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Endoscopy Assisted Oncoplastic Breast Surgery (EAOBS)

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ABSTRACT

Endoscopic oncoplastic breast surgery represents a minimal invasive approach with the aim of both removing cancer safely and also restoring the breast image. It has less noticeable scar, excellent cosmetic outcomes, high patient satisfaction rate and recently reported relatively long term safety. Operative techniques for both endoscopic breast conserving surgery and endoscopic nipple/areola/skin sparing mastectomy have been described in detail. Two different working planes in which one of them is subcutaneous and the other one is sub-mammary planes are being used during the surgery. Surgical technique needs some instruments such as endoscopic retractor, light guided specific mammary retractor, wound protector and bipolar scissor. Endoscopic breast retractors provide magnified visualization and extensive posterior dissection facility. Tunneling method and hydrodissection simplify the technique in the subcutaneous field. Oncoplastic reconstruction techniques are also applied after the tumor resection by endoscopic method. Complication rates of endoscopic breast surgery are similar to open breast surgery rates. Quite successful local recurrence, distant metastasis and overall survival rates have been declared. However 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.

Keywords: Breast cancer, endoscopic surgical procedures, breast conserving surgery, video-assisted surgery, subcutaneous mastectomy

Indication and Patient Selection

Breast-Conserving Surgery (EAO-BCS) is performed for T1-T2 tumors. The skin, pectoral muscle and chest wall invasions are contraindications. It cannot be performed in cases of multifocal tumors (1, 2). The exclusion criteria include tumor close to skin, thoracic deformity, hemorrhagic diathesis, elderly age, poor health condition and patient's reluctance towards this method (3). The other limitations of breast-conserving surgery are applicable for this, as well. Some studies cited clinically positive axilla as a contraindication (1-7). There are also studies limiting the technique to cases that would have less than 20% of volume loss (1, 8). If the potential loss of volume in the breast is estimated at 20-40%, volume replacement techniques may be more appropriate in place of volume displacement method (1, 9-11).

EAO-BCS is rather targeted at Cup A and Cup B breasts. Also, the location of tumor is important, too. For tumors located in the inner or lower part of the breast, the spaces to emerge following excision have to be filled in via volume displacements through periareolar and axillary incision (1, 8). Oil necrosis may be frequent especially when reconstruction is performed with wide-ranging mobilization and volume displacement in old patients with low breast density (1, 8, 11, 12).

Mastectomy (EASM): Skin-sparing mastectomy (EA-SSM) and nipple-/areola-sparing mastectomy (EA-NSM) can be performed with the assistance of endoscopy. Both techniques can be employed in breast cancer, ductal carcinoma in situ, risk-reducing mastectomy, large Phyllodes tumor and benign breast diseases that would require mastectomy. When mastectomy is required, EA-NSM is preferred with priority. The patient selection criteria are the same as in open surgery.

For endoscopically-assisted subcutaneous mastectomy (EASM), the skin, pectoral muscle and chest wall invasions are contraindications. Tumor that is close to skin, inflammatory cancer, thoracic deformity, hemorrhagic diathesis, elderly age, poor health condition and the patient's reluctance towards the method are accepted as exclusion criteria. Large (Cup C or above) breast and breasts that are too flabby are not eligible for EASM. As for EA-NSM, the other exclusion criteria reported in the literature are as follows: tumor larger than 3 cm, tumor that is more than 2 cm near the nipple, bleeding nipple, tumor near the area under the nipple, Paget's disease and large central tumor. Furthermore, clinically positive axilla, local recurrence and tumor with negative estrogen and progesterone receptors with a high potential

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Figure 1. Marking and drawing on the breast. The tumor margins (innermost), excision margins (middle ring), margins of dissection and mobilization to be performed in the anterior and posterior sites (outermost) and the lymph node incision in the axilla are shown

for distant metastasis are accepted as exclusion criteria in many clinics. No consensus are present for patients that would receive preoperative or post-operative radiotherapy. The results indicate that this technique can be performed in such patients (13-15).

Marking

Breast-Conserving Surgery:

The projections of tumors or lesions on the skin are marked before surgery under ultrasound guidance (Figure 1). The excision margins are determined at 1-2 cm away from the tumor margins (1, 3, 6-9, 16). At the beginning of surgery, all-round color stain injections are performed at the excision margins (1, 4, 8, 11) (Figure 2). Since the blue stain is generally used for marking sentinel lymph nodes, the marking should be done using a stain that is not mixed with the blue stain in EAO-BCS. The stains used according to the literature include Gentiana Violet (4, 16), Diagnogreen (17), Indigo Carmine (3, 7) and Pyocyanin (8, 18). Furthermore, these stains are used by being mixed with gel (1% Lidocaine Gel or Xylocaine Gel) at a ratio of 1/1 in order to prevent the injected stain from being absorbed and spreading.

Mastectomy:

The projections of tumors or lesions on the skin are marked by drawings prior to surgery. The all-round margins of breast tissue are also included in marking. Furthermore, the marking of internal thoracic and artery branches on the breast in the parasternal area would be beneficial for the preservation of blood flow during dissection (1, 8, 19).

Incision

Axillary and periareolar incisions are the most frequently used incisions in both mastectomy and breast-conserving surgery. The incision used in axilla is a generally an incision that is 2 cm, which is made for sentinel lymph node, and it is used for dissection performed in the posterior part of the breast (1-4, 6-9, 11, 16, 17, 20). To create a skin flap, a periareolar incision is used. In addition to this incision, an additional skin excision in the shape of half moon is used to enlarge the incision, thereby facilitating the removal of excised tissue through here. The site for periareolar incision is determined on the basis of



Figure 2. Subcutaneous stain injections at several points on the excision margins are seen

the location of tumor in the breast. The incision is kept at a size that is approximately 2/5 of the perimeter of areola (2, 3, 8, 11). Since work is done through a small incision with EAO-BCS, the skin around the incision during the procedure may be injured. To prevent this, a wound protector (Alexis; Hakko Co; Johnson & Johnson) is used (1, 5-8, 11, 16) (Figure 3).

Although there are recommendations in the literature for mastectomy such as long (5-10 cm), single axillary incision and lateral breast incision (17, 19, 21, 22), these are not currently used at an extensive rate. A comparative series demonstrated that 5.5 cm axillary incision had superiority over open skin conserving mastectomy (22). Periareolar incision is performed laterally on the breast. This ensures facilitation in the placement of implant or expander and in the creation of a pocket.

Another technique used in EASM is the endoscopic technique where trocars are also used. With this technique, the working area is created via insufflation over a single-port entry on a single axillary incision of 4-6 cm, and then an anterior site dissection is performed followed by a posterior site dissection (23, 24). In this series of 10 cases, the average operation time was reported as 250 minutes, rate of partial nipple necrosis corrected with medical treatment as 30%, hematoma as 10% and infection as 10%.

Posterior Dissection

Dissection in the retromammary space is performed between the posterior face of the breast and the pectoral muscle (Figure 4). Retractors with optical systems (Vein Harvest, Ultra Retractor, Vein Retractor) are also used for blunt dissection while bipolar scissors or electro-cautery is used for coagulation (1, 5, 8, 11, 16, 17) (Figure 5, 6). Techniques for creating the work area using pre-peritoneal dissection balloon (17, 21) or insufflation (22) were used in the past as part of posterior dissection; however, they are not preferred today.

In cases of Breast-Conserving Surgery, mobilization is performed in such a way as to cover an area further beyond the tumor margins in order to facilitate especially volume displacements. In cases that will undergo mastectomy, the dissection site is consistent with the anatomic margins of the breast.



Figure 3. The dissection performed using special lighted breast retractor in deep sites while the skin flap is prepared in the posterior site is observed. Wound protective material is also used for areola dissection



Figure 4. Endoscope (retractor) is inserted through the axillary incision and the posterior site is dissected with electro-cautery as seen. Here, endoscope is also used as a retractor

Anterior Dissection (Creation of a Skin Flap)

This dissection is performed between the breast and skin and periareolar incision is used (Figure 7). Before the dissection, injections of physiological saline solution with Epinephrine at a ratio of 1/1,000,000 (approximately 150 cc) are administered in this plane (Figure 8). This technique is termed the “Tumescent Technique” or “Hydrodissection” and it not only facilitates dissection, but also ensures that they are performed with less bleeding (8). Following hydro-dissection, the dissection is completed by using an optical system and bipolar scissors between the subcutaneous plane and the breast tissue (8) (Figure 9). Attention should be shown during dissection to make sure that the flap is not too thin. Very thin flaps increase the potential for ischemia and necrosis in the skin (8). For dissection, “harmonic scalpel” or electro-cautery may also be used (1, 2, 7, 9, 16, 17) (Figure 10). The flap is gently retracted using a special lighted breast retractor (Mamma Retractor-Four Medics, Tokyo; Cold Light Retractor-Komagowa, Spain; Oral Retractor- TISE) in order to facilitate the dissection.

Subcutaneous dissection is made easier by the tunnel method. With this technique, a multiple tunnel is opened using scissors on the sub-

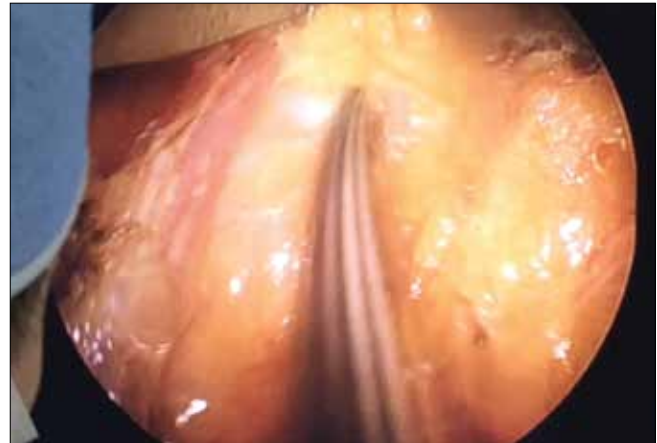


Figure 5. Dissection in the posterior site is seen in the monitor. Sharp dissection is performed with a pair of bipolar scissors in the plane between the breast tissue and pectoral muscle under imaging guidance and the breast tissue is mobilized



Figure 6. Dissection using a pair of bipolar scissors under endoscopic guidance in the posterior site is seen in the monitor. The breast tissue is mobilized in the space between the breast tissue and pectoral muscle and at the edge of the pectoral muscle in the outer lateral side

cutaneous plane in a radial way towards the periphery from the nipple (7). Then, the septa between tunnels are cut. One of the different methods employed as part of the tunnel method is the creation of tunnels using bladeless trocars (Optiview, Bladeless Trocar, Endopath, Visiport Plus) (1, 3-6, 8, 11, 13, 16, 17, 20).

One of the techniques for subcutaneous dissection, which is recommended in the literature, yet has not been widely adopted in practice, is the use of traction sutures placed on the skin to facilitate dissection (10, 11, 16) or the use of needles stuck on the skin in order to delineate the excision margins (16).

Specimen Excision and Reconstruction

Breast-Conserving Surgery: The tissue that has been excised is removed through the periareolar incision. Some surgeons use “Endo-catch” in order to remove the specimen (1, 16). The cavity is marked using clips (1, 4, 8). All the oncoplastic techniques used in reconstruc-



Figure 7. The periareolar incision line is drawn before anterior site dissection is started. The incision entrance will have been slightly enlarged with a skin incision in a half moon shape



Figure 8. Before starting dissection in the anterior site, injections of physiological saline solution with Epinephrine at a ratio of 1/1.000.000 are performed in the previously marked mobilization area. This procedure would ensure a dissection that is not only easy, but also causes relatively less bleeding

tion can be employed here, as well. The most commonly used techniques include the volume displacement, volume replacement and filling techniques.

Volume Displacement: This is the most commonly used technique. The breast tissue that is mobilized by being removed over the pectoral muscle posteriorly and from the skin anteriorly is pulled from both sides towards the cavity in the middle under the guidance of imaging and stitched together using sutures. If plication develops on the skin following volume displacement, skin mobilization is performed on a wider area (1-4, 6, 8, 19).

Volume Replacement: If the excised tissue is 30% of the total breast or more or the cavity that emerged cannot be closed with volume displacement, the latissimus dorsi flap or lateral thoracic adipose tissue flap mobilized with endoscopic technique can be brought to the cavity by working through the axillary incision (1, 9).



Figure 9. Working through the periareolar incision, the skin traction is ensured, advancement in the subcutaneous plane is made and the breast tissue is separated from the skin

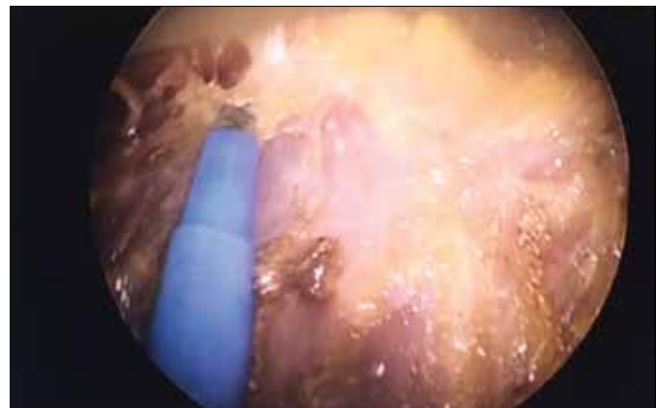


Figure 10. After the completion of the mobilization of skin flap in the anterior site, the tumor tissue has been excised in line with the margins and hemostasis control is achieved in the tumor bed as accompanied by endoscopy. At the same time, breast tissue with enough mobilization for the volume displacement procedure is prepared

Cavity Filling: The site of the excised breast tissue is filled in with a new synthetic material. These techniques do not have a proven success. The materials that have been tested include absorbable synthetic mesh (Vicryl Mesh, Johnson&Johnson) wrapped in an adhesion barrier (Interceed, Johnson&Johnson) (4, 16, 17, 25). A study reported excessive fluid buildup in almost all the cases and an infection rate of 11%. This method is not recommended in patients with collagen disease or on steroids (17). Furthermore, “Oxidized Cellulose” (Surgicel, Johnson&Johnson) was also tested in order to wrap the mesh used for filling in the cavity (1, 5, 16, 17, 25). The mesh here causes the growth of granulation, reactive fluid and fibrosis tissue while “oxidized cellulose” prevents the mesh from adhering to the skin (25).

Mastectomy: For reconstruction after EASM, the methods that are employed in the open technique are used. Reconstruction with implant is performed with priority. A technique with dual or single procedure is preferred depending on the case or the surgeon. During the EASM procedure, mastectomy is completed and then work is done

through the periareolar incision. An endoscopic retractor is used to start dissection of the pectoralis major muscle from its lateral margin with the aid of imaging, the area under the muscle is entered with sharp dissection and a pocket for implant is created using an expander. An implant or expander is inserted in the pocket through the axillary incision (11, 13, 21).

Operation Time

In general, longer times are reported for the endoscopic surgeries of the breast (11). The operation times are closely related with the reconstruction technique that is used. The endoscopic procedures performed at the beginning bring about an additional 30–40 minutes on average to the conventional surgical times (7, 11, 12, 22). However, this time is associated with the learning curve. Operation times equal to those of open surgery when the learning process was completed have been reported.

Cost

The increased cost is associated with the materials that are used. Single-use instruments increase the cost. Re-usable instruments reduce the average cost. A study reported that the essential setup cost of the system to be able to start endoscopic breast surgery in addition to open surgery was \$10,000 (3). In another study where a rough cost analysis was performed, the cost of endoscopic lumpectomy was reported as \$1150 and open lumpectomy as \$500 (11, 22).

Cosmetic Results

Generally speaking, reasonable aesthetic results are reported with EAO-BCS. Two studies reported better results as compared to open surgery (1, 2, 8, 17, 18). A significant difference is achieved especially in terms of scars (1, 8, 18). For a comprehensive and objective assessment, a 4-point-scoring aesthetic evaluation should be made and the quality of life should also be questioned. The assessment methods appropriate for this include the “Breast Cancer-Specific Quality of Life Questionnaire” (EORTC-QLQ-BR23) or “Patient Satisfaction Rate” (FACT-B) by EORTC (European Organization for Research and Treatment) (1, 18).

In the “5-item” system, which is commonly used in cosmetic assessment (ABNSW), the important assessment parameters include asymmetry, breast shape, nipple shape, skin condition and wound scar. The scoring is done using a 4-points scoring system (excellent=3, good=2, moderate=1, poor=0). A score of 11 points in total or above is considered as good or excellent breast aesthetics (1, 5, 7, 8).

The Japanese Breast Cancer Society, on the other hand, uses an 8-item classification. The themes used include the breast size, breast shape, breast scar, breast hardness, nipple and areola size, nipple and areola shape, nipple and areola color, nipple and areola position and inframammary groove condition. Every theme is scored according to a 3-point system (good: 2 points, moderate: 1 point, poor: 0 points). In total, a score of 11–12 points is considered an excellent cosmetic result, 8–10 points good, 5–7 points moderate and 0–4 points a poor cosmetic result (1, 8).

The results of endoscopic-assisted breast surgeries are generally reported as minimal scar and excellent cosmetic results. Kitamura reported an excellent result of 85% with the endoscopic technique and of 60% with the open technique in a study comparing this technique with open surgery (11, 22). As for the questionnaire studies related to patient satisfaction, it is seen that the majority of patients receiving EOSM are pleased with the result.

Complications

The complications reported with endoscopic breast surgery are generally the same in type and equal in rate with open surgery. Fan reported in his comparative series that the complication rates were equal for endoscopic and open technique and that they varied according to the surgical technique and type of reconstruction performed (11, 12). The most frequently encountered complication is the development of seroma (21). Superficial or deep skin burns and ecchymoses due to the inadequate protection of skin are also often encountered (7, 9, 11–13, 26–28). The wound site infection rates range between 1% and 9% and they are not higher than in open breast surgery (11, 13). The infection rates are higher for mastectomy and implant procedures. The requirement to remove the prosthesis due to infection develops in approximately 10% cases where implants were used (21). When the insufflation technique is used to create a surgical working area, subcutaneous emphysema is often seen in the breast and surrounding tissues (11, 27, 28). Furthermore, asymmetry, deformity and skin plication may develop in the breast and nipples depending on the reconstruction technique and procedure. There are no studies comparing endoscopic breast surgery with open surgery in relation to post-operative pain and the use of analgesics (11).

Breast-Conserving Surgery: Especially in elderly patients and patients with low breast density, oil necroses may be seen when reconstruction is performed with wide-ranging mobilization and volume displacement using the endoscopic technique (1, 8, 12, 25). The complication rate for the EAO-BCS is approximately 10% on average. Skin and nipple necroses are rather rare in EAO-BCS.

Mastectomy: In terms of severe complications, skin and nipple necroses may be encountered. Especially the “tumescent technique” has resulted in increased skin ischemia and necroses (8).

Nipple Necrosis: It is one of the serious complications developing with EA-NSM. The rates reported in the literature are in the range of 0–20% (13). Full or partial necrosis may develop. The ratio of complete necrosis is below 10%. The reason why different rates are seen in the literature is that the tissue left in the tissue with EA-NSM is variable. No standard tissue thicknesses exist on which consensus has been achieved. Leaving a tissue with a thickness of 5 mm on an area with a width of 2 cm has been recommended (13). Another factor influencing the rate of complications is the use of cautery in dissection. For the dissection of the area below the nipple, the use of scissors rather than cautery is recommended.

An important factor in nipple necroses that develop following EA-NSM is the incision performed. Radial or lateral incisions should be preferred rather than medial incisions (13). For transareolar incisions, nipple necrosis develops at the highest frequency with a rate of 80%. Partial or full necrosis develops at a rate of 17% in periareolar incisions and a rate of 4–8% in radial or inframammary incisions (15).

One of the factors effective in the development of nipple necrosis following EA-NSM is the “coring” technique which is performed in certain centers. The tissue under the nipple is completely excised by being cored with oncological concerns and only the nipple skin is left behind. The rates of necrosis in cases where the nipple is cored amounts to 40% and nearly 24% of them are complete necrosis (13).

The most important factors influencing nipple necrosis are the ones that pertain to the patient. Patients who have diabetes, vascular dis-

ease and smoke have higher rates of nipple necrosis. Nipple necroses secondary to perfusion disturbance in large (Cup C and above) and overly flappy breasts also have higher rates (14, 24). Most of the nipple necroses, especially partial ones, improve with medical treatment and do not require excision (21).

Loss of Sensation in the Nipple/Areola

The loss of sensation in the skin, nipple and areola following endoscopic breast-conserving surgery is rare. It is reported to generally improve in a period of 6 months to 1 year in patients receiving mastectomy.

Loss of Blood

In the initial periods when endoscopic technique entered into use, Kitamura reported that the endoscopic mastectomy group had more bleeding in his study where he reported the early results (11, 22). In the consequent years, 3 different studies were performed in relation to intraoperative bleeding and postoperative drainage with the EASM technique and no differences were found between endoscopic and open methods (1, 8, 11, 12). A study where reconstruction was made using the filling method following EAO-BCS found that bleeding was lower than with the open method (1, 17).

Oncological Results

Breast-Conserving Surgery: Rates that are equal to those of open surgery are reported with respect to local recurrence, distant metastasis and overall survival while certain studies report better oncological results. However, the average follow-up durations are between 12 and 40 months and this is a rather short period to make a clear decision about oncological results (1, 3, 4, 6-9, 11, 26).

Local Recurrence: There are 6 studies assessing local recurrence following EAO-BCS. The studies where local recurrence is cited in the range of 0-4% have average follow-up durations of 12-38 months (1, 3, 4, 6-9, 11). Nakajima specified tumor size as a risk factor for local recurrence in EAO-BCS with local recurrence rates of 3.7% for T1 tumors and 5.1% for T2 tumors in his series (1, 9, 11). To date, local recurrence on periareolar or axillary incision in any of the EAO-BCS cases has not been reported.

Distant Metastasis: Three studies related to the development of distant metastasis in patients who received EAO-BCS have been reported (1, 4, 8, 9). In the study with an average follow-up period of 40 months, it was reported that the distant metastasis rate was associated with the tumor diameter (1, 9, 26). In a study with 244 cases, no differences were found in terms of distant metastasis among patients undergoing EAO-BCS and open surgery (11, 26). Another study citing a metastasis rate of 10%, distant metastasis was attributed to the high axillary involvement ratio (41%) and high tumor load was blamed (9, 11).

Overall Survival: Five studies related to overall survival in patients undergoing EAO-BCS have been reported. The follow-up periods of the studies are short, but the results look excellent (1, 3, 4, 7-9, 11). A study citing data sorted by the tumor diameter reported an overall survival rate of 97.3% for T1 tumors and 95.7% for T1 tumors (1, 9, 11). Another study demonstrated that there were no differences in terms of survival among Stage I and Stage II patients who underwent EAO-BCS (1, 26).

Mastectomy: As in the open nipple-conserving mastectomy technique, discussions on the oncological risk of breast tissue left behind

the nipple with EAO-BCS are also ongoing (13). The collection and examination of biopsy from the tissue under the nipple during EAO-BCS constitutes a method that is rather widely implemented. However, suspicion of tumor or marginal positivity at the nipple are identified at rates amounting to 9% in the paraffin wax cross-sections in post-operative period in spite of this procedure, which may require these cases to undergo nipple excision in the aftermath (21). There are also studies recommending radiotherapy during or after surgery for the breast tissue remaining behind the nipple (11, 13, 29).

Local Recurrence: Eight of the published papers cited the local recurrence rates (2, 11, 19, 20, 27, 29-32). No recurrences were reported in studies with an average follow-up period of 2 years on average and in non-prospective studies (11, 13, 21). It is obvious that studies with longer follow-up periods are required in the light of studies indicating that recurrence is increased especially after the 3rd year (9, 11). A non-randomized study compared EASM and open, skin-conserving mastectomy cases in terms of local recurrence and it was reported that none of the cases had recurrence (7, 11). Another study compared EASM and open breast-conserving surgery and no was demonstrated with the rate being 1.9% for open breast-conserving surgery and 8% for EASM (11, 12).

Distant Metastasis: Three studies in the literature cited distant metastasis rates (11-13, 22) and a rate in the range of 4.5-10% with the longest follow-up period being 38 months was reported. No differences in terms of distant metastasis were identified among EASM and open skin-conserving mastectomy patients in 2 studies with 143 patients in total (11, 12, 22).

Overall Survival: One of the studies where EASM was performed and overall survival was reported, no significant differences were identified between EASM and open skin-conserving mastectomy. In other studies, a survival rate of 100% was reported for EASM with an average follow-up period of 12 months to 4 years (11, 12, 16, 21, 22).

Advantages

The most important advantages of endoscopically assisted breast surgery are "less scar", "better cosmetic" and "more patient satisfaction."

Disadvantages

Longer Operation Time: The reason behind is that work is done on a more limited surgical site. Furthermore, an influencing factor is that it is a new technique and requires training. The learning period also influences the learning period. The "Tumescent Technique" reduced the operation time (1, 8).

Additional Cost: EASM technique requires a new group of instruments and materials. The single-use instruments used in other laparoscopic surgeries have not yet been approved for endoscopic breast surgery. This deficiency creates a cost- and legislation-related problem in the implementation of this technique. For the solution, simple and re-usable instruments should be developed for the field of endoscopic breast surgery. In five studies reported in the literature, re-usable endoscopic retractors were used (1, 3, 7-9, 11, 20).

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Molecular Classification of Breast Carcinoma: From Traditional, Old-Fashioned Way to A New Age, and A New Way

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ABSTRACT

Breast carcinoma comprises a group of diseases with specific clinical, histopathologic and molecular properties. Traditional classification use morphology to divide tumors into separate categories with differing behavior and prognosis. However, there are limitations of traditional classification systems, and new molecular methods are expected to improve classification systems. Molecular subtypes of breast carcinomas have been characterized in the last 11 years, and have been studied extensively. Much of the information accumulated in recent years, and molecular taxonomy seems to be still developing and undergoing change. The main question is whether new molecular techniques such as gene expression profiling will be accepted as gold standard in determining breast cancer subtypes, and whether molecular classification is useful in specific subtypes of breast cancer as it is in ductal carcinoma (nonspecific type). In addition, critical review of the literature reveals major problems such as poor definition, lack of reproducibility and lack of quality control in current molecular techniques and classifications. Therefore, current molecular approaches are not yet used in routine clinical practice and treatment guidance since they are immature and can even lead to incorrect assessment.

Keywords: Breast cancer, the molecular classification, immunohistochemistry, microarray gene expression

Introduction

Breast cancer is a significant and common disease that has a negative effect on women health, and is one of the leading causes of cancer related deaths. It constitutes 23% of all cancer patients and account for 14% of cancer related deaths (1). Egyptian physicians have accepted it as a fatal disease, and extensive surgical treatment was applied for many years until the end of the 19th century (2). At the beginning of the last century, it was enough to know that the patient had breast malignancy and all patients were administered a uniform treatment. Over time, the observation that patients with the same type of cancer show varying prognosis, and identification of increasing form of different morphological variants by pathologists during the last 50 years has led to discussion on breast cancer classification. Currently there are 20 major types and 18 minor subtypes of breast cancer that have been defined and included in the recently published WHO classification (3). However, there are doubts as to whether these variants are biologically significant or not. In addition, definition of so many variants is suggested to result from the pathologist's own design. On the other hand, pathologists have been stating that breast cancer is a heterogeneous disease rather than a single disease for quite a long time. Now, it is obvious that breast cancer is a heterogeneous disease with different histological and biological properties due to genetic, epigenetic and transcriptome changes, with varying clinical findings and treatment responses, and with multiple entities. This phenotypic difference influences breast cancer diagnosis, treatment and thus prognosis. The basis of all this chaos seems to be based on absence of specific markers, and not fully understanding epithelial cellular development of breast tissue (4, 5). With the advancement of molecular techniques such as gene expression profiling, "heterogeneity in breast cancer concept" has now become generally accepted. Thus, a new "taxonomy" began to develop in the classification of breast cancer. This development has led to a concern between surgeons and oncologists that standard histopathological analysis reports prepared by pathologists will not contain some important data in the regulation of patient care and consequently patient treatment may not be regulated properly. Thus, pathologists were introduced to the so-called new era "Molecular Classification" that is developed from the traditional old fashioned "morphological" classification new age classification. Targeted therapies and more importantly, individualized treatment programs have become possible with the implementation of this classification.

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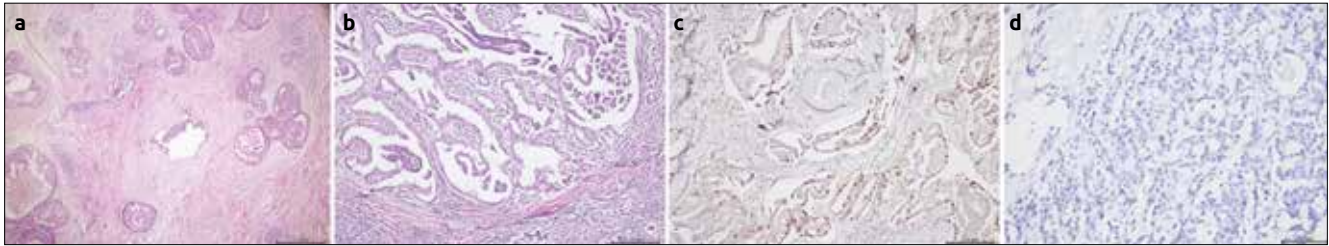


Figure 1. a-d. Intratumoral heterogeneity with H&E, IHC and CISH. (a) Comedo-type ductal carcinoma in situ morphology containing focal invasive ductal carcinoma (b) Heterogeneity in breast carcinoma lymph node metastasis (papillary, micropapillary and ductal morphology) (c) ER positivity and heterogeneity in breast carcinoma (d) Intratumoral heterogeneity with CISH

Traditional, Old Fashioned Practice

Invasive breast cancer is currently classified as non-specific ductal carcinoma and specific subtypes. Special subtypes of breast cancer have specific definitions, while the non-specific type is like a dumpster containing all carcinomas other than specific subtypes. Non-specific invasive ductal carcinomas constitute about 60-75% of all breast cancers. Specific types constitute 20-25% of all, and the most common types within this group are lobular, tubular, papillary, and mucinous tumors (3, 4). Heterogeneity within a single tumor (intratumoral) or between morphologically similar same type of tumors (intertumoral) is currently well-known and accepted (Figure 1). Therefore, pathologists have attempted to produce new systems to allow clinicians to monitor their patients better. An absolute necessary component of pathology reports is “histological grade”, and is determined by the evaluation of the degree of tumor differentiation (tubule formation), nuclear pleomorphism / degree and proliferation (mitosis rate).

Microscopic Grading in Breast Carcinoma (Nottingham Modification of the Bloom-Richardson system)

Tubule formation

- 1 point: Tubule formation constitutes more than 75% of the tumor,
- 2 points: Tubule formation constitutes 10-75% of the tumor,
- 3 points: Tubule formation constitutes less than 10% of the tumor.

Note: Tubule formation evaluation should take into account the entire tumor.

Nuclear pleomorphism

- 1 point: Nucleus shape and size difference mild,
- 2 points: Nucleus shape and size difference moderate,
- 3 points: Nucleus shape and size difference significant.

Note: The area containing cells with most prominent nuclear pleomorphism should be evaluated.

Mitotic Count

Mitotic counting process should only be done at the periphery of the tumor and should be started from the most mitotic active areas. The suggested application is counting within the same field, but it is not necessary to use subsequent fields. Areas rich in tumor that are free of normal breast tissue are preferred as much as possible. Prophase cells should not be counted. Due to differences in image area due to varying brands of microscopes, there are determined and accepted values for the number of mitotic count. Based on these values mitotic count are scored as 1, 2 and 3.

A total score is obtained by scores on tubule formation, nuclear pleomorphism and mitotic count. The histological grade is determined based on the obtained total score, as shown in Table 1.

Histological evaluation by this method is semi-quantitative, but provides very strong prediction for determining patient prognosis (6). In addition, it is known that histological grading is associated with histological type as well as with molecular changes such as estrogen-progesterone receptor expression and HER-2 amplification (7). In the traditional approach, a number of powerful parameters such as tumor size and extension pattern (particularly lymph node involvement status) determine the stage of the disease, and these are important prognostic factors. The principles of a staging system that can be applied to all types of cancer and parameters of tumor, node, metastasis (TNM) were defined by Pierre Denoix, and has gained wide acceptance shortly afterwards (8, 9). The TNM system is used as a common language among treatment centers widely all over the world, to guide treatment planning, provide a possibility to demonstrate the effectiveness of the treatment during follow-up and predict prognosis. However, with advances in diagnosis and treatment of breast cancer, improving technology and increased knowledge, initiatives to evaluate tumor biology in detail, accumulation of new data showing that most prognostic factors are related to biological features of the tumor, and most importantly the observation of very different survival rates within tumors with the same TNM group and same histological type have led to the search for alternative solutions.

The TNM_{EIO} system was suggested by the European Institute of Oncology (EIO) in an effort to include tumor characteristics affecting treatment decisions in the TNM system (10). In this system, all anatomical and biological properties such as ER, PR, HER-2 of the tumor are included. It was suggested that if the diameter of the breast carcinoma is 1.3 cm it can be defined as T1.3, similar application can be used for lymph node invasion, the number of all examined lymph nodes including sentinel lymph and the number of lymph nodes with invasion (e.g. N0/1, N3/9, Ns0/9, s: sentinel lymph node), and the site of metastasis is presented with a suffix to M (M_H: Hepatic metastases, M_L: Lung metastasis). According to this system, a tumor with a maximum size of 1.8 cm, ER positive, PR negative, HER2 positive, with liver metastases, and invasion in 2 out of 26 lymph nodes is coded as T1.8, ER +, PR-, HER2 +, N2/26, M_H. Some centers prefer more aggressive treatment modality in tumors with lympho-vascular invasion.

Indexes such as Nottingham Prognostic Index (11), Adjuvant! Online (AO) (12) and St. Gallen criteria (13) are widely used when deciding on treatment, in order to increase the success of predicting survival and development of metastatic disease. Histopathologic evaluation is very effective in directing clinical treatment of breast cancer pa-

tients. However, the significant differences detected among patients with the same histological subtype (eg, tubular carcinoma) and the same histological grade-the same stage (eg, node-negative disease) in response to treatment and long-term survival, as well as benefits of tamoxifen treatment in ER positive patients, and of trastuzumab treatment in patients with HER-2 amplification, all support the belief that breast cancer is a heterogeneous group of diseases, thus pointing out the importance of biological properties of the tumor in its management. Although the value of clinical data and algorithms are limited with results from undersized clinical studies, it is promising that new generation molecular methods can provide a more precise classification, thus more targeted and perhaps individualized treatment options.

New Era, New Beginning

All kinds of molecular analytical methods applied to cancer tissue help us determine the prognostic and predictive factors of the cancer. Together with the introduction of microarray-based technological applications, which is one of these beneficial molecular analytical methods, the development and use of genomic and expression profiling studies has led to development of a breast cancer classification system based on tumor biology rather than morphology. Studies conducted with this method also support the idea that breast cancer is a molecularly heterogeneous disease with different clinics, and that it is a complex disease containing different gene expression patterns that influence prognosis (14-17). The results of these studies are believed to be more objective than the currently used relatively subjective histopathological evaluation. New era, new methods applied with new technology provide definition of various aspects of breast cancer again but in a different way, and allows us correlating these with morphological appearance of breast cancer. Nevertheless, it must be remembered that new molecular technological evaluation methods are not completely independent, and in fact, the data obtained incorporate many assumptions.

Perou and Sorlie proposed “Molecular Classification” terminology in breast cancer for the first time with a comprehensive study showing the differences in gene expression in 2000 (14). In this study breast cancer was divided into different sub-groups according to various gene expression: “Luminal” (often differentiated in two or three subgroups; reflecting ER, ER regulatory genes and the expression of genes expressed in normal luminal epithelial cells), “HER-2 positive” (reflecting ErbB2 / HER-2 amplification and overexpression), “basal” (reflecting ER, PR, and HER-2 negative and the expression of genes expressed in normal breast basal and / myoepithelial cells). A normal-like subgroup has been described, but the importance of identifying this subgroup and its consequences are not clear, because it seems to represent samples with low tumor cell content and more normal tissue components. Such molecular subtypes were formed by differentiation of numerous intrinsic genes (showing very little difference in the repeated samples of the same tumor but high rates of difference in different tumors) and clustering of patients in a hierarchical order to separate into different groups in terms of transcription (14). Since only samples belonging to a retrospective evaluation of numerous cases can be classified with this method, the “Single Sample Predictor (SSP)” has been defined. With the implementation of SSP, inclusion of a single tumor to a specific subtype was provided by using the closest main class of the tumor (16-18). SSP2003, the first described SSP, includes 500-gene expression (16). SSP2003 is further differentiated with repetitions of intrinsic gene lists, yielding two new SSPs: SSP2006 and PAM50 (17, 18). There are certain

limitations of SSPs defined in this way. Pusztai et al. (19) emphasized such limitations in detail, and showed that even small changes in the initial set of defined SSPs can lead to significant changes in hierarchical clustering that is used defining subgroups. Thus, the stability of the method has been questioned (19, 20).

It was shown that three main subtypes can be identified in a stable manner by only using genes related to ER and HER-2 phenotypes instead of using hundreds of intrinsic genes (21). These subtypes are ER- / HER2- (basal-like), HER2+(HER2-Enriched), and ER+/HER2- (luminal A and B combined). Mackay et al. (22) pointed out that there was no inter-observer harmony in defining subtypes from dendrograms generated by hierarchical clustering. Such complex studies and assessments have led to new, alternative classification approaches (23): In this approach model, an mRNA expression predictor that classifies breast tumors in four molecular entities, by quantitative measurement of three genes, namely ESR1, ERBB2 and AURKA. The AURKA mentioned in this context is a proliferation module providing separation between low and high-proliferative tumors (aurora kinase A [AURKA]). The four entities defined by this model are as follows: ER +/ HER2-/ low proliferative, ER +/ HER2-/ high proliferative, HER2+and ER-/ HER2-.

The defined model is a simplified subtype classification model (Subtype Classification Model-SCM) and contains only ESR1, ERBB2 and AURKA genes, and is simply known as SCMGENE. It was reported that major breast cancer intrinsic subtypes can be defined by SCMGENE determinants (ESR1, ERBB2 and AURKA), and that it provides a firm distinction for clinical use similar to 50 genes predictor (PAM50). A recent study compared results from PAM50 and SCMGENE in terms of different factors (such as patient prognosis, pathologic complete response, biological differences) (24). This study concluded that classification into major molecular subtypes that are clinically relevant was the best model of those including wider gene panels.

Despite the ongoing debate on advantages of molecular subtyping methods of breast cancer over each other, basically luminal A, luminal B, HER2, basal and normal-like molecular subgroups represent different prognostic subgroups, has led to rapid acceptance of the proposed classification system into clinical practice. Efforts have been made to ensure widespread use of molecular classification system as a diagnostic tool and prove its validity. It was proved that various data from different patient study groups and different array platforms overlap with the classification system quite tightly (15-18).

Detection of difference in response to treatment and metastatic pattern according to molecular subtypes further increased the value of molecular classification (25, 26).

Ultimately, the idea that a patient with breast cancer can be classified according to the molecular subtype of the tumor and thus directed to appropriate, specific, targeted therapies has become very attractive. Nowadays the search for specific, targeted, personalized treatment programs are ongoing in all types of cancer. There are controversies if data obtained from the assessment of histological grade of the tumor, ER and HER-2 status can provide appropriate treatment that the molecular classification will bring.

What are the molecular subgroups?

The current molecular classification divides breast cancer into five groups as luminal A, luminal B, HER-2, basal and normal breast

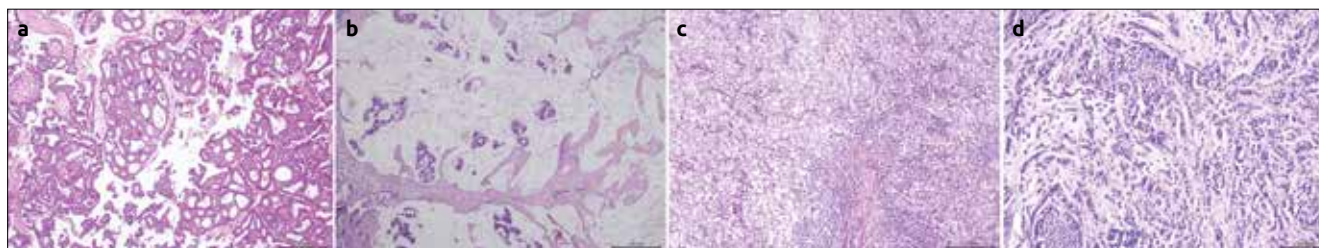


Figure 2. a-d. Specific subtype examples (a) Invasive cribriform carcinoma (b) Mucinous carcinoma (c) Medullary carcinoma (d) Invasive lobular carcinoma, containing lobular carcinoma insitu foci

Table 1. Histologic type scoring

Total Score	Histologic Grade
3-5	I
6-7	II
8-9	III

like. Further grouping of these subgroups seem possible and necessary. Recently, HER-2 subgroup is divided into three groups that clinically behave differently, one of them reported to have a highly aggressive behavior. Because of these differences, determinants that can explain difference in prognosis of patients with HER-2 have been tried to develop (27). Based on these studies, it is expected that differences in prognosis despite treatment programs directed with molecular indicators that provide data on tumor molecular identity, prognosis, and individualized treatment will be an even more pronounced subject in the near future. For example, based on HER-2 patients who were resistant to treatment with monoclonal antibodies (Herceptin) targeting the extracellular domain or those who relapsed after treatment, possible causative mechanisms were investigated (28-30). It was reported that a portion of HER-2 positive breast cancer patients with poor prognosis express a heterogeneous group of HER2 carboxy-terminal fragments known as p95HER2 (29). One of these fragments, 611-CTF, is the oncogene of HER2. Thus, it was concluded that 611-CTF gene status was probably effective in the progression of p95HER2 positive tumors. In addition, the expression of HER2 isoform that encodes a receptor without exon 16 is known as delta 16HER2, and is recognized today as one of the trastuzumab resistance mechanisms (31).

Molecular Subgrouping Valid in Clinical Use

Most of molecular subgrouping studies were performed on non-specific types of ductal carcinoma and is well known, this histological group contains non-specific tumor types. Therefore, efforts aiming to separate this group of heterogeneous group into subgroups seem to be meaningful. Molecular subgrouping can be provided by using a few immunohistochemical markers. A panel including ER, PR, HER2, Ki-67, epidermal growth factor receptor (EGFR) and basal cytokeratins (CK14 and CK5 / 6 etc) can be used to distinguish between “luminal”, HER2 and triple negative tumors. In fact, there is no consensus on the determinants defining “basal” tumors, nevertheless it is considered that the use of EGFR and CK5 / 6 can aid in identification of this subgroup and predict prognosis (32).

Proliferation markers are very important in molecular subgrouping besides ER and HER-2, especially in ER-positive tumors. However, the appropriateness of using Ki-67 or more detailed mitotic index scoring system as a proliferation marker has been questioned. The

application of a Ki67 scoring as positive / negative or high / low in patient follow-up and treatment is controversial and there is no consensus on this issue today. Separation of luminal tumors into subgroups is mainly based on proliferation intensity. Therefore, a gene expression profiling study combined with IHC was conducted in order to determine the Ki67 limit value that can be used routinely to distinguish luminal A tumors from luminal B tumors (33). The limit value in this study was determined as 13.25%. It is obvious that application of such a precise limit in clinical practice is not very realistic. It seems that there is need for more practical prognostic tests that can be evaluated in routine diagnostic pathology laboratories and used in clinical practice. Similar to histological evaluation, molecular tests that show the average gene expression level show that breast cancer is a heterogeneous tumor. This situation could partly explain the mismatch in tumor distinction into molecular subtypes. Various algorithms have been developed to place each tumor into one of the five basic molecular subtypes (luminal or luminal B, normal breast-like, HER2 and basal) (16-18). These algorithms are defined as “Single Sample predictors” (SSP), as previously referred to. Since each new diagnosed breast cancer patient should be separated into a specific molecular subgroup in order to determine the prognosis and decide on specific treatment, application of such algorithms will be required.

Major molecular subtypes According to gene expression profiles in breast cancer are summarized in Table 2 (34, 35).

Special Type Tumors

Histopathological special types of breast cancer constitute approximately 25%, have different architectural patterns, are less associated with clinical features, and have a better prognosis than non-specific type ductal carcinoma. Most of the gene expression profiling studies are related to non-specific type ductal carcinoma. Evaluation of molecular properties for specific types of breast cancer has not been systematically studied as much as in non-specific ductal carcinoma. Genomic and gene expression studies have also shown that special histological types are much more homogenous than the non-specific ductal carcinoma. This emphasizes the importance of morphological assessment made by histopathologists (Figure 2). Special types of breast cancer can be explained by specific somatic re-organization, resulting in specific development patterns that pathologists have been defining morphologically for years. Indeed, some special types are associated with specific genetic alterations that describe both their special developmental pattern and their specific behavior (36). The most descriptive molecular feature of lobular carcinoma is the loss of E-cadherin. In addition, translocations observed in various malignancies other than the breast were observed in secretory carcinoma, and adenoid cystic carcinomas (37, 38). Weigelt et al. (39) demonstrated that each specific subtype in 113 breast tumors containing 11 different special types (other than lobular and apocrine special type)

Table 2. Major molecular subtypes of breast cancer

	Molecular Subtype			
	Luminal A	Luminal B	HER2/neu	Basal like ^a
Gene expression pattern	Expression of luminal (low molecular weight) cytokeratins, high expression of hormone receptors and related genes	Expression of luminal (low molecular weight) cytokeratins, moderate-low expression of hormone receptors and related genes	High expression of HER2/neu, low expression of ER and related genes	High expression of basal epithelial genes and basal cytokeratins, low expression of ER and related genes, low expression of HER2/neu
Clinical and biologic properties	50% of invasive breast cancer, ER/PR positive, HER2/neu negative	20% of invasive breast cancer, ER/PR positive, HER2/neu expression variable, higher proliferation than Luminal A, higher histologic grade than Luminal A	15% of invasive breast cancer, ER/PR negative, HER2/neu positive, high proliferation, diffuse TP53 mutation, high histologic grade and nodal positivity	~15% of invasive breast cancer, most ER/PR/HER2/neu negative (triple negative), high proliferation, diffuse TP53 mutation, BRCA1 dysfunction (germline, sporadic)
Histologic correlation	Tubular carcinoma, Cribriform carcinoma, Low grade invasive ductal carcinoma, NOS, Classic lobular carcinoma ^b	Invasive ductal carcinoma, NOS Micropapillary carcinoma	High grade invasive ductal carcinoma, NOS	High grade invasive ductal carcinoma, NOS Metaplastic carcinoma, Medullary carcinoma
Response to treatment and prognosis	Response to endocrine therapy	Response to endocrine therapy (tamoxifene and aromatase inhibitors) not as good as Luminal A	Response to trastuzumab (Herceptin)	No response to endocrine therapy or trastuzumab
	Variable response to chemotherapy	Variable response to chemotherapy (better than Luminal A)	Response to chemotherapy with anthracyclins	Sensitive to platinum group chemotherapy and PARP inhibitors
	Good prognosis	Prognosis not as good as Luminal A	Usually unfavorable prognosis	Not all, but usually worse prognosis
PARP poly-adenosinediphosphate ribose polymerase				
^a Basal like tumor group includes a low-grade group with low proliferation but expression of basal type (high molecular weight) cytokeratin and triple negative phenotype (like adenoid cystic carcinoma, secretory carcinoma).				
^b Classical lobular carcinoma generally exhibits luminal A properties, while pleomorphic lobular carcinoma usually shows features of other molecular subtypes.				

actually belonged to only one molecular subtype (luminal, HER2, have proven that normal breast-like and basal) by gene expression profiling study. According to this study, neuroendocrine and mucinous carcinomas have very similar genetic profiles, which was an expected finding due to the histopathologic observation of these two components within the same tumor. Adenoid cystic, medullary, and metaplastic carcinomas were within basal group, as expected. However, it was interesting that despite these carcinoma's good prognosis, they were included in poor prognosis category with other basal tumors (39). This situation is defined in basal phenotype non-specific type ductal carcinoma and reflects the significant heterogeneity of basal-type. In addition, it should be emphasized that "histopathological evaluation" is much more important than molecular subtyping in diagnostic application for special types such as these.

Histological and molecular characteristics of specific types of breast cancer are shown in Table 3.

Exclusive Subtype: Lobular Carcinoma

Five to 15% of all breast cancers are invasive lobular carcinomas (ILC), and it is the most common "special type". The very special biological and clinical behavior patterns of ILC are more important than the fact that they are histopathologically different forms from non-specific ductal carcinoma. Although ILC has better prognostic features as compared to IDC, they exhibit a similar to or worse outcome than ductal carcinoma in long-term follow-up (40-43). The slow progress

and diffuse growth pattern that results in diagnostic delay, difficulty in detection by routine screening programs, and difficulty in obtaining reliable and safe surgical margins may be suggested as reasons for this situation. Thus, ILC presents with distant metastases. The ILC metastasis pattern is also very interesting by its being quite different from IDC, with metastasis to bone, gastrointestinal tract, gynecological organs and peritoneal cavity (44-46). This complex structure of ILC may also partly be explained by a large number of variants. These variants can be listed as solid, alveolar, pleomorphic, mixed ductal / lobular, tubulolobular, signet ring cell and histiocytic type (47). Except the pleomorphic subtype, our information on these variant's biological and clinical behavior is limited (48-53). Only a few studies showed association between alveolar and solid types with classical type (54).

ILC cells have characteristic cytologic features and a diffuse growth pattern. Mostly, they are histological grade 2 and do not show lymphovascular invasion. Generally, they are ER and PR positive, and they rarely express HER2, p53, EGFR and basal cytokeratin.

Molecular analysis of lobular carcinoma is not studied as much as non-specific ductal carcinoma. They are mostly luminal subtype, but basal and HER2 subtypes were also identified.

Weigelt et al. (39) suggested a close relationship between tubular carcinoma and lobular carcinoma based on their observation of very

Table 3. Histologic and molecular properties of specific type breast cancer

Molecular subtype	Common histologic types	HG	ER status (by IHC)	HER2 status (by ISH/IHC)	Ki67 (by IHC)	Specific IHC/ molecular properties
Luminal A	Classical, lobular, tubular, cribriform	1 or 2	+	-	Low	Luminal CK +, E-cadherin +/-
Luminal B	Micropapillary	2 or 3	+/-	-/+	High	Luminal CK +, p53 mutations
Basal like	Medullary, metaplastic, adenoid cystic, secretory	3	-	-	High	Basal CK+, p53 mRNA repair loss, EGFR +/- mutations
Mol. apocrine	Apocrine, pleomorphic lobular	2 or 3	-	-/+	High	Androgene receptor+
Claudin-low	Metaplastic	3	-	-	High	Cancer like stem cell, EMT like, low E-cadherin level

As depicted in the table, most specific type breast cancer are homogenous entities and are included in only one molecular subtype (such as adenoid cystic carcinoma basal like, micropapillary carcinoma luminal type). However, specific types such as classical and pleomorphic lobular carcinoma and apocrine carcinoma are heterogeneous. The table depicts probable histologic grade, ER, HER2, Ki67 status for each molecular classification.

close hierarchical clustering in lobular and tubular carcinomas. In genomic analysis, lobular carcinomas show a similar genomic profile to low-grade ductal carcinomas, and this genomic profile is very different from high-grade ductal carcinomas. This finding shows a close developmental relationship between “low-grade (low-grade ductal and lobular)” and ER positive tumor types. Results of initial genomic studies detected that boundaries between ductal and lobular carcinomas were unclear, therefore they supported the idea that all low-grade cancers (ductal, lobular and tubular) represent a low-grade tumor family beginning from a general precursor, such as columnar cell lesions (55-58). Expression profile studies of lobular, ductal and low-grade ductal carcinomas were studied with the idea that a classification such as ductal and lobular might not be proper and it was found that they had similar profiles (59-61). However, despite similar profiles were detected in tubular, lobular and low-grade tumors, differences in specific gene expressions suggest that these types are different entities. Especially in lobular tumors, decreased functions of genes associated with cell adhesion and extracellular matrix were described. Thus, these differences determined in gene expression in lobular tumors reflect characteristic differences in the development pattern of invasive lobular carcinomas and the loss of E-cadherin that is a cell adhesion molecule (62, 63).

Including lobular breast cancer in a classification like molecular luminal A, luminal B, HER2 or basal form may cause a lack of understanding in the complex structure and heterogeneity of breast cancer, because lobular breast cancer is a very special subtype in all breast cancers

Studies investigating changes in epigenetic mechanisms such as DNA methylation, and in genetic information carriers that do not code but can lead to functional changes such as microRNA (miRNA) will enable more accurate and complementary description of molecular structure of breast cancer. A comprehensive study that used various technological platforms with different breast cancer types has identified subtype-specific mutations and copy number changes that enabled understanding tumor biology and achieving the targeted treatment by evaluation of many cancer development pathways in different subtypes (64). However, the implementation of treatment programs targeting these changes will depend on an increase in the number of such studies, and results from larger study groups.

Conclusion

Molecular subtyping developed in breast cancer emphasized biological heterogeneity, which has been histopathologically defined by pathologists for a long time. In the last twenty years, identification of HER2 pathway and the relevant use of Herceptin, the use of DNA repair mechanisms and PARP inhibitors were possible by clarification of breast cancer biology with molecular methods and the emergence of new horizons for the development of new therapeutic interventions. The perception on what we know and what we have just defined on genomic architecture underneath different subtypes of breast cancer will probably change with the new generation of molecular methods including next-generation sequencing. We must not forget that molecular classification of breast cancer is still in the development stage and has limitations of today. Old fashioned, traditional histopathological subgrouping has many features for us to prefer this classification especially in special types (such as lobular or ductal, secretory, micropapillary, adenoid cystic carcinoma). In this regard, accepting and applying the conventional histopathological methods and new molecular studies, as a “partnership” seems to be the best way for follow-up in breast cancer. It is clear that we are not in an era where either pathologists can leave their microscope aside and make a classification of breast cancer based on computer, or oncologists can implement follow-up programs just based on molecular classification.

In conclusion, the traditional old-fashioned way should be together with a molecular classification based new-fashion way.

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Autoimmune Thyroid Disease and Breast Cancer Prognosis

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ABSTRACT

Objective: The association of breast cancer and thyroid autoimmunity has been suggested by many studies in the literature, but the causality still needed to be proven. With this study we aimed to search the correlation between thyroid autoimmunity and breast cancer prognostic factors.

Materials and Methods: To this prospective cohort study 200 consecutive breast cancer patients, who were operated in our clinic were included. Patients' serum thyroid hormone, anti-thyroglobuline (anti-TG) and anti-thyroid peroxidase (anti-TPO) levels and tumors' prognostic parameters (tumor size, axillary involvement, histological grade, lymphovascular invasion, receptor status, Ki-67 proliferation index) were collected. The correlation between serum thyroid autoantibody levels and tumor's prognostic factors were studied.

Results: The prevalence of thyroid autoimmunity (high levels of serum anti-TPO and/or anti-TG) was 18.5% (n=37). Patients with thyroid autoimmunity had a significant lower rate of axillary involvement and a lower rate of Ki-67 proliferation index (22% vs. 46% [p=0.007] and 12.73% vs. 20.72% [p=0.025], respectively) and were more commonly included to the "low-risk" group (<14%) according to their Ki-67 scores (68% vs. 46%; p=0.015). Other parameters did not differ between the two groups.

Conclusion: We found a favorable correlation between thyroid autoimmunity and axillary involvement and also Ki-67 proliferation index score, which are two crucial and strongly predictive parameters of breast cancer prognoses. This supports the idea of thyroid autoimmunity being a favorable prognostic parameter. Further studies are necessary to investigate the reasons of protective or predictive effect of high thyroid peroxidase levels in breast cancer patients.

Keywords: Breast cancer, autoimmune thyroid disease, prognostic factors

Introduction

The higher prevalence of both benign thyroid diseases and breast cancer in women compared to men and their increased prevalence in the postmenopausal period suggest that certain shared factors may be influential in the etiology of these two diseases. Some studies determined that the prevalence of AITD (auto-immune thyroid disease) was higher among breast cancer patients (1-4). A recent meta-analysis reported a significant increase in the risk of breast cancer detection in a person with AITD [odds ratio (OR): 2.92] (5). As a consequent step, the researchers investigated whether the concomitance of AITD in breast cancer patients had an effect on the disease prognosis upon which they obtained conflicting results. While the concomitance of AITD was reported as a positive prognostic factor in some papers (6-10), other papers defended the contrary position (2, 11). This study investigated the correlation between AITD and breast cancer prognostic factors. The hypothesis of the study was constructed as follows: prognostic parameters are observed to be more positive in breast cancer patients with concomitant AITD and AITD constitutes a positive prognostic factor for breast cancer.

Materials and Methods

Study Type and Population

This study was planned as a prospective cohort study. The study population consisted of patients scheduled for surgery at our clinic with diagnosis of breast cancer. Within this cohort, patients with at least one of their thyroid autoantibodies at a high level were considered "AITD-positive" while patients with both thyroid autoantibodies at a high level were considered "AITD-negative."

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Table 1. Inclusion and exclusion criteria for the study**Study inclusion criteria:**

1. Having been diagnosed with histopathological breast cancer in the pre-operative period
2. Having accepted taking part in the study and providing patient consent

Study exclusion criteria:

1. Not agreeing to take part in the study
2. Stage 4 breast cancer diseases
3. Previous surgery due to thyroid disease or current drug therapy

Ethics Committee Approval for the Study

The approval from the Ethics Committee for this study was obtained from the "Research-Review Commission" of our hospital with the issue number B.30.2.MAR.0.01.02/AEK/750.

Inclusion and Exclusion Criteria for the Study

The patients who presented to our clinic for treatment with breast cancer diagnosis and met the study inclusion criteria were included in the study (Table 1). Before the patients were included in the study, their consents were received.

Study objectives

Primary objective of the study:

- To compare the prognostic and predictive parameters of breast cancer patients that has concomitant AITD (tumor stage, tumor size, axillary lymph node involvement, histological degree, lymphovascular invasion, hormone receptor status, c-erbB2 expression, multifocality/multicentricity) with breast cancer patients that do not have concomitant AITD.

Secondary objective of the study:

- Identification of AITD prevalence in breast cancer patients.

Collection of Serum Specimens

Before surgery, 10 cc blood samples were collected from the patients in a yellow tube (tube containing a separator and a coagulation activator) and sent to the laboratory for analysis.

Recorded and Measured Variables

The demographic information of individuals included in the study (sex, age, menopausal status) and their serum thyroid hormone and antibody levels [thyroid stimulating hormone (TSH), free-T3 (s-T3), free-T4 (s-T4), anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg)] was recorded. The upper limits in thyroid antibody levels were accepted as 34 IU/mL for anti-TPO and as 115 IU/mL for anti-TG. Patients with at least one of these values at a high level were considered AITD-positive. The normal ranges for TSH, s-T3 and s-T4 were accepted as 0.27-4.2 uIU/mL, 1.8-4.6 pg/dL and 1-1.8 ng/dL, respectively.

Additionally, the cancer stages of patients as per staging by American Joint Committee on Cancer (AJCC), tumor diameter, histological degree of the tumor as per the Modified *Scarff-Bloom-Richardson* grading system, lymphovascular invasion status, hormone (estrogen and progesterone) receptor expression, c-erbB2 expression, Ki-67 proliferation

index, metastasis status in axillary lymph nodes and multicentricity/multifocality were recorded based on their pathology reports. For all metastases larger than 0.2 mm in the axillary lymph nodes on the same side as the tumor, the axilla was considered positive (N+). Tumoral invasion in all the lymphatic and vascular structures around the tumor was considered as lymphovascular invasion. The tumors observed to have estrogen and/or progesterone receptors in at least 5 out of 100 cells that examined were considered positive while cells observed with less than 5 receptors were considered negative. As for the c-erbB2 assessment, tumors identified to be 3+ or 2+ with immunohistochemical method and observed to have amplification according to the FISH (*fluorescence in situ hybridisation*) test were accepted c-erbB2-positive while other tumors were accepted c-erbB2-negative. During molecular subtyping classification, tumors that were estrogen receptor-positive and c-erbB2-negative were considered as "Luminal A", tumors that were estrogen receptor-positive, c-erbB2-positive with a high proliferation score as "Luminal B", tumors that were estrogen receptor-negative, but c-erbB2-positive as "Her-2 type" and tumors that were estrogen receptor-negative and c-erbB2-negative as "triple negative." In the Ki-67 proliferation index analysis, the immunohistochemical (IHC) staining method was used. The ratio of cancer cells that were stained with nuclear antigen Ki-67 under light microscope to the total cancer cells was recorded as a percentage value. As accepted in the literature, those with an index value <14% were accepted low risk (12).

Statistical analysis

The study data were recorded and statistically analyzed using the SPSS (Statistical Package for the Social Sciences) version 19 (IBM Corporation, New York, United States of America) software program. For the comparison of categorical data, the Chi-square test was used and for the comparison of perpetual data, the *independent student t* test was used. During the analysis of categorical data, the "odds ratio (OR)" was also calculated and the OR remained within the 95% confidence interval. The results were illustrated as average value $\pm$ standard deviation. For the analysis, a p value below 0.05 was considered significant.

Findings**Demographic, Clinical and Pathological Findings**

Two hundred consecutive patients operated on at our clinic with the diagnosis of breast cancer between "1, June, 2012 and 1, June, 2014" were included in the study. All of the patients were female and the average age was calculated as 52.59 $\pm$ 12.85 [26-90]. Their average age at menarche was found as 13.44 $\pm$ 2.87 [11-14] years, average menopausal age as 47.31 $\pm$ 4.42 [37-55] years and average age at first pregnancy as 23.31 $\pm$ 5.4 [14-39] years. The rate of miscarriage among patients included in the study was 24.2% and the rate of abortion was 31.9%. For menopausal patients, 10.8% of them had received hormone replacement therapy and 23.9% of them had breast cancer in their family history (Table 2).

When the thyroid hormone and autoantibody levels of the patients were examined, the autoimmunity prevalence was identified as 18.5% (n=37). Twenty-four (64.9%) of these 37 patients were found to be autoimmune euthyroidic, 8 of them (21.6%) hyperthyroidic, 4 of them (10.8%) subclinical hyperthyroidic and 1 (2.7%) of them hyperthyroidic. Eight (4.9%) out of 163 patients not observed to have any auto-immunities were observed as subclinical hyperthyroidic, 3 of them (1.8%) as hyperthyroidic, 2 of them (1.2%) as hyperthyroidic and 1 of them (0.6%) as subclinical hyperthyroidic. The remaining

Table 2. Demographic characteristics of patients

Age (average years±SD [range])	52.59 ±12.85 [26-90]
Age of menarche (average years±SD [range])	13.44±2.87 [11-14]
Menopausal age (average years±SD [range])	47.31±4.42 [37-55]
Age at first pregnancy (average years±SD [range])	23.31±5.4 [14-39]
Miscarriage rate (%)	24.2
Abortion rate (%)	31.9
Rate of having received HRT* (%)	10.8
Rate of breast cancer in family history (%)	23.9
*HRT=hormone replacement therapy	

Table 3. Distribution of patients as per their thyroid functions

	n (%)
Autoimmunity (+)	
euthyroidic	24 (64.9)
hyperthyroidic	8 (21.6)
subclinical hyperthyroidic	4 (10.8)
hyperthyroidic	1 (2.7)
Autoimmunity (-)	
euthyroidic	149 (91.5)
subclinical hyperthyroidic	8 (4.9)
hyperthyroidic	3 (1.8)
hyperthyroidic	2 (1.2)
subclinical hyperthyroidic	1 (0.6)

Table 4. Tumor characteristics

	n (%)
Stage	Stage 1
	60 (28.1)
	Stage 2
Histological type	Stage 3
	90 (43.3)
	50 (23.6)
Molecular sub-types	Invasive ductal carcinoma
	174 (87)
	Invasive lobular carcinoma
	19 (9.5)
	Other
	7 (3.5)
	Luminal A
	104 (51.7)
	Luminal B
	26 (12.9)
	Her-2
	22 (11.4)
	Triple negative
	48 (23.9)

149 (91.5%) patients were observed to have normal thyroid autoantibody and hormone levels (Table 3).

A great majority of the patients (n=90) included in our study had stage II tumors, 87% had invasive ductal types and 9.5% had invasive lobu-

lar cancers. Considering the molecular sub-types, 51.7% of them were observed to have Luminal A breast cancer and 23.9% triple negative breast cancer (Table 4).

Effect of thyroid autoimmunity on the breast cancer prognostic factors

The rate of axillary involvement in patients observed to have autoimmunity was significantly lower as compared to those not observed to have autoimmunity (22% vs. 46%; $p=0.007$; OR:0.328 [0.141-0.761]). While the Ki-67 proliferation index average was 12.73% [0-80] in patients with accompanying autoimmunity was, it was calculated as 20.72% [0-90] for other patients ($p=0.025$). Considering the rates of inclusion in the low risk group (<14%) as per Ki-67 index, 68% of the patients with accompanying autoimmunity were in the low risk group whereas this rate was calculated as 46% in the other group ($p=0.015$; OR:2.565 [1.178-5.585]). No significant differences were identified between two groups with respect to other prognostic factors (Table 5).

Discussion and Conclusions

In this prospective cohort study investigating the effect of thyroid autoimmunity on breast cancer prognostic and predictive factors, the rate of axillary lymph node involvement in breast cancer patients with accompanying autoimmunity was observed to be significantly lower in comparison with other patients. The average Ki-67 proliferation index in breast cancer patients with accompanying autoimmunity was identified to be significantly lower than the other patient group and more patients were included in the low-risk group with respect to Ki-67 proliferation index. No differences were observed between two groups in terms of other parameters.

The fact that the target population of both breast cancer and thyroid diseases is women and that its incidence peaks in the post-menopausal period led the researchers to investigate the potential association between these two diseases and several benign thyroid diseases to date have been association with breast cancer (1-4). A recently published meta-analysis reviewed all these studies and concluded that there was an association between breast cancer and autoimmune thyroid disease (5). These were then following by studies comparing the thyroid autoimmunity and breast cancer prognostic parameters (6-10). Certain publications defended that the rising anti-TPO levels in breast cancer patients with accompanying autoimmunity constituted a positive parameter in terms of cancer prognosis. These papers specified that rising antibody levels constituted a parameter at least as important as axillary lymph node involvement and tumor size (7, 8). However, a study that was published later claimed that autoimmunity was a negative prognostic factor for breast cancer. This study conducted by Cengiz et al. (11) emphasized that lymphovascular invasion and axillary lymph node involvement rates were higher in breast cancer patients with accompanying immunity. In our study, axillary lymph node involvement rate (22%) in breast cancer patients with accompanying autoimmunity was observed to be significantly lower in comparison with the other group (46%). The lower rate of axillary lymph node involvement in patients with autoimmunity (+) could be attributed to the high level of anti-TPO in this group. Even though thyroid autoantibodies are known to play an important role on cellular cytotoxicity in thyroid, a similar effect has not yet been demonstrated for the breast tissue (13). Both breast tissue and thyroid tissue transmit iodine from their membranes to the inside of cells (1). Therefore, both tissues demonstrate antigenic characteristics due to sodium-iodide-symporter canals and

Table 5. Comparison of autoimmunity and breast cancer prognostic parameters

		Autoimmunity present (n=37)	Autoimmunity none (n=163)	p
Tumor diameter: mm (avg±SD)		24.97 ±14.55	24.60 ±13.82	0,889
Axillary involvement: n(%)	Positive	8 (22)	75 (46)	0.007; OR*=0.328 [0.141-0.761]
	Negative	29 (78)	88 (54)	
Histological Grade: n(%)	1 & 2	21 (56)	80 (49)	0.482
	3	16 (44)	83 (51)	
LVP**; n(%)	Positive	16 (43)	94 (58)	0.116
	Negative	21 (57)	69 (42)	
Ki-67; % avg[range]		12.73 [0-80]	20.72 [0-90]	0.025
Ki-67 <14 vs. ≥14; n(%)	<14	25 (68)	75 (46)	0.015; OR*=2.565 [1.178-5.585]
	≥14	12 (32)	88 (54)	
Molecular sub-type: n(%)	Luminal A	17 (46)	86 (52)	0.446
	Luminal B	3 (8)	23 (14)	
	Her-2 (+)	6 (16)	17 (10)	
	Basal type	11 (30)	37 (24)	
Number of tumor foci: n(%)	multifocality	1 (3)	18 (11)	0.273
	multicentricity	2 (5)	11 (7)	
	unifocality	34 (92)	135 (82)	

* Odds ratio

** Lymphovascular invasion

peroxidase activity (14, 15). However, anti-TPO antibodies have not yet been proven to engage in interaction with receptors located on cancerous breast tissue and the mechanism through which it reduces axillary lymph node involvement should be the subject of future studies.

Tumor proliferation has a very important role in predicting its recurrence risk (16, 17). Ki-67, which was defined by Gerdes et al. in 1980s, is a nuclear protein associated with cellular proliferation (18) and several studies to date have demonstrated high Ki-67 values to be a poor prognostic parameter showing tumor aggressiveness and it has been observed that patients with high Ki-67 values have lower survival rates (19-22). In our study, Ki-67 proliferation index was observed to be significantly lower in the patient population with accompanying autoimmunity (12.73% vs. 20.72%). Significantly more patients in the group of patients with autoimmunity were in the group with low risk in terms of Ki-67 index (<14%) (68% vs. 46%). The fact that proliferation is lower in patients with accompanying autoimmunity is a positive prognostic parameter and supports the hypothesis in our study. The development mechanism of this association is not yet known. To the best of our knowledge, Ki-67 index was compared with autoimmunity for the first time in this study in the literature with meaningful results obtained.

No reliable data demonstrating the prevalence of autoimmune thyroid diseases in Turkey have yet been reported. This prevalence is at the level of 1-2% in the United States of America (23, 24). The frequency of AITD in breast cancer patients progressing with significant or sub-clinical hyperthyroidism was reported as 30% while high thyroid antibody level was reported as 34% (7, 25). In a study we previously con-

ducted on 100 breast cancer patients and 100 healthy control group subjects, the high thyroid autoantibody level prevalence was identified as 25% for cancer patients and as 18% for healthy subjects (6). In this study, which has been conducted on 200 women with breast cancer, high thyroid autoantibody level prevalence was calculated as 18.5% in breast cancer women. Identification of the prevalence of autoimmune diseases in healthy subjects and breast cancer patients in Turkey through community-based studies to be conducted with larger cohorts would provide remarkable contribution to the literature.

The strength of this study is that it is one of the two largest studies in terms of sample size among prospective studies investigating this subject in the literature. Another strong point of this study is that it compared Ki-67 mutation index and autoimmunity. As for the weakness of the study, it is the fact that we did not have 5-year-survival rate values while making interpretations about breast cancer prognosis. However, it is planned to determine the 5-year-survival values of the cohort and then to identify whether autoimmunity makes a difference by way of contribution to the literature.

The lower rate of axillary involvement in breast cancer patients with accompanying AITD and the lower Ki-67 infiltration index of the tumors in this group according to the results of this study may suggest that thyroid autoimmunity may accompany positive prognostic factors with respect to breast cancer. For that reason, we are convinced that screening persons diagnosed with breast cancer for autoantibody levels would be useful in that it may not only enable diagnosis and timely treatment of the concomitant AITD, if any, but it may also offer information on prognostic factors for breast cancer.

Ethics Committee Approval: Ethics committee approval was received for this study.

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

Peer-review: Externally peer-reviewed.

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Relation between Mastalgia and Anxiety in a Region with High Frequency of Posttraumatic Stress Disorder

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ABSTRACT

Objective: Mastalgia, the most important breast-related symptom, refers to the pain that arises from breast tissue. Not only hormonal reasons but also psychogenic factors may cause mastalgia. Mastalgia is a subjective complaint and includes emotional components. The present study aimed to investigate the relation between mastalgia and level of anxiety in females.

Materials and Methods: This case-control study had consisted of premenopausal females over the age of 20 years. Control group consisted of premenopausal females over the age of 20 years without mastalgia participated. The case and control groups each included 70 females. Females who had a previous breast surgery for any reason, were pregnant or in lactation period, or had a family history of breast cancer were excluded. The case and control groups each examined VAS and GAD-7 questionnaires.

Results: The GAD-7 scale was performed for both the case and control groups to assess the level of anxiety. Test indicated that the level of anxiety was significantly higher in the cases with mastalgia than in the controls. The VAS and GAD-7 scale scores were compared in the case group to assess the relation between degree of pain and level of anxiety. There was no significant relation between these scores, which indicated that pain, contrary to expectations, was not increased as the level of anxiety increased.

Conclusion: Psychological factors such as anxiety, stress, and depression should be kept in mind after eliminating organic reasons via physical and necessary radiological examinations. A psychiatrist should be consulted since mastalgia is a condition that influences quality of life.

Keywords: Mastalgia, anxiety, posttraumatic stress disorder

Introduction

Pain is an emotion that has existed since the inception of mankind, which negatively affects all their characteristics in life, reduces or eliminates workforce and results in fear and restlessness (1). Mastalgia defines pain that originates in the breast tissue. It is the most important breast-related symptom and its prevalence is known to be approximately 40-80% (2). Mastalgia is divided into two groups: cyclic and non-cyclic. Mastalgia that emerges 7-10 days before menstruation lasting 1-4 days and causes slight pain is considered cyclic mastalgia and is thought to be influenced by hormones in its etiology (3, 4). It is seen at a rate of 8-10% among premenopausal women. Non-cyclic mastalgia, another type of mastalgia, does not increase before menstruation as in cyclic mastalgia and it is felt throughout the whole month. Non-cyclic mastalgia is not expected to be related to menstrual cycle. Such kind of pain may be due to mastitis and breast cysts while they may also be due to non-breast reasons such as muscular and pleural diseases. Its reason is mostly unknown and it may develop both before and after menopausal in women (5).

The psychosomatic reasons of mastalgia were emphasized in several studies and it was defended that mastalgia could be caused by hormonal reasons as well as psychogenic factors (5). In this study, we investigation the relationship between levels of anxiety and mastalgia among women with symptoms of mastalgia presenting to the General Surgery outpatient clinics due to conditions such as post-traumatic stress disorder, generalized anxiety disorder and panic disorder, which developed in the regional population following 2 big earthquakes of magnitude 7.2 that occurred in the city of Van, where we live, in the year 2011 claiming the lives of 644 people.

Materials and Methods

This study was conducted between January, 2014 and April, 2014 at the outpatient clinics of General Surgery, Radiology and Psychiatry. The authorization for the study was obtained with the approval number 2014/2 from the Ethics Committee of Van Regional Teaching

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and Research Hospital and the study was conducted. While premenopausal women with cyclic or non-cyclic breast pain above the age of 20 agreeing to take part in the study were admitted in the case group, premenopausal women above the age of 20 who came to the hospital for another reason and did not have any breast symptoms were included in the control group. Women who underwent breast surgery for any reason, were pregnant or lactating and had family history of breast cancer were excluded from the study. The case group included 70 people and the control group also included 70 people. The study was conducted with approval from the ethics committee of the hospital. Women in both groups up to the age of 40 received only breast ultrasonography (USG) in terms of radiological imaging while women above the age of 40 received both breast USG and mammography. The patients who were identified to have any organic pathology according to the imaging findings were excluded from the study.

Both groups were given the socio-demographic data form created by us at the outpatient clinic and 4 questions in total were asked to learn their name-surname, age, marital status and educational level. Furthermore, a questionnaire exploring whether their pain was cyclic or non-cyclic, bilateral or not, whether they received hormone replacement therapy, smoked, consumed tea and coffee, had history of hyperlipidemia, their age of menarche and whether they had normal menstruation. In this questionnaire, a visual analogue scale (VAS) was used with a table ranging from 0 to 10 in order to assess the pain of the case group and their pain levels were scored (6, 7). Then, the Generalized Anxiety Disorder-7 (GAD-7) test composed of 7 questions was used in order to measure the anxiety levels of patients (8).

The GAD-7 test was originally developed by Kessler et al. (9) in 2001 and it was adapted to Turkish by Konkan et al. (10) in 2013 with its validity and reliability having been proven. GAD-7 is a short test completed by self-reporting, which was improved by Spitzer et al. according to DSM-IV-TR criteria to assess generalized anxiety disorder. The 7-point foursome Likert scale, which is used to assess the experience questioned in the scale points within the last 2 weeks, (0=None, 1=Multiple days, 2=More than half the days, 3=Almost every day) is a paper & pencil type of scale. Based on the total scores obtained in the scale, the cut-off points set for mild, moderate and severe anxiety were 5, 10 and 15, respectively. The GAD diagnoses for patients with a total score of 10 or more need to be investigated and verified through other methods. With the total score threshold selected as 10, its sensitivity for GAD diagnosis was identified as 89% and its specificity as 82% (11).

Our study is a randomized case-control study. The factors preventing a full understanding of the questionnaire by participants were as follows: the level of education in the area where the study was conducted was low and almost all of the study participants did not speak Turkish at a mother tongue level.

Statistical analysis

All of the data were statistically analyzed using the 20.0 version software program. Depending on the type and distribution of data; Independent Student-t, One-way ANOVA, Two-way ANOVA, Chi-Square, Pearson's Correlation, Mann-Whitney U and Spearman Correlation tests were used as appropriate. Findings with a statistical value of $p < 0.05$ were considered significant.

Findings

In our study, the average age of the patient group (32.14 ± 8.5) and the average age of the control group (32.63 ± 8.4) were not significantly dif-

Table 1. Comparison of mastalgia-related control groups with respect to demographic data

	Case group n=70	Control group n=70	p
Age (years)	32.14 ± 8.5	32.63 ± 8.4	0.734
Coffee (cups/day)	0.14 ± 0.69	0.24 ± 0.69	0.392
Tea (glasses/day)	6.33 ± 5.29	7.43 ± 4.55	0.189
Smoking (packs/day)	1.69 ± 5.64	1.54 ± 4.27	0.866
Age of menarche (age)	13.51 ± 1.11	13.29 ± 1.11	0.228
Number of menstrual cycles	65.70	72.90	0.360

The data are illustrated in line with average $\pm$ standard deviation.

ferent. (Independent Student- T-test, $p=0.734$). When we compared smoking, tea and coffee consumption between control and case groups and statistically analyzed the parameters (Independent Student-T test), the results were as follows: $p:0.866$ for smoking, $p:0.189$ for tea and $p:0.392$ for coffee. We have not identified any significant differences between the case group and control group (Table 1). Since cyclic pain was under hormonal control, we felt the need to examine the menstruation and menstrual cycle since cyclic pain is under the control of hormones. For the age of menarche (Independent Student-T test), the result was $p:0.228$ and for menstrual cycle (Chi-Square analysis), it was $p: 0.360$ and we did not identify any statistically significant difference between the case and control groups. We used the GAD-7 test in order to assess the level of anxiety, which could be reason for mastalgia in patients apart from oncological pathologies. Therefore, we administered the GAD-7 test in both the case and control groups. In both groups, it was assessed whether the GAD-7 scores were in line with normal distribution by using visual (Histogram, branch - leaf) and analytical (Kolmogorov-Smirnov (Kolmogorov-Smirnov, Shapiro-Wilk) methods. Since the distribution was not normal, the Mann-Whitney U test, a non-parametric test, was used to compare the two independent groups. The GAD score of case group was identified as 8.06 ± 3.8 (Average $\pm$ standard deviation) and the GAD score of the control group as 3.96 ± 2.7 (MWU, $p < 0.001$). This value is statistically significant and it shows that patients with mastalgia among those who took part in the study had noticeably higher anxiety levels as compared to those who were not ill (Figure 1). After that, the relationship between the level of pain and level of anxiety were examined. The average VAS score of the patient group was 7.33 and the average GAD-7 level was 8.06. Since the GAD-7 scores did not have normal distribution, Spearman correlation test was used. (Spearman rho, $r=0.006$ $p=0.962$ $n=70$). As a result of this analysis, no correlations were identified between the VAS score and GAD-7 score in the case group (correlation co-efficient= 0.006). We saw that those with increased anxiety did not have increased pain. When we examined the relationship of VAS score with other factors in the case group, no significant correlations with smoking, tea, coffee and age of menarche could be identified (Regression co-efficient = 0.091 with p values of 0.211, 0.556, 0.195, 0.65, respectively). No significant correlations could be found during the analysis of correlation with other categorical variables, either (cyclic pain and menstrual cycle). (Figure 2, 3).

Discussion and Conclusions

Mastalgia is one of the most frequent breast symptoms and it does not have a clear definition. Mastalgia may develop in approximately half

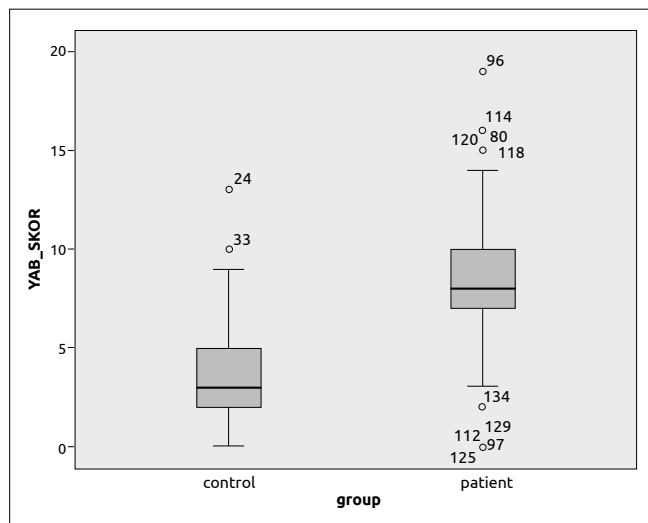


Figure 1. Comparison of study groups on the basis of GAD-7 scores

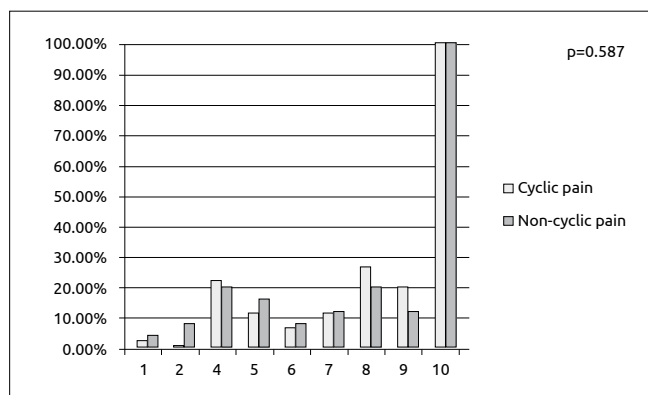


Figure 2. Correlation between cyclic pain and degree of pain as per VAS score in the case group

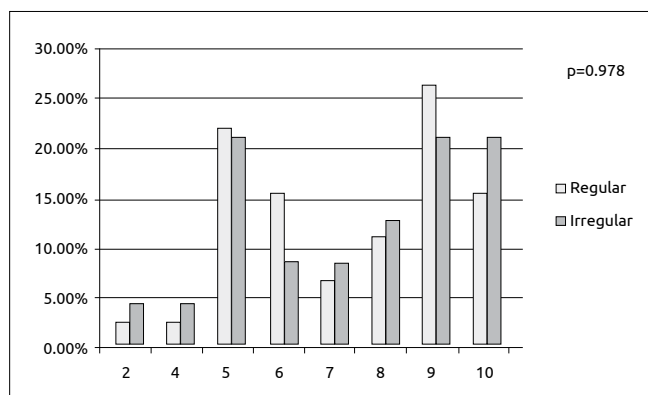


Figure 3. Correlation between the order of menstrual cycle and degree of pain as per VAS score

of women below the age of fifty. Nearly 70% of women presenting to breast clinics have mastalgia symptoms (2, 12). There are several organic pathologies influencing this important symptom. The most important factor influencing mastalgia is menstrual cycle. Cyclic mastalgia is influenced by hormones, develops 7-10 days before menarche and lasts 1-4 days (3, 4). A large part of cyclic breast pain is mild and moderate in degree and considered as part of normal changes occurring during menstrual cycle (13). The best way to assess cyclic pain is to create a pain chart. 2/3 of women with breast pain have cyclic

mastalgia. Non-cyclic mastalgia is generally observed in elderly women and it can generally be categorized in 3 groups as follows: localized pain on the chest wall, reflective pain and diffuse real breast pain (5, 14). We also examined amenorrhea in the case and control groups by keeping this organic reason into consideration; however, we were not able to identify any statistically significant differences between the two groups.

The organic effect of smoking, tea consumption and caffeine intake on mastalgia is not known. People who smoke and excessively consume tea and coffee have a mastalgia risk that is 4-5 times more than in normal people and the definitive reason for this could not clearly be shown in various studies (2). Departing from this theory, we investigated the smoking levels as well as tea and caffeine intakes of both groups. However, we were not able to identify any statistically significant differences between the two groups in this examination, either.

Following these organic pathologies, we studied the stress and psychological factors, which are other important factors influencing mastalgia. In a study conducted in Turkey, Coşar et al. (5) studied a group of women undergoing mammography and stated that the group who had pain did not have any differences in their depression scoring as compared to the group who did not have pain. However, Aksu et al. (16) specified in a similar study that the group included in follow-up due to mastalgia symptom had higher anxiety and worry levels as compared to the other group. Colegrave et al. (17) stated that anxiety and worry levels in patient groups, who had mastalgia and were not identified to have any pathology in physical examinations and radiological results, could be high. Mood disorders such as anxiety are still observed in patients presenting to the psychiatry outpatient clinics in the study area especially in the aftermath of the earthquake of a magnitude 7.2, which occurred in 2011 claiming the lives of 644 and causing thousands of people to be injured and lose their property. Therefore, we thought that this situation could influence mastalgia. Furthermore, we also took into account that women in our region could be suffering from early and involuntary marriage (part of regional customs) as well as the resulting psychological depression. Hence, we administered the GAD-7 test in both groups.

Based on an evaluation of the case and control groups in our study, we identified that we did not detect any organic pathologies with respect to mastalgia, the result of GAD-7 test was statistically significantly higher in the case group in comparison with the control group. In other words, those with mastalgia had higher anxiety levels as compared to those without mastalgia. However, we made a combined assessment of the pain and anxiety levels in the patient group and saw that there were no correlations between them.

In the region where we conducted the study, problems related to ethnic origin and language are frequent and it could have been the case that certain questions were wrongly perceived and inaccurately answered by the patients and physicians. Problems might have occurred especially during the administration of GAD-7 test due to the intellectual level of patients with respect to their understanding of the test and expression of their own anxiety levels even though the test is composed of only seven questions. Furthermore, we are of the opinion that some participants with high levels of anxiety assigned misleading points to the VAS and GAD-scores. Even though we asked every question twice, some participants preferred not to listen, to indicate the shortest and easiest answer they could grasp using sign language and to skip the question. Furthermore, an interesting aspect that we would like to

highlight with respect to female patients, who were generally escorted by their husband or their husband's family given the patriarchal nature of the region where the study was conducted, is the following: the case group and control group did not give any answers below the points of 9 and 10 in the VAS scoring process. One needs to keep in mind that the discrepancy in correlation between VAS and GAD-7 scores in the case group might have arisen out of these reasons.

Mastalgia is the most frequent symptom of breast diseases. After organic reasons are ruled out with physical examination and required radiological studies, psychological factors such as anxiety, stress and depression should definitely be considered. Since this is a condition that influences quality of life, a psychiatrist should also be certainly consulted.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was not obtained due to retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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

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Surgeons' Approaches and Professional Perspectives on Breast Masses: A National Survey in Turkey

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ABSTRACT

Objective: General surgeons' approaches to breast masses in their daily practices and their perspectives for issues on breast diseases and breast surgery are investigated through a survey.

Materials and Methods: Answers of 524 general surgeons for the survey "Approach to breast diseases and breast surgery" between November 2012 and February 2013 were assessed. Demographic features, approaches to the breast masses, and answers for the clinical scenarios of surgeons were questioned. Surgeons were asked about management of breast cancer and the future role of surgeons for oncoplastic breast surgery and breast diseases.

Results: Participants were representing 14.6% of all general surgeons in Turkey. The survey revealed that breast diseases are the most common cause for admission in general surgery outpatient clinics. Needle biopsies were employed by 241 (60%) respondents. Three hundred and seventy-one (71%) participants indicated that breast cancer management could be accurately conducted by the general surgeons. Two hundred and seventy-three (52%) respondents think that oncoplastic breast surgery should be performed by a general surgeon and 241 (41%) respondents predict that the role of general surgeons for breast diseases and breast surgery will decrease in the future.

Conclusion: Basic approaches towards breast masses need to be improved in our country despite the highest frequency of breast diseases in outpatient admissions. The views and opinions of surgeons on breast diseases and the course of breast surgery in different regions and different communities need to be defined and clarified.

Keywords: Breast mass, Surgeons' approach, survey

Introduction

Female breast changes throughout a woman's life under the effect of hormonal milieu; women consult doctors for symptoms that are observed because of these changes. Although vast majority of breast masses are benign, 10% of patients with breast complaints have breast malignancies (1). The most common breast lesions are cysts and fibroadenomas (2). Different approaches for breast masses in different regions have been published (3). Surgeons do not have uniform practices for breast masses (4). These approaches may vary according to the surgeon's level of knowledge, infrastructural facilities of the institutions, and trained manpower of the country. Thirty years ago, Fisher argued that breast cancer is a systemic disorder. He claimed that surgical treatment has come to the end of the road with the advent of new chemotherapy (CT), hormonotherapy (HT), and/or radiotherapy (RT) regimens (5). Although surgery continues to play an active role in breast cancer treatment, there is a debate on oncoplastic breast surgery (OBS) and the future and present management of breast cancer.

Management of breast diseases and breast surgery is undertaken by general surgeons in our country. There are 3594 active working surgeons in Turkey (6). There is no formal subspecialization on breast surgery in Turkey. This survey investigated surgeons' approaches for breast masses in daily practice and their perspectives on some controversial issues on breast diseases and breast surgery. According to our literature search (Pubmed, Cochrane database, etc.), this is the first and/or most comprehensive breast surgery perspective survey on this subject. The current status for breast surgery has been presented in this study.

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Table 1. Characteristics of participants of the survey

Characteristics	N (%)
Institution	
State hospital	207 (39)
Training/research hospital	151 (29)
University hospital	84 (16)
Private hospital	72 (14)
Military hospital	10 (2)
Time in specialty (years)	
<10	189 (36)
10-20	177 (34)
21-30	105 (20)
>30	53 (10)
Number of annual breast surgery	
<20	131 (25)
20-50	173 (33)
51-80	100 (19)
81-150	68 (13)
>150	52 (10)
Frequency of breast diseases in office practice	
1 st	153 (29)
2 nd	146 (28)
3 rd	150 (29)
4 th	38 (7)
5 th or more	37 (7)
Average time for examination of breast patient (minute)	
1-5	105 (21)
5-10	258 (49)
10-15	94 (18)
15-25	56 (10)
25-40	11 (2)
Attendance for breast meetings	
Yes	283 (54)
No	241 (46)

Materials and Methods

This study is approved by the Ethics Committee of Tepecik Training and Research Hospital in accordance with the Declaration of Helsinki. Between November 2012 and December 2012, a survey form entitled "Questionnaire for Surgeons' Approaches and Professional Perspectives on Breast Masses" was e-mailed once to 2800 members of the Turkish Surgical Association (TSA) with a short informative note via the website of TSA (Plexus IT Inc.). The survey was completed online after 6 weeks. Afterwards, more surgeons were reached directly, by phone or e-mail for 8 weeks, until February 2013. The survey was designed as a multiple choice questionnaire by three authors. The objectives of the study were investigated through 17 questions of the survey. The questions may be interpreted in three groups.

Demographic questions: Affiliation, time spent as a surgery consultant, mean annual breast surgery number (including surgical biop-

sies), frequency of breast diseases in general surgery outpatient clinics, average time spent for breast diseases in office examination (average examination time), and attendance at breast meetings such as congress, symposium, etc. in the past 2 years have been questioned.

Clinical scenarios for approaches to breast masses: Most preferred biopsy method for dominant masses of breast, ultrasonography practice of surgeons on their own, approach for breast mass of a 53-year-old woman, and most commonly observed breast lesion in women aged between 20 and 45 years have been questioned. In addition, the following approaches have been questioned: In Scenario A, the initial approach for a 28-year-old patient who has no risk factors (family history of breast cancer, prior breast biopsy, etc.) with a 1.5×1.5 cm solid, fixed, smooth palpable breast mass in the right upper external quadrant; in scenario B, the initial approach for a 57-year-old patient who has no risk factors with solid, fixed, smooth palpable breast mass in the left lower external quadrant; and in scenario C, the initial approach for a 49-year-old patient with risk factors (family history of breast malignancy) who has a 2×2 cm solid, fixed, smooth, painful breast mass in the left upper internal quadrant, with a mammography and sonography revealing diffuse cysts in both breasts and a 2×1.5 cm simple cyst in the left upper internal quadrant with no lymphadenopathy (BIRADS-2).

Questions on professional perspectives

General surgeons were inquired about how they define (easy, difficult, complicated, etc.) diagnosis and treatment of breast diseases (practice perspective) and how they foresee the future role surgeon in diagnosis and treatment of breast diseases (future perspective). Finally, the role of the surgeon in OBS (OBS perspective) and in breast cancer management (management perspective) was questioned.

All answers were anonymized; duplicate responses were not allowed. Participants did not obtain any incentive benefit like a fee or a gift. Incomplete responders and/or surgeons who claimed not to perform breast cancer surgery were excluded from the study.

Data were analyzed by using SPSS v. 15 (Statistical Package for Social Sciences version 15, SPSS Inc, Chicago, USA). The results were classified by percentage distribution and were presented descriptively.

Results

Twenty-three of 547 participants were excluded from the study because of an incomplete response. The remaining 524 surgeons were representing 14.6% of all practicing surgeons in Turkey.

Table 1 demonstrates demographic features, Table 2 shows approaches for breast masses and responses for clinical scenarios, and Table 3 shows professional perspectives.

The largest group of participants were from training hospitals (n:358, 68%). The frequency of breast diseases in polyclinic practice ranked first for 153 (29%) participants and second for 146 (28%) participants. Two hundred and fifty-eight (49%) responders were spending 5-10 min on an average for the examination of a breast outpatient. Two hundred and forty-one (46%) participants attended a breast surgery meeting in the past 2 years. Needle biopsies were utilized by 314 (60%) and excisional biopsies were utilized by 199 (33%) responders. Three hundred and sixty-seven (70%) participants defined mammography and 61 (12%) participants defined magnetic resonance imaging (MRI) as the most effective method for imaging a breast mass of a 53-year-old woman. The most common breast lesion in women aged be-

Table 2. Approaches of surgeons

Approaches	n (%)
Biopsy method	
Needle (Fine needle, Tru-cut)	314 (60)
Excisional	173 (33)
Incisional	26 (5)
Frozen biopsy	11 (2)
Sonography usage of surgeon	
No	428 (83)
Yes (sometimes)	53 (10)
Yes (frequently)	22 (4)
Yes (always)	16 (3)
Preference for breast assessment in a 53 year-old patient	
Mammography	367 (70)
MRI	61 (12)
Physical examination	59 (11)
Sonography	37 (7)
Most common lesions for ages 20-45	
Cysts	257 (49)
Fibroadenoma	168 (32)
Physiologic nodularity	98 (19)
Malignity	1 (0.2)
Scenario A	
Sonography	309 (59)
Needle biopsy (Fine needle, Tru-cut)	94 (18)
Excisional biopsy	68 (13)
Follow-up	53 (10)
Scenario B	
Mammography- Sonography	299 (57)
Needle biopsy (Fine needle, Tru-cut)	216 (24)
Excisional biopsy	84 (16)
MRI	4 (1)
Scenario C	
Aspiration	210 (40)
Needle biopsy	313 (25)
Follow-up	84 (16)
Excisional biopsy	68 (13)
Frozen biopsy	31 (6)

tween 20 and 45 years was breast cysts for 257 (49%) participants. The initial approach in scenario A was ultrasonography (US) for 309 participants (59%), mammography and US for 299 participants (57%) in scenario B, and aspiration biopsy for 210 participants (40%) in scenario C.

Breast diseases and treatments were defined as easy by 178 responders (34%) and as quite easy by 74 responders (14%). Two hundred and forty-two responders (46%) estimate that the role of surgeons in breast diseases and treatment will diminish in the future. Three hundred and seventy-one participants (71%) think that breast cancer management can be accurately performed by the general surgeons. Two hundred

Table 3. Professional perspectives of surgeons

Perspectives	n (%)
Diagnosis and treatment of breast diseases	
Quite easy	74 (14)
Easy	178 (34)
Intermediate	162 (31)
Difficult	42 (8)
Difficult/complicated	68 (13)
Surgeon's future role in breast diseases	
will be diminished	241 (46)
will remain same	236 (35)
will increase	47 (9)
Management of a breast cancer patient should be led by	
Surgeon	371 (71)
Medical oncologist	120 (23)
Family physician	27 (5)
Radiation oncologist	6 (1)
OBS	
should be performed by general surgeon	273 (52)
should be performed by general surgeon-plastic surgeon collaboration	120 (23)
General surgeon should seek help for free flaps and prosthetic reconstruction	73 (14)
should not be performed by general surgeon	21 (4)
No idea	37 (7)

and seventy-three (52%) responders are of the opinion that OBS should be performed only by a general surgeon.

Discussion and Conclusions

The survey has succeeded in sampling the demography of surgeons in Turkey with its wide contribution all over the country. The "Report on general surgery manpower, workforce and workload," which is published by TSA, introduced that general surgeons were distributed nationwide to the following institutions: 67% hospitals of Ministry of Health, 13% university hospitals, 16% private hospitals, and 2% military hospitals, (6). Our survey exhibited this distribution as 68% hospitals of Ministry of Health, 16% university hospitals, 14% private hospitals, and 2% military hospitals.

The survey has revealed problems in basic approaches to breast masses. Diagnosis of breast masses involve physical examination followed by imaging studies, and if required, pathological sampling (7). While initial approaches for scenario A and scenario B were imaging for 309 (59%) and 299 (57%) responders, respectively, 162 (31%) and 210 (40%) responders' choice as initial approach for scenario A and scenario B was biopsy (needle or excisional), respectively. Unjustifiable breast biopsies for young patients impose both unnecessary workload on physicians and distress and risk to the patients. A diagnostic practice involving breast biopsy prior to an adequate imaging study may cause overlooks in some differential diagnoses in women of all ages (8). Because the cancer anxiety in the society is growing bigger, approach to patients with breast masses should be optimal.

The survey showed that the use of percutaneous needle biopsies is inadequate. Needle biopsy, which is cheap, easily applicable, and does not complicate subsequent procedures, replaced excisional biopsies to a great extent. A study from Canada demonstrated a 97% use of needle biopsies for diagnosis of breast masses (9). Cantürk et al. (10) reported a 60% rate of needle biopsy use in university hospitals of Turkey. Our survey showed a 60% use of needle biopsies and a 38% use of excisional biopsies. Cosmetic outcomes and potential subsequent imaging problems of excisional biopsy are evident. Requirement for improvement in diagnostic approaches for breast masses is obvious. In this survey, 367 (70%) responders indicated that mammography is the most effective diagnostic tool to assess the breast mass of a 53-year-old woman. Mammography is the essential imaging tool for breast masses; MRI and US are complementary modalities (11). The diagnostic accuracy of physical examination for breast masses is reported to reach 74% with experienced surgeons (12). In our study, 59 participants (11%) chose physical examination as the most useful diagnostic tool. Employment of mammography, which is inexpensive and widespread, could be encouraged for suitable cases. The survey indicated that the most common breast lesion in women aged between 20 and 45 years is cysts, which is seen in half of them, and the second most common lesion is fibroadenoma, which is seen in one-third of them, as concordant with the current literature (13).

The study revealed a dominant role of surgeons in OBS practice. OBS is the most developing field in breast surgery in the past 20 years, with longer survivals and improved quality of life in breast cancer treatment. However, the debate continues about who (general surgeon/plastic surgeon) can perform OBS. While one-fourth of the responders think that general surgeons and plastic surgeons should collaborate to perform OBS, more than half of the responders think that OBS should be performed by general surgeons alone. Chang et al. (14) emphasize the significant role of plastic surgeons in breast cancer and breast reduction surgery. Gwack et al. (15) reported that breast reconstructions for early stage breast cancers were performed by most breast surgeons in South Korea. Zucca et al. (16) stated that breast surgeons in Brazil could manage to perform OBS techniques without any help by learning reconstruction techniques. Meanwhile, in a survey for plastic surgeons in the United States, Alderman et al. (17) found that the interest of plastic surgeons for postmastectomy reconstruction started to decline. Because of the high numbers of patients requiring OBS and the limited number of plastic surgeons, training general surgeons for OBS may be a solution. Most of the surgeons wish to perform OBS on their own in our country.

The survey indicated that breast diseases are the most common cause for surgery outpatient clinic admissions. Breast diseases were the most common cause for surgery outpatient clinic admissions for one-third of the respondents. High incidence of benign breast disorders in young women and the anxiety caused by the increasing risk of breast cancer with increasing age causes women to refer a surgeon. The interest of mass media on breast cancer enhanced the sensitivity of the population for early diagnosis. Half of the respondents spared 5-10 min for the examination of these outpatients.

There is no formal subspecialization for breast surgery in Turkey. The survey revealed that surgeons mostly consider diagnosis and treatment of breast diseases as easy and think that the future role of surgeon will diminish. Diagnosis and treatment of breast diseases was defined as easy by 252 (48%) respondents. Nearly half of the respondents think that the role of surgeon will diminish in the future. Until the 1980s,

breast surgery mainly included biopsy and amputation. Breast operations were generally performed at end of the daily operation list and were performed by residents. It was thought that these operations were easier and less prone to development of complications. Breast and axillae conserving procedures, improvements in breast imaging studies, and spreading of screening programmes have expanded the field of surgery in breast diseases. These procedures are defined as difficult or complicated only by 68 (13%) respondents. Despite that common superficial apprehension, with developing adjuvant diagnosis and treatment modalities, multidisciplinary approaches and treatment planning, which starts with the breast conservation course, could lead to the development of complications in the surgery and the process as a whole. Only one-tenth of surgeons estimate an increase in the future role for surgeons. While an increase in sensitivity of patients towards breast diseases and breast and cosmetic conservation procedures may expand the role of general surgeons, advances in healthcare technologies and intervening of radiologists, oncologists, plastic surgeons, and family physicians in this field could limit the potential role for breast surgeons. Endoscopic breast surgery and radiofrequency ablation therapy could replace breast surgery in a suitable group of patients. This trend seems to depend on advances in healthcare technology rather than in surgery.

Surgeons think that they can accurately conduct breast cancer follow-up. The debate continues on who can conduct breast cancer follow-up, which screens local recurrences, new primary tumors, and provides psychological support. Three hundred and seventy-one (71%) respondents stated that breast cancer follow-up can be accurately performed by general surgeons. Most of the local recurrences and distant metastases after breast cancer are caught by patients (18). A survey from Canada demonstrated that 73% of family physicians contribute to the breast cancer follow-up (19). Given the inadequacy of the number of medical oncologists and the newly established family physician care system in Turkey, it is reasonable for surgeons to undertake follow-up of breast cancer, which are easy-to-access, and widely get involved in diagnosis and treatment of these group of patients.

Limitations

This study has some limitations. The answers were assessed according to the participants' statements and were not confirmed with official records and were presented briefly. Infrastructural facilities and qualified manpower of respondents were ignored. Non-palpable masses were not investigated. Assessments are limited with items of the survey and may include authors' biases. Lastly, because the results are presented definitively, they may not reflect different tendencies.

Although breast disorders are the most common cause of admissions in outpatient clinics, approaches of general surgeons towards breast masses need to be improved. National quality standards and practice guidelines could be defined and supervised for their applications in countries with limited resources and special conditions. Although general surgeons wish to perform OBS, they also think that the role of surgeons will diminish in the diagnosis and treatment of breast diseases. Thus, we suggest to define and document perspectives of surgeons on breast diseases and breast surgery in different regions and populations.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Tepecik Training and Research Hospital.

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

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Taste Alteration in Patients Receiving Chemotherapy

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ABSTRACT

Objective: This study is aimed to determine factors that affect conditions of patients receiving chemotherapy in terms of experienced taste alteration.

Materials and Methods: In this descriptive study, 184 patients receiving chemotherapy were included in the sample. Data were collected during the period of December 2013 to May 2014 using "Patient Characteristics Identification Form" and "Chemotherapy-induced Taste Alteration Scale (CiTAS)." The data were analyzed using SPSS 20 (SPSS Inc., Chicago IL, USA) statistical software in terms of number, percentage, Mann-Whitney U test, and Kruskal-Wallis H test.

Results: The mean age of the patients was 55.5 ± 11.8 and 57.1% of them were female. The clinical diagnosis of the patients were most frequently breast cancer (n=46), colorectal cancer (n=45), and lung cancer (n=25). Furthermore, 37.5% of the patients were in clinical stage II; 15.8% of the patients received paclitaxel+herceptin and 14.1% received gemcitabine+cisplatin chemotherapy protocols. Data demonstrated significant differences in mean scores ($p < 0.05$) taken from "Decline in Basic Taste" and "Phantogeusia and Parageusia" subscales with patients with or without xerostomia. There were significant differences in the average scores of the subscales between those with and without a sore mouth "Discomfort" and "General taste alterations" ($p < 0.05$).

Conclusion: It has been established that patients receiving chemotherapy experience substantial alteration in taste by exposure of different subscales of CiTAS. Analysis of scores collected from different subscales of CiTAS with respect to sociodemographic and pathological differences showed that patients with xerostomia and sore mouth experienced more severe taste alterations.

Keywords: Chemotherapy, taste alteration, nursing

Introduction

Taste alteration is a frequently encountered situation in patients receiving chemotherapy. The rate of incidence of taste alterations varies among patients (1). According to the study by Bernhardson et al., which was conducted with a total of 518 patients diagnosed with different types of cancer, the rate of incidence was 67% (2). The rate of taste alterations in breast cancer patients ranges between 55% and 84% (3, 4). In another study conducted on patients receiving chemotherapy for treatment of breast and gynecological cancers, 16% of the breast cancer patients experienced severe taste alteration, 12.6% experienced moderate taste alteration, and 22% experienced mild taste alteration, whereas 7% of the gynecological cancer patients experienced severe taste alteration, 12.4% patients experienced moderate taste alteration, and 22.5% experienced mild taste alteration due to the chemotherapy (5). The following are the taste alterations observed in the patients:

Hypogeusia: decline in taste sensitivity,

Ageusia: complete lack of taste functions of the tongue,

Parageusia: perversion of the sense of taste,

Cacogeusia: unpleasant taste that does not originate from food or beverage,

Phantogeusia (taste hallucination): continuous abnormal taste in the mouth, usually bitter or metallic, and

Hypergeusia: increase in taste sensitivity (6-8).

Taste alterations frequently encountered in patients receiving chemotherapy have physiological, psychological, and social influences on these individuals. These effects reduce the life quality of the patients (1, 2, 9-11). The taste alteration, adversely affecting the life quality of individuals, should be evaluated in a comprehensive manner for effective and appropriate management of the symptoms. For this purpose, there are many objective and subjective methods available for clinical use (8). The objective methods include all mouth taste test, regional

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taste test, taste recognition test, chemical gustometry, electrogustometry, filter paper disc method, positron emission tomography, and magnetic resonance. The etiology of taste alterations, the condition of experiencing alterations in basic tastes, and the level of taste alteration are determined by these methods (8, 11, 12). In the subjective evaluation of taste alterations, Common Terminology Criteria for Adverse Event v4.0 and Scale of Subjective Total Taste Acuity are used. These subjective evaluation tools evaluate the intensity of taste alteration and their effects on the individual partially (11, 13, 14). The decline in basic taste, general taste alterations, phantogeusia and parageusia, and disorder and taste subscales of the patients are more comprehensively evaluated by "Chemotherapy-induced Taste Alteration Scale (CiTAS)" developed by Kano and Kanda. CiTAS is an easy-to-use and practical measurement tool that does not require too much time. Information obtained using CiTAS can make great contributions to the training/consultancy roles of the nurses regarding symptom controls.

Materials and Methods

The aim of this study is to determine factors that affect conditions of patients receiving chemotherapy in terms of experienced taste alteration. The study was conducted on a total of 184 patients receiving chemotherapy at a university hospital hematology clinic and outpatient chemotherapy unit during the period of December 2013 to May 2014. Written permission was obtained from the Gazi University Medical Faculty Institutional Review Board. The sample selection criteria of the study: age ≥ 18 years, illiterate, conscious and receiving chemotherapy 7-10 days before the study, experiencing chemotherapy induced taste alteration, and voluntary participation. Patients receiving radiotherapy with chemotherapy were excluded. "Patient Characteristics Identification Form" and CiTAS were used to obtain the data.

Data collection process: The patients were informed regarding the study before chemotherapy, and their consent was obtained. The data regarding Patient Characteristics Identification Form was obtained by the researcher. CiTAS was filled out by the patients by considering the previous week. The time spent for each data collection tool was 20-25 min.

Patient Characteristics Identification Form comprises 22 questions regarding sociodemographic characteristics and habits of the patients in addition to the disease and treatment.

CiTAS, which is a scale with 18 items and 5 subscales, was developed by Kano and Kanda in 2013. CiTAS is a 5-point Likert-type scale.

1st Subscale (2nd-6th items) Decline in Basic Taste: The condition of sensing the bitter, sweet, salty, sour, and umami taste by individuals is assessed.

2nd Subscale (13th-18th items) Discomfort: The relationship between taste alterations and nausea-vomiting, experiencing alterations in the sense of smell, having difficulty eating hot/oily/meat, and reduced appetite is assessed.

3rd Subscale (10th-12th items) Phantogeusia and Parageusia: The condition of individuals based on their experiences of phantogeusia and parageusia are assessed.

4th Subscale (1st, 7th-9th items) General taste alterations: The condition of individuals regarding their experiences of ageusia, cacogeusia, and hypogeusia is assessed (8).

For the assessment of the scale, scores received from each subscale are evaluated rather than the total score received from the entire scale. The subscale scores are obtained by dividing the number of the items into the sum of scores of those items. The maximum score is 5 points, whereas the minimum score is 1 point that can be received from subscales. The increase in the score shows that the intensity of taste alterations and discomfort are also increased (8).

Statistical analysis

The data obtained were analyzed by SPSS 20 (SPSS Inc., Chicago IL, USA) software package. In the analysis of the data, number and percentage tests were used, whereas Mann-Whitney U test was used for comparisons and Kruskal-Wallis H test was used for comparisons conducted with at least three groups. The relationship between variables was analyzed by Spearman correlation analysis. The significance level was determined as $p < 0.05$.

Results

The mean age of the patients was 55.5 ± 11.8 years (minimum=18, maximum=76, $n=184$); 57.1% of the patients were female. The mean age of female patients was 53.8 ± 12.2 years, whereas it was 57.8 ± 10.8 for male patients. Furthermore, 25% of the patients were diagnosed with breast cancer, whereas 22.8% were diagnosed with colorectal cancer and 13.6% were diagnosed with lung cancer. Moreover, 37.5% of the 37.5% of the patients were in clinical stage II. Chemotherapy protocols were as follows: 15.8% received paclitaxel+herceptin; 14.1% received gemcitabine+cisplatin; and 13.6% received fluorouracil, calcium folinate, irinotecan, and bevacizumab. Moreover, 65.8% of the patients had previously received chemotherapy, whereas 33.7% had been diagnosed with diseases other than cancer; 64.7% received some other drugs in addition to chemotherapy. The percentage of smokers during treatment was 6.2%, whereas the percentage of drinkers was 9.8%; 53.3% of the patients brushed their teeth for oral care, and 40.2% complained about mouth sores and 59.2% had reported to experience xerostomia (Table 1).

In the analysis results conducted on the basis of sociodemographic and disease characteristics of the subscale scores obtained from CiTAS, taste alterations were more frequently observed in patients who also experienced sores in the mouth along with xerostomia. There was no significant difference between other variables (age, sex, any other disease diagnosed, receiving drugs other than those for chemotherapy, smoking/oral care habits, diagnosis, stage, and treatment protocol) and average scores obtained from CiTAS subscales (Table 2, 3).

Discussion and Conclusions

Chemotherapy-induced taste alteration is a frequently encountered problem (8). In this study intended to determine the factors affecting chemotherapy-induced taste alteration, age groups/sex variables had no significant effect on subscales of CiTAS. Sensory functions weaken along with the age; one of these senses is the sense of taste (15). Imami et al. determined the ratio of experiencing chemotherapy-induced taste alteration as 75% in patients who were ≥ 70 years old, higher than that in any other age group (16). Schiffman et al. (17) stated that the sense of taste rarely disappears (ageusia) in the elderly, and the cases of hypogeusia and dysgeusia are encountered more often. In addition, taste perception concentration for sensing the sweet, salty, sour, and bitter tastes reduces as an individual becomes older (17). In this study, it has been shown that sex has no significant effect on the average scores obtained from subscales of CiTAS. However, according to sev-

Table 1. Patient sociodemographic characteristics, habits, and disease/treatment characteristics (n=184)

Characteristics	Number	%
Age groups (year)		
18-40	20	10.9
41-50	33	17.9
51-60	65	35.3
61 and over	66	35.9
Gender		
Female	105	57.1
Male	79	42.9
Diagnosis		
Lymphoma	20	10.9
Multiple myeloma	19	10.3
Breast Cancer	46	25.0
Lung Cancer	25	13.6
Colorectal Cancer	42	22.8
Over Cancer	13	7.1
Pancreatic Cancer	6	3.3
Other*	13	7
Clinical Stage		
I	20	10.9
II	69	37.5
III	53	28.8
IV	42	22.8
Treatment Protocol		
Paclitaxel, herceptin	29	15.8
Fluorouracil, calcium folinate, irinotecan, bevacizumab	25	13.6
Paclitaxel	19	10.3
Gemcitabine, cisplatin	26	14.1
Carboplatin, paclitaxel	15	8.2
Cyclophosphamide, bortezomib, dexamethasone	11	6.0
Fluorouracil, calcium folinate, oxaliplatin	13	7.1
Rituximab, cyclophosphamide, doxorubicin, vincristine, prednol	12	6.5
Doxorubicin, bleomycin, vinblastine, dacarbazine	8	4.3
Other**	26	14.1
Habits		
Cigarette		
Non-smoker	96	52.2
Former smoker	76	41.3
Smoker	12	6.5
Alcohol		
Does not Drink	166	90.2
Used to Drink, but quitted	18	9.8
Oral Care		
Brushing teeth	98	53.3
Rinsing mouth with water	27	14.7

Mouthwash	19	10.3
Brushing teeth+Mouthwash	40	21.7
* Malignant neoplasm of brain (n=3), prostate cancer (n=1), bladder cancer (n=2), testicular cancer (n=3), gastric cancer (n=2), and nasopharyngeal cancer (n=2).		
** Fluorouracil+calcium folinate (n=5), ifosfamide+gemcitabine+vinorelbine (n=4), irinotecan+cetuximab (n=4), gemcitabine+bevacizumab (n=3), cisplatin+docetaxel (n=2), docetaxel (n=2), bleomycin+etoposide+cisplatin (n=2), brentuximab+cyclophosphamide+procarbazine+prednisone (n=2), topotecan (n=1), and cisplatin+doxorubicin (n=1).		

eral studies, female patients experience more chemotherapy-induced taste alteration than male patients (2, 18).

The average scores of patients diagnosed with some other diseases, obtained from subscales of "Decline in basic taste" and "Discomfort," were higher than the average scores of those not having any other disease. In the study by Jensen et al., the percentage of patients experiencing chemotherapy-induced taste alteration was 84%; 24% of the patients had allergic diseases, whereas 13% had muscle/joint ache and 7% had hypertension (4).

In our study, the average scores of patients taking drugs in addition to chemotherapy, obtained from subscales of CiTAS, were higher than those who did not take any other drugs. In another study, the percentage of patients who had to take some other drugs in addition to chemotherapy was 33%. The percentage of the patients experiencing chemotherapy-induced taste alteration was determined as 84%; however, the effect of taking other drugs on the taste alteration was not evaluated (4). On the other hand, in the literature, drugs that cause taste alteration include antibiotics, analgesics, antihypertensives, antidepressants, anticonvulsants, bronchodilators, muscle relaxants, psychopharmacological, antiepileptics, and mouthwashes (9, 19-21). Some diseases accompanying cancer and drugs used for treatment of these diseases may cause taste alterations by affecting the sense of taste.

In this study, although not statistically significant, the average scores of non-smoking patients obtained from subscales of "Decline in basic taste" and "Discomfort" were higher than those of smoking patients. On the other hand, the average scores of non-smoking patients obtained from subscales of "Phantogeusia and Parageusia" and "General taste alterations" were higher than those of smoking patients. However, in the study by Zabernigg et al., which was conducted on chemotherapy-induced taste alteration, statistically significant difference was observed between smoking and non-smoking patients in terms of experiencing taste alteration (22).

In our study, the oral care habits of patients did not affect subscales of CiTAS. The scores of patients engaged in oral care by brushing teeth+mouthwash obtained from subscales of "Decline in basic taste," "Discomfort," and "General taste alterations" and their total scores of CiTAS were found to be higher than scores of other groups. In the subscale of "Phantogeusia and Parageusia," the score of the group stating that "I rinse my mouth with mouthwash" was higher than score of other groups. The alcohol in mouthwash used in oral care causes oral mucosa irritation, taste alterations, and tissue healing delay (23).

In our study, the average scores of patients experiencing xerostomia, obtained from subscales of "Decline in basic taste" and "Phantogeusia and Parageusia," were found to be higher than the scores of those who did not experience xerostomia. However, the average scores of patients with mouth sores, obtained from subscales of "Discomfort" and "General taste alterations," were higher than scores of those without mouth sores. In the study of Jensen et al., which was conducted to

evaluate oral mucosal lesions, microbial changes, and taste alterations occurring in patients diagnosed with breast cancer and receiving adjuvant chemotherapy, there was no relationship between chemotherapy-induced taste alterations experienced by the patients and salivary flow rate and xerostomia (4). However, it is also known that saliva is important for regular functioning of the sense of taste and stimulation of taste receptors. Oral mucositis is considered as a reason causing chemotherapy-induced taste alteration. The changes occurring in mucosa are developed depending on stimulation of taste receptors and changes occurring in dissolving of taste molecules (21). It is believed that the changes occurring in the oral mucosa may affect the sense of taste either directly or indirectly.

In our study, it was also observed that diagnosis and disease stages of the patients have no effect on subscales of CiTAS. According to the study by Kano and Kanda, who investigated the chemotherapy-induced taste alterations, 29% of the patients were diagnosed with breast cancer and 23% were diagnosed with colorectal (8). However, disease and diagnosis stages of the patients were not compared with their taste alterations. According to a study by Gamper et al. on patients (n=109) receiving chemotherapy for treatment of breast and gynecological cancers, 16% of the breast cancer patients experienced severe taste alteration, whereas 12.6% of these patients experienced moderate taste alteration and 22% experienced mild taste alteration, and 7% of the gynecological cancer patients experienced severe taste alteration, whereas 12.4% experienced moderate taste alteration and 22.5% experienced mild taste alteration due to the chemotherapy (5). Considering the literature, the chemotherapy protocol received by the patients rather than clinical diagnosis and disease stages affect taste alterations experienced by the patients.

In our study, the average scores of patients taking gemcitabine and cisplatin, obtained from subscale of "Decline in basic taste," was found to be higher, whereas the average scores of patients taking "Doxorubicin, bleomycin, vinblastine, and dacarbazine" protocol, obtained from the subscales of "Phantogeusia and Parageusia," "Discomfort," and "General taste alterations," were higher than the scores of other groups. According to the study by Kano and Kanda, all their study patients experienced chemotherapy-induced taste alteration. The most common chemotherapy protocols received by the patients are paclitaxel (19%) and folinic acid+fluorouracil+oxaliplatin (12%) (8). According to another study conducted by Bernhardson et al., the chemotherapy protocols received by patients experiencing 75% taste alterations include cyclophosphamide+fluorouracil+epirubicin (14%), paclitaxel+docetaxel (14%), and fluorouracil+calcium folinate+oxaliplatin (13%) (2). The major chemotherapeutic agents causing phantogeusia are cyclophosphamide, doxorubicin, fluorouracil, methotrexate, and cisplatin (4). However, cisplatin and doxorubicin lead to more severe phantogeusia (1).

In our study, according to the subscales of CiTAS, patients experience taste alterations. Considering correlations between all subscales and variables depending on disease, treatment, and demographic charac-

Table 2. Patient sociodemographic characteristics and CiTAS scores depending on habits

Sociodemographic characteristics and habits	n (%)	Decline in Basic Taste Mean±SD	Phantogeusia and Parageusia Mean±SD	Discomfort Mean±SD	General taste alterations Mean±SD
Age groups (year)					
18–40	20 (10.9)	1.7±1.0	2.9±0.9	2.8±1.2	2.7±1.0
41–50	33 (17.9)	1.7±1.0	2.5±1.0	2.7±1.2	2.5±0.9
51–60	65 (35.3)	1.7±1.0	2.6±1.0	2.8±1.2	2.9±1.0
61 and over	66 (35.9)	1.8±1.0	2.7±0.9	2.6±1.3	2.7±1.1
		H=1.02 p=0.794	H=2.36 p=0.499	H=0.99 p=0.802	H=2.22 p=0.526
Gender					
Female	105 (57.1)	1.8±1.1	2.8±1.2	2.8±1.0	2.8±1.1
Male	79 (42.9)	1.7±1.0	2.7±1.3	2.5±1.0	2.8±1.1
		U=4125 p=0.947	U=3982.5 p=0.642	U=3520 p=0.078	U=4017 p=0.714
Diagnosed with another disease					
Yes	62 (33.7)	2.0±1.1	2.6±1.0	2.8±1.3	2.7±1.0
No	122 (66.3)	1.7±1.0	2.7±1.0	2.7±1.3	2.8±1.1
		U=3187 p=0.071	U=3320 p=0.175	U=3598 p=0.588	U=3609.5 p=0.612
Receiving drugs other than chemotherapy					
Yes	119 (64.7)	1.8±1.1	2.7±1.0	2.8±1.3	2.9±1.1
No	65 (35.3)	1.7±0.9	2.7±1.0	2.6±1.2	2.6±1.1
		U=3735.5 p=0.691	U=3834 p=0.922	U=3377.5 p=0.153	U=3379 p=0.156
Cigarette					
Non-smoker	96 (52.2)	1.8±1.1	2.7±1.0	2.8±1.4	2.9±1.0
Former Smoker	76 (41.3)	1.7±1.0	2.6±1.0	2.7±1.2	2.7±1.1
Smoker	12 (6.5)	2.0±1.0	2.6±1.0	3.1±1.1	2.7±1.3
		H=1.195 p=0.549	H=0.654 p=0.721	H=1.415 p=0.492	H=1.491 p=0.474
Oral Care					
Brushing teeth	98 (53.3)	1.7±1.0	2.6±0.9	2.7±1.3	2.7±1.1
Rinsing mouth with water	27 (14.7)	1.7±0.8	2.7±0.9	2.6±1.4	2.9±1.3
Mouthwash	19 (10.3)	2.0±1.3	3.0±1.2	2.7±1.3	2.7±1.1
Brushing teeth+Mouthwash	40 (21.7)	2.0±1.2	2.6±1.0	3.1±1.3	3.0±1.0
		H=4.82 p=0.184	H=1.29 p=0.729	H=2.79 p=0.424	H=3.16 p=0.366
Sore Mouth					
Yes	74 (40.2)	2.0±1.2	2.8±1.0	3.1±1.2	3.0±1.1
No	110 (59.8)	1.7±0.9	2.6±1.0	2.5±1.2	2.6±1.1
		U=3590 p=0.159	U=3555.5 p=0.145	U=3006 p=0.002	U=3239 p=0.018
Xerostomia					
Yes	109 (59.2)	1.9±1.1	2.8±1.0	2.9±1.3	2.9±1.1
No	75 (40.8)	1.6±0.9	2.5±0.9	2.6±1.3	2.6±1.0
		U=3255 p=0.014	U=3227.5 p=0.015	U=3593.5 p=0.162	U=3432 p=0.064

Table 3. Patient CiTAS scores depending on the disease and treatment characteristics

Disease and treatment characteristics	n (%)	Decline in Basic Taste Mean±SD	Phantogeusia and Parageusia Mean±SD	Discomfort Mean±SD	General taste alterations Mean±SD
Diagnosis					
Lymphoma	20 (10.9)	1.7±0.9	2.7±1.0	2.7±1.0	2.6±1.1
Multiple myeloma	19 (10.3)	1.4±0.3	2.1±0.8	2.6±1.1	2.4±0.9
Breast cancer	46 (25.0)	1.8±1.0	2.5±1.0	2.7±1.3	2.6±1.0
Lung cancer	25 (13.6)	1.9±1.1	2.8±0.9	2.9±1.2	2.9±1.1
Colorectal cancer	42 (22.8)	1.6±0.9	2.8±0.8	2.4±1.1	2.8±1.0
Over cancer	13 (7.1)	1.6±0.9	3.1±1.1	2.9±1.4	2.9±1.1
Pancreatic cancer	6 (3.3)	1.7±1.2	2.7±0.8	3.2±1.7	3.2±1.0
Other*	13 (7)	2.1±1.4	2.5±0.9	2.9±1.4	2.9±1.2
		H=2.6 p=0.919	H=10.9 p=0.143	H=3.9 p=0.784	H=5.4 p=0.605
Clinical Stage					
I	20 (10.9)	1.5±0.7	2.7±0.9	2.6±1.3	2.8±1.2
II	69 (37.5)	1.6±0.9	2.6±0.9	2.5±1.2	2.8±1.0
III	53 (28.8)	1.8±1.1	2.6±1.0	2.9±1.1	2.6±1.0
IV	42 (22.8)	2.0±1.1	2.8±0.9	2.9±1.4	2.9±1.1
		H=3.26 p=0.352	H=1.28 p=0.732	H=3.95 p=0.265	H=2.65 p=0.448
Treatment Protocol					
Paclitaxel+herceptin	29	1.7±0.9	2.3±0.8	2.9±1.2	2.6±1.0
Fluorouracil+calcium folinate+irinotecan. bevacizumab	25	1.7±1.1	2.9±0.8	2.5±1.2	3.0±1.1
Paclitaxel	19	1.8±1.1	2.6±1.1	2.6±1.4	2.7±0.9
Gemcitabine+cisplatin	26	2.2±1.3	2.8±1.0	2.9±1.4	2.9±1.2
Carboplatin+paclitaxel	15	1.9±1.0	2.6±0.8	2.8±1.4	2.6±1.2
Cyclophosphamide+ bortezomib+dexamethasone	11	1.4±0.4	2.0±0.8	2.7±1.2	2.2±0.8
Fluorouracil+calcium folinate+oxaliplatin	13	1.2±0.4	2.5±0.9	2.4±1.2	2.6±1.1
Rituximab+Cyclophosphamide+ doxorubicin+vincristine+prednol	12	1.7±0.9	2.3±0.9	2.6±1.2	2.5±1.0
Doxorubicin+bleomycin+ vinblastine+dacarbazine	8	1.7±0.9	3.2±1.2	3.3±0.8	3.2±1.2
Other*	26	1.7±1.0	2.8±1.0	2.6±1.2	3.0±1.0
		H=5.103 p=0.825	H=12.737 p=0.174	H=5.782 p=0.761	H=8.957 p=0.441

teristics, xerostomia and mouth sores cause taste alteration in majority of the cases. To elucidate changeable/unchangeable risk factors for experiencing taste alteration in patients receiving cancer treatment, more descriptive and randomized controlled studies are required.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi University Medical Faculty Institutional Review Board.

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

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Mastalgia-Cancer Relationship: A Prospective Study

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ABSTRACT

Objective: Mastalgia is an important symptom affecting approximately 70% of women and it disrupts the quality of life especially due to the worry of having cancer. In our study, the type and severity of mastalgia symptom of patients who presented to the outpatient clinic with mastalgia complaint were assessed along with their physical examination findings and radiology results. The purpose of the study is to demonstrate the relationship between mastalgia and malignancy when assessed in combination with the risk factors of patients.

Materials and Methods: The age, family history, menopausal status, age at the first childbirth, menarche, presence/absence of hormone replacement therapy, type of mastalgia, comorbidities and examination findings of 104 patients, who presented to the General Surgery outpatient clinic with mastalgia symptom, were recorded and assessed in the light of radiological study results.

Results: With respect to the mastalgia types of the patients, 38.5% had cyclic pain, 57.7% non-cyclic pain and 3.8% other types of pain. Mild mastalgia was present in 46.2% of the patients, moderate mastalgia in 24% and severe mastalgia in 29.8% of them. According to the BIRADS category, 48.1% of the patients were identified to have BIRADS 1 mass lesions, 39.4% BIRADS 2, 9.6% BIRADS 3 and 2.9% BIRADS 5 mass lesions. The patients who were identified to have BIRADS 5 mass lesions described non-cyclic and severe pain in the post-menopausal period. They had palpable masses along with the pain symptom.

Conclusion: Our study suggests that mastalgia symptom does not per se result in suspicion of malignancy, but physical examination and radiological imaging should also be used as needed for confirmation. Studies with a larger patient population are needed to shed light on the mastalgia epidemiology and its relationship with cancer.

Keywords: Mastodynia, breast cancer, ultrasonography, mammography

Introduction

Breast pain, which is termed “mastalgia” or “mastodynia” in the literature, is an important symptom of which the etiology and treatment have not been fully clarified and which causes approximately 70% of women to see a doctor at one period in their lives (1). Mastodynia is defined as nipple as well as tension, discomfort and pain in one or both of the breasts (2). It significantly influences the daily lives of women and it causes a serious uneasiness due to the worry of having cancer. Our main objective for patients with symptom of mastalgia according to contemporary study methods is to rule out the diagnosis of cancer. Various factors related to mastalgia etiology have been held accountable in the literature (3). A large breast volume, changes in diet and lifestyle, hormone replacement therapy (HRT), ductal ectasia and mastitis rank the first among them. Increased water and salt retention related to mastalgia developing in the premenstrual period was also held responsible (4). Especially changes in the levels of estrogen and progesterone, major hormonal factors, were discussed. Even though it is stated that high dose caffeine intake is associated with mastalgia, the discussions are controversial; on the other hand, there are publications reporting decreased symptoms with reduced caffeine in diet (5). The identification of the character of breast pain for patients presenting with breast pain plays an important role in diagnosis, treatment and follow-up (6). Breast pain is classified as cyclic and non-cyclic (7). Cyclic breast pain is defined as sensitivity felt in the first 2-3 days of menstruation in 2/3 of cases (8). As for non-cyclic breast pain, it is pain that does not follow the normal menstrual pattern and it is often one-sided. Its localization in the breast is variable (7). In case of extra-mammary pain, it may result in spinal or para-spinal problems and traumatic pain originating in the chest wall with the muscle-skeletal system ranking the first. Furthermore, it may be associated with biliary, pulmonary, esophageal and cardiac diseases (9). When breast pain is believed to be benign in character, psychological support methods, primarily placebo or suggestion, are deemed the first choices; however, there are also medical treatment options with proven efficiency (10). The search for solution in cases that are re-

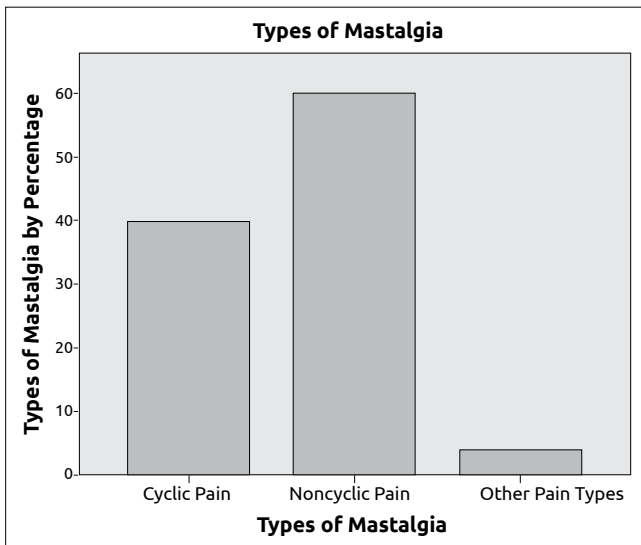


Figure 1. Percentage rates of mastalgia types

sistant to all treatment options is ongoing. In our study, mastalgia was investigated as an important problem influencing the quality of life for women and the cases were assessed in the light of medical records, examination findings and radiological study results. The main aim of the study is to demonstrate the relationship of mastalgia and the patients' risk factors with lesions that are suspected for malignancy.

The study is intended to contribute to the epidemiology of "mastalgia" in Turkey with the demographic data, personal history, physical examination results and study results.

Materials and Methods

One hundred and four patients, who presented at the General Surgery Outpatient Clinic of Dışkapı Yıldırım Beyazıt Teaching and Research Hospital with the symptom of mastalgia between June, 2010 and September, 2013, were included in the study. Before the study was started, approval was obtained from the local ethics committee of our hospital. After the study was explained to the patients, their written consents were obtained. The patients who presented for the first time to the general surgery outpatient clinic with the symptom of breast pain were included in the study. The patients, who were on follow-up due to breast pain, had repeated presentations or history of surgical intervention in their breasts, were not included in the study. The age, family history, menopausal status, age at the first childbirth, menarche, presence of hormone replacement therapy (HRT), cyclic or non-cyclic character of mastalgia as well as comorbidities of the cases were inquired and their physical examinations, breast USG (ESAOTE Gold Platform MyLab 60, Genoa, Italy) and mammography (Amulet, Fujifilm, Tokyo, Japan) studies were conducted. These findings for patients were recorded in the 'Mastalgia Assessment Form'. The mammography and ultrasonography findings were evaluated using the BIRADS (Breast Imaging-Reporting and Data System) classification described by the "Radiological Society of North America". The severity of pain was categorized in 3 groups. According to the assessment of cyclic and non-cyclic pain, the patients in both groups with pain lasting 1-2 minutes less than one week were included in the mild pain group; the patients with pain lasting 8-15 days or 1-2 hours in the moderate group and the patients with pain lasting more than 15 days or feeling continuous pain in the severe pain group. As a result of an examination of their breasts the patients with and without pathological findings

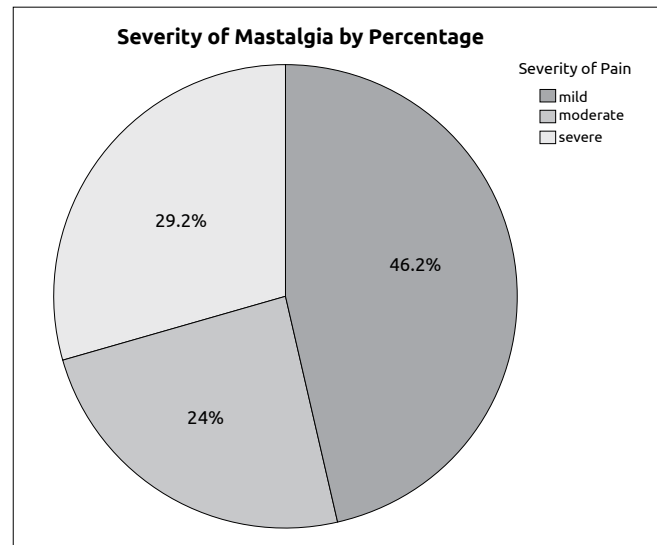


Figure 2. Percentage rates of mastalgia severity

were grouped separately. Breast ultrasonography was requested for 62 patients aged below 40 and ultrasonography as well as mammography was requested for 42 patients above the age of 40.

Statistical analysis

The data obtained were statistically analyzed using the software program "SPSS 17 (SPSS Inc., Chicago, Illinois, USA)". As statistical analysis method, descriptive statistics (frequency, percentage distribution, mean, median, etc.) were used. For the comparison of BIRADS scores of qualitative data, Chi-square test was used. The average values are stated as average ($\pm$) standard deviation. A value of $p \leq 0.05$ at a confidence interval of 95% was considered statistically significant.

Findings

The average age of 104 patients we included in the study is 38.6. The average age for the first menstruation was 12.6, average menopausal age was 50. Sixteen out of 104 patients were post-menopausal. In 43.3% (n:45) of the patients, there were comorbidities. Seventeen of 45 patients described mild, 13 moderate and 15 severe pain. In 12.5% (n:13) of the patients, history of cancer in the family was identified. Four of these patients define mild, 2 moderate and 7 severe pain. 14.4% (n: 15) of the patients received HRT. Among patients with history of HRT, 3 patients described mild pain, 3 patients moderate and 9 patients severe pain. 34.6% (n:36) of the patients had menstrual irregularity. Considering the types of mastalgia that the patients had, 38.5% had cyclic pain (n:40); % 57.7% had non-cyclic pain and 3.8% (n:4) had other types of pain (Figure 1). 46.2% of the patients (n:48) had mild mastalgia; 24% (n:25) had moderate and 29.8% (n:31) had severe mastalgia (Figure 2). Fourteen out of 16 post-menopausal patients described non-cyclic pain while 2 described cyclic pain. When the radiological study results of the patients were examined according to the BIRADS category, 48.1% of the patients were identified to have mass lesions in the category BIRADS 1, 39.4 in the category BIRADS 2, 9.6% in category BIRADS 3 and 2.9% in category BIRADS 5. None of the patients were radiologically found to have BIRADS4 mass lesions (Figure 3).

When the types of pain were examined, 18 out of 40 patients describing cyclic mastalgia were identified to have mass lesions in the category BIRADS 1, 16 in BIRADS 2 and 6 patients in BIRADS 3. Thirty one patients describing non-cyclic pain were identified to have mass lesions

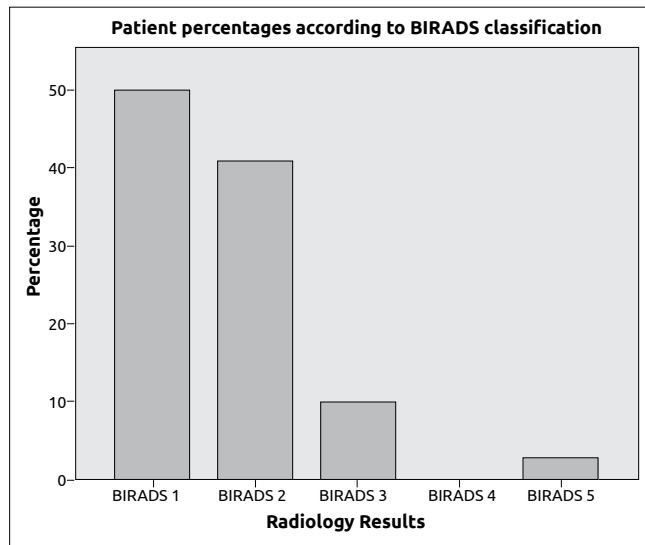


Figure 3. Patient percentages according to BIRADS classification

in the category BIRADS 1, 22 patients in BIRADS 2, four patients in BIRADS 3 and three patients in BIRADS 5. No statistically significant relations could be found between the type of pain and BIRADS category according to the results. ($p:0.37$) When the severity of pain was examined, 26 of 40 patients describing mild pain were identified to have lesions in the category BIRADS 1, 18 patients in BIRADS 2 and one patient in BIRADS 3. Thirteen out of 25 patients describing moderate pain were identified to have lesions in the category BIRADS 1, 9 patients in BIRADS 2 and 3 patients in BIRADS 3. Eleven patients describing severe pain were identified to have mass lesions in the category BIRADS 1, 14 patients in BIRADS 2, 3 patients in BIRADS 3 and 3 patients in BIRADS 5. According to these results, no statistically significant relations were identified between the severity of pain and BIRADS categorization ($p:0.16$). The patients identified to have lesions in the categories BIRADS 1 and 2 were recommended to return for control one year later while those identified to have lesions in the category BIRADS 3 were recommended to have 6-month follow-ups. Tru-Cut biopsy was performed in 3 patients identified to have lesions in the category BIRADS 5 and surgery was conducted in 3 patients with the diagnosis of invasive ductal carcinoma. The method of suggestion was primarily applied in the cyclic and non-cyclic mastalgia group. The patients that described other types of pain were referred to the physical therapy outpatient clinic. The patients who received suggestion and supportive bra and had therapy failure were started on medical treatment methods.

Discussion and Conclusions

Mastalgia is the most common symptom in breasts and it is the most frequent reason for presenting to an outpatient clinic in relation to breast (11). Even though studies support the view that no strong relations exist between breast pain and breast cancer, the uneasiness and fear of breast cancer caused by pain are persistent (12, 13). In assessing the relation of mastalgia with cancer, it is important to determine the type of mastalgia and to uncover the underlying reason for pain using other diagnostic tools in the ensuing period. As per the types of mastalgia reported in the literature, cyclic mastalgia has an incidence of 2/3 while non-cyclic mastalgia has an incidence of 1/3. Especially cyclic mastalgia has been associated with edema in the breast stroma which causes patients to have bilateral and diffuse symptoms in the luteal phases of hormones and menstrual cycle (7). Non-cyclic pain is a pain

that is described as unilateral and focal in mostly post-menopausal women aged 40-50 years and above (14). In our study group patients, 38.5% had cyclic types of mastalgia while 57.7% had non-cyclic and 3.8% had other types of mastalgia. According to our results, the incidence of cyclic mastalgia was expected to be higher in our population with an average age of 38.6 while non-cyclic mastalgia was in the forefront. This result might have resulted from the fact that the type of mastalgia of patients was determined according to their medical history and this assessment was subjective. Even though mastalgia is not considered a symptom of cancer per se, its presence does not rule out the presence of cancer, either. In a study performed by Preece et al. (15), it was found important that pain in the presence of breast cancer was unilateral and continuous for its differentiation from cyclic premenstrual mastalgia. This study also examined 17 patients among 240 breast cancer patients, who had only mastalgia in their initial presentation, and it was found that the majority of these patients had T0 and T1 early stage breast cancers. This situation showed the relationship between the symptom of mastalgia in patients, who had no physical examination findings, with early stage and small tumors. All the three cases in our study identified to have lesions in the category BIRADS 5 described non-cyclical, persistent and severe pain. Furthermore, palpable masses were also detected in the physical examinations of these patients. This result demonstrates once again the requirement to assess the symptoms and findings in a combined fashion for the diagnosis of breast cancer. Considering that non-cyclic pain mostly develops in post-menopausal patients, the results of our study are consistent with the literature (7). On the other hand, the study by Kızılkaya et al. (16) identified malignancies in two out of 530 patients with only mastalgia symptoms and both these patients described non-cyclic pain in the pre-menopausal period. In a study performed by Fariselli et al. (17) in Italy with 200 patients, only 5 out of patients who had no physical examination findings and described only local mastalgia were identified to have sub-clinical cancer. Our study found no statistically significant correlations between the types of pain and BIRADS categories, which may be explained by the limited number of cases in our study population. In our study, no statistically significant relations were found between the severity of pain and suspicion of malignancy. There are no studies conducted on this subject in the literature.

The first step of approach for patients presenting with mastalgia symptoms includes the assessment of pain type, review of the associated risk factors and completion of physical therapy in a meticulous way. It should be clarified whether the mastalgia symptom is underpinned by a pathology using breast ultrasonography and/or mammography depending on the patient's current situation. Both literature data and our study results suggest that pain does not constitute per se a symptom which may trigger suspicion of cancer. A patient presenting with only mastalgia and no physical examination and radiological results should be explained that pain does not constitute an additional risk for cancer. The limitation of our study was that it was designed as a study based on the medical history of patients in a cross-sectional time period. We are convinced that studies with longer durations conducted on larger patient populations with detailed medical history findings and supported by serum markers are needed.

Ethics Committee Approval: Ethics committee approval was received for this study.

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

Peer-review: Externally peer-reviewed.

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Stewart-Treves Syndrome after Bilateral Mastectomy and Radiotherapy for Breast Carcinoma: Case Report

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ABSTRACT

Stewart-Treves syndrome is an angiosarcoma that occurs because of chronic lymphedema, which in most cases is a complication after mastectomy with axillary node dissection and postoperative radiation. Prognosis for this rare tumor is poor. The best therapy is early and radical excision. Chronic lymphedema seems to be an important pathogenic factor. We report a 59-year-old patient with chronic lymphedema and lymphangiosarcoma of the left upper limb who had a left modified radical mastectomy with axillary node dissection and postoperative radiation nine years ago. Additionally, the patient underwent a right modified radical mastectomy with axillary node dissection and postoperative radiation one year ago. In this report, we present a case of Stewart-Treves syndrome after the patient was operated for bilateral breast carcinoma, a review of literature, and principles of treatment.

Keywords: Bilateral breast cancer, chronic lymphedema, angiosarcoma

Introduction

Lymphangiosarcoma of the upper limb was described in post-mastectomy patients by Stewart and Treves in 1948 (1). Lymphangiosarcoma following breast cancer is a rare entity. Today, it still is a potentially highly lethal vascular tumor. The tumor is best described in the upper limb following breast cancer treatment, but a small number of cases have arisen in lymphedema of the lower limb or upper limb without breast cancer and mastectomy (2). Lymphangiosarcoma has a poor prognosis (3, 4) with a 5-year survival of <5% with multimodality treatment. Wide surgical resection is the best treatment method (3-5). A review of literature suggests that mastectomy resulting from breast cancer-related lymphedema is the main predisposing factor (6). Other risk factors of lymphedema that have been reported are association trauma, filarial infection, and idiopathic acquired lymphedema (2).

Case Presentation

A 59-year-old woman underwent a modified radical mastectomy with axillary node dissection on the left side for invasive ductal carcinoma nine years ago. Postoperatively, the patient was irradiated with a total dose of 50 Gy to the. Target volume included the chest wall, supraclavicular fossa, and internal mammary node. Chronic lymphedema of the left upper limb developed after radiation therapy. In addition, our patient underwent radical surgery (a modified radical mastectomy with axillary node dissection) on the right side and radiation therapy for invasive carcinoma one year ago. Nine years after the first radiation therapy, the patient presented with a solid blue-reddish nodular lesion approximately 17 cm on the left upper limb to antecubital area.

The histopathological analysis of a punch biopsy demonstrated a vascular tumor. Low power view showed extensive infiltration of the dermis by a vascular tumor (Figure 1). The appearances are numerous anastomosing vascular channels of varying caliber. The endothelium, which was single and multilayered, typically plump, pleomorphic, and mitotically active, and forms papillae, nested within the vascular lumina (Figure 2, 3). On immunohistochemical analysis, the tumor cells expressed CD34 (Figure 4), CD31 (Figure 5), and factor 8. The tumor cells were enclosed within a reticulin sheath. The Ki-67 proliferation index was observed to be 80%.

We considered a palliative chemotherapy regimen using a combination of etoposide and ifosfamide. The patient did not have any significant chemotherapy complication. Lesions decreased by 80% after chemotherapy.

Discussion and Conclusions

Stewart-Treves syndrome (STS) was originally described as a lymphangiosarcoma of the upper extremity occurring many years after radical mastectomy for breast cancer (1). Currently, there are two million breast cancer survivors in the United States alone, and 20% of them suffer from breast cancer-related lymphedema (7).

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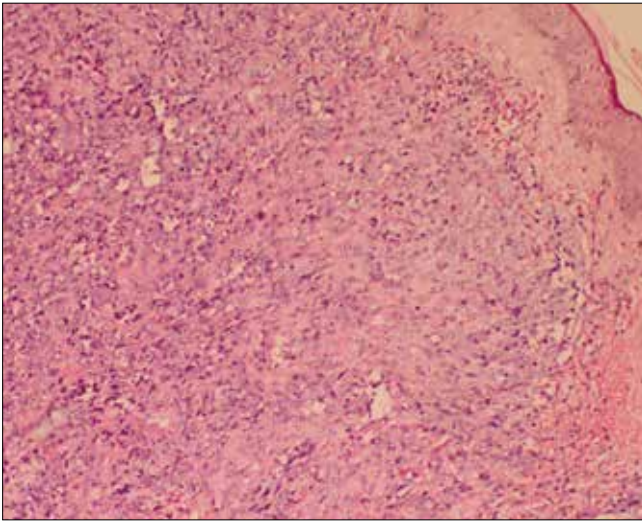


Figure 1. Extensive infiltration of the dermis by a vascular tumor; 10×HE

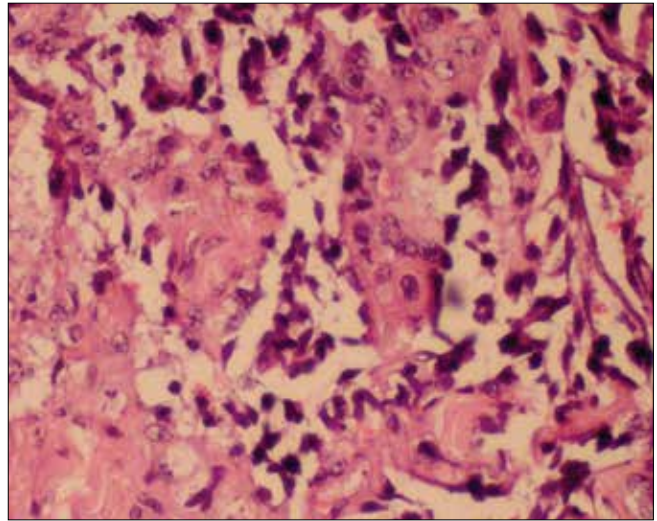


Figure 3. The endothelium that was typically plump and pleomorphic; 40×HE

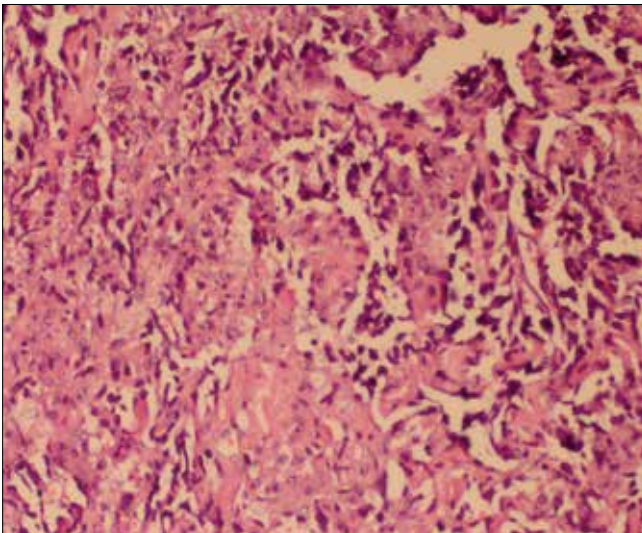


Figure 2. The endothelium that was single and multilayered; 20×HE

Lymphedema-associated angiosarcoma classically arises on the arms of elderly females who have undergone radiotherapy many years previously (STS). It may also develop in other forms of iatrogenic lymphedema, congenital lymphedema, and very rarely in lymphangiomatous malformation and in association with elephantiasis (8).

Typically, the tumor presents in women who have a severe longstanding lymphedema of the arm following breast surgery (1, 2). In most cases, lymphedema is present for approximately 10 years before the tumor arises, usually in the inner portion of the upper arm. Radiotherapy can usually be excluded as an etiologic factor because the sarcoma nearly always develops beyond the areas of chronic radiodermatitis. Our patient had a bilateral modified radical mastectomy with axillary node dissection and postoperative radiation ten years ago and right modified radical mastectomy with axillary node dissection and postoperative radiation one year ago.

Lymphedema-induced angiosarcomas have also been described in men (9) and in a lower extremity (10). We report a 59-year-old woman with STS of the upper limb.

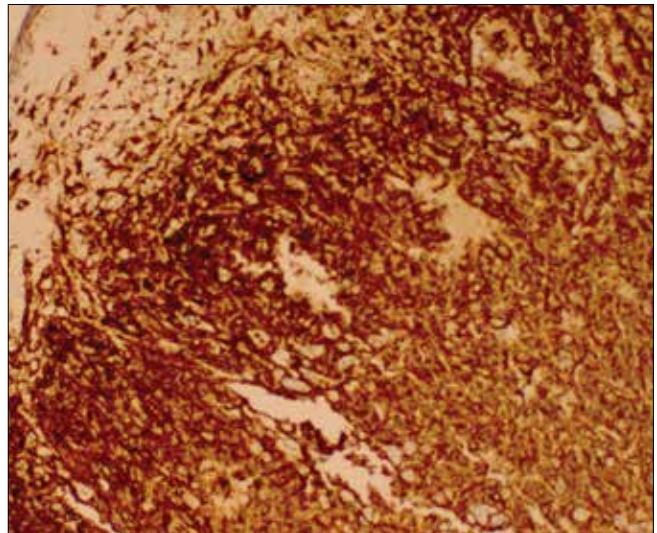


Figure 4. On immunohistochemical analysis, the tumor cells expressed CD34; 20×HE

A skin biopsy of the lesion showed irregular anastomosing vascular channels lined by endothelial cells with different degrees of atypia and mitotic activity alternating with areas of closely spaced cells with a high mitotic index and spindle-like morphology. Immunohistochemical staining for CD31, CD34, F8, and Ki67 are helpful for the establishment of the diagnosis of lymphangiosarcoma. In our case, the tumor was in the form of numerous anastomosing vascular channels of varying caliber. The endothelium, which was typically plump, pleomorphic, and mitotically active and forms papillae, nests within the vascular lumina. On immunohistochemical analysis, the tumor cells expressed CD34, CD31, and factor 8.

The presence of endothelial cell atypia, multilayering, and mitotic activity allows distinction from benign hemangioma and Masson's tumor. Immunohistochemical staining for CD31, CD34, factor 8, and Ki67 are helpful for the establishment of the diagnosis of lymphangiosarcoma.

Lymphangiosarcoma is an aggressive, malignant vascular tumor following long-lasting chronic lymphedema. Regardless, this malignancy

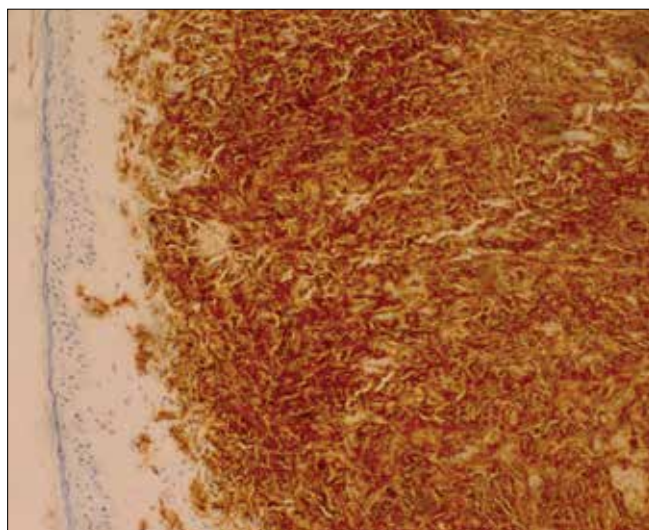


Figure 5. On immunohistochemical analysis, the tumor cells expressed CD31; 20×HE

significantly worsens patients' outcomes and needs to be diagnosed and treated early.

Chemotherapy and radiation therapy do not improve survivorship significantly. Early amputation or wide local excision offers the best chance for long-term survival. Some authors recommend radical resection in the form of disarticulation or amputation. Surgical treatment can be preceded or followed by radiation therapy. The decision to perform a primary amputation for STS of the extremity is based on the location and local extent of the tumor and the expected function of the extremity after tumor resection. The higher risk of metastases for patients who require primary amputation is accounted for by independent risk factors associated with their tumors' predominantly large size. Locally advanced tumors or metastatic forms can be treated with mono- or poly-chemotherapy that is systemic or local (11). Overall prognosis still remains dismal. Untreated patients usually live 5–8 months after diagnosis (12).

Our patient not accepted to amputation. Therefore, we considered a palliative chemotherapy regimen using combination of etoposide and ifosfamide. The patient did not have any significant chemotherapy complication. Lesions decreased by 80% after chemotherapy. Follow-up examination of our patient has alived at one year after diagnosis.

In conclusion, STS is a rare entity and has a generally poor response to chemotherapy. Early detection and diagnosis have a crucial prognostic value. The development of new chemotherapeutic agents effective in lymphangiosarcoma is required.

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

Peer-review: Externally peer-reviewed.

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Docetaxel-induced Scleroderma in A Breast Cancer Patient: A Case Report

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ABSTRACT

Paclitaxel and docetaxel are antineoplastic drugs derived from the yew tree, *Taxus brevifolia*. They are the members of the taxane family and act by inhibiting mitotic activity due to the suppression of microtubule depolymerization. They are used in the treatment of ovarian cancer, breast cancer, gastric cancer, small cell lung cancer, and