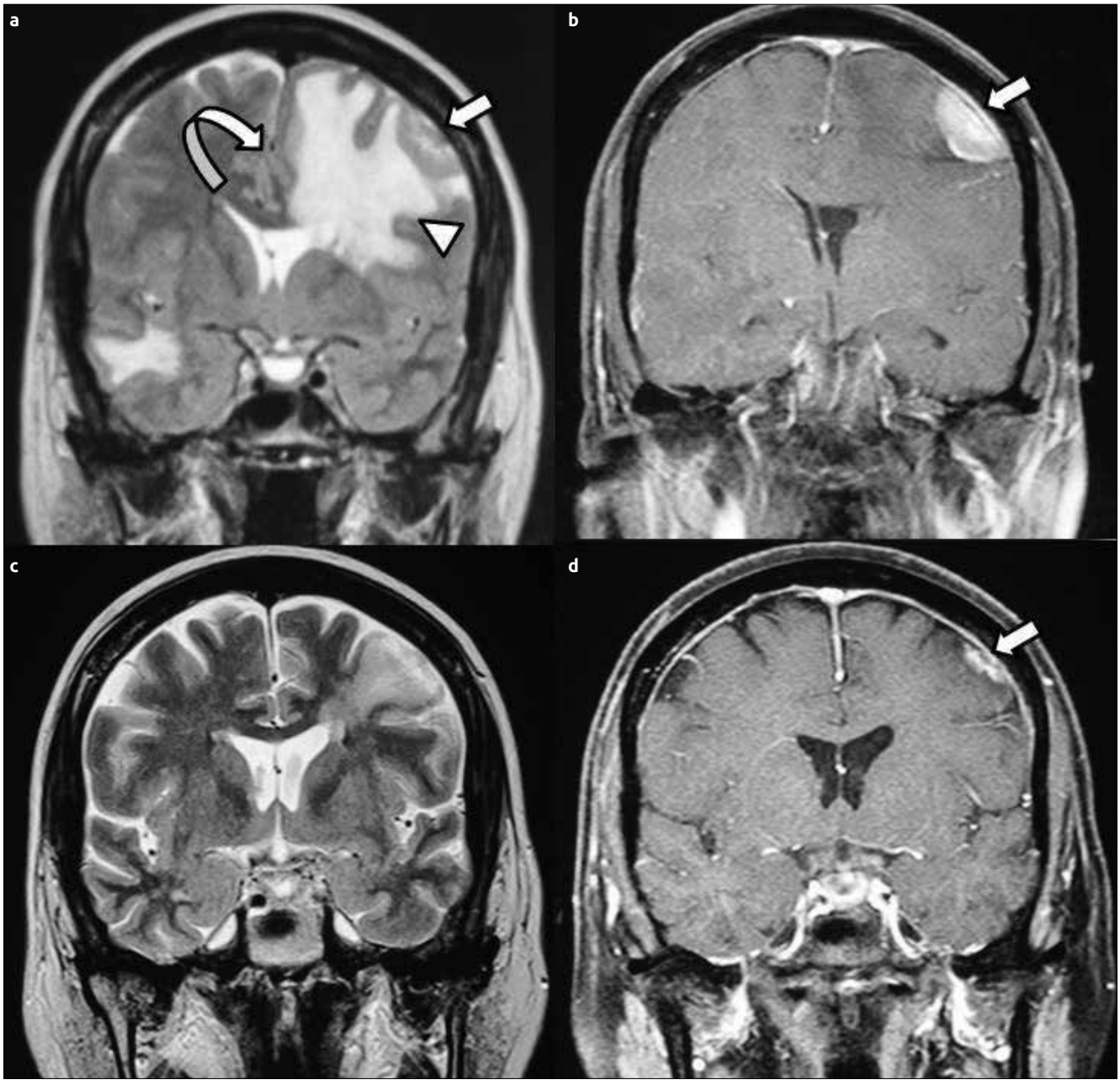

Figure 1. a-d. Coronal T2-weighted MR image shows dural metastases (arrow) adjacent to the left frontal lobe and surrounding edema (arrow head). Note that the edema causes midline shift effect (curved arrow) (a). Contrast-enhanced coronal T1- weighted MR image shows homogenously enhancing dural-based mass (arrow) (b). Coronal T2- weighted MR image obtained after radiotherapy and lapatinib based therapy show regression of the surrounding edema and normalization of the midline (c). Contrast-enhanced coronal T1- weighted MR image obtained after treatment shows regression in size of the dural-based mass (arrow) (d)

Whole brain RT was performed with a scheme of 36Gy, 300 cGy/fx, 12 fx. Subsequently lapatinib plus capecitabine chemotherapy was started. After first course of therapy, symptoms disappeared. Because of hand and foot syndrome was occurred, dose of capecitabine was reduced by 20%, two weeks later.

Volumetric reduction of CNS lesions was achieved in interval radiologic evaluation. The T2-weighted MR images after the therapy showed regression of the surrounding edema and normalization of the midline. Contrast-enhanced T1- weighted MR images showed regression in size of the dural-based masses (Figure 1).

In tenth month, complaints of hand and foot syndrome have intensified again. The treatment was switched to lapatinib plus letrozole for three months. The patient had been asymptomatic for thirteen months. She was feeling so good, but wanted to stop the therapy. Therefore, treatment was continued with letrozole alone.

In ninth month after stopping of lapatinib, symptomatic (convulsion and dizziness) new brain metastasis were detected. The radiosurgery treatment with Cyberknife (20 Gy/2fx) was performed. The reinduction with lapatinib plus capecitabine was started. The patient has been symptomless and steroid free for two years with lapatinib reinduction.

Achieved survival was longer than 45 months after the diagnosis for brain metastasis, although lapatinib treatment has been interrupted. She is still asymptomatic and progression free.

Discussion and Conclusion

Brain metastasis of breast cancer has worst outcome. It occurs more often in the patients with HER2+ tumors than with hormone positive tumors (5). HER2+ tumors treated with trastuzumab based therapy have been associated with an increased risk of brain metastasis (6). Trastuzumab related increasing survival might allow occurrence of brain metastasis. Approximately half of the patients with HER2+ metastatic breast cancer die from CNS metastasis (7).

Lapatinib is a potent reversible and selective inhibitor of the tyrosine kinase domains of epidermal growth factor receptor and human epidermal growth factor receptor (HER)-2. It binds to the intracellular ATP-binding site of the receptor. This binding leads to blockage of mitogen-activated protein kinase (MAP kinase) and phosphatidylinositol 3-kinase (PI3K), Akt, and mammalian target of rapamycin (mTOR) dependent transduction pathways. Therefore, it causes growth arrest and induces apoptosis of tumor cells. Unlike trastuzumab, lapatinib can bind and inhibit p95HER-2. p95HER-2 is the truncated form of HER-2, has not an extracellular domain but possessing greater kinase activity than wild-type HER-2.

It is known that lapatinib can cross the blood-brain barrier. It is extensively used for treatment of metastatic HER2+ breast cancer. The addition of lapatinib to capecitabine resulted in an improvement survival of metastatic HER2+ breast cancer in phase 3 study. In retrospective exploratory analysis of this study, lower number of CNS metastases at first event have been reported in the patients received lapatinib plus capecitabine (8).

There are currently no studies as a head-on-head comparison of lapatinib based therapy with trastuzumab in this situation, but studies about efficacy of lapatinib have been investigated in CNS metastases of HER2-positive breast cancer. Iwata H et al. reported a subset analysis of a phase II study of lapatinib (4). Of six patients, two patients had shown volumetric reduction >20 % in their CNS lesions, one of whom had >50 % reduction. Three patients, including two of these patients, had shown >20 % volumetric reduction in non-CNS lesions.

A multicentric phase 2 study evaluated the CNS activity of lapatinib (9). CNS objective responses to lapatinib were observed in 6% of 242 patients. In 21% of patients, 20% and more volumetric reduction was detected. It was associated with improvement of progression-free survival. These results suggested the modest CNS activity of lapatinib.

The LANDSCAPE phase 2 study investigated lapatinib plus capecitabine for previously untreated brain metastases from HER2+ breast cancer (3). 38 out of 45 enrolled patients had extra-CNS metastases at baseline. Of forty-two evaluable patients, 2 patients had a complete response, 22 patients had a partial response, and 15 patients had stable disease for CNS lesions. Only 7% of patients had progressive disease. Median time to CNS progression was 5.5 months. Median overall survival was 17 months.

Herein, our presented case has long time survival more than 45 months after first detection of brain metastasis. In pre-lapatinib era, median survival was 13 months in breast cancer patients with brain metastasis as a first recurrence site and 24 months in patients achieved complete response (10). Because both combinations of lapatinib with capecitabine and letrozole were effective and reinduction treatment was successful, presented case has strongly supported activity of lapatinib treatment in brain metastasis of HER2+ breast cancer.

Lapatinib might be considered as a good option in treatment of brain metastasis from HER2+ breast cancer until reports of new efficient therapy options (pertuzumab, TDM1 etc.).

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

Peer-review: Externally peer-reviewed.

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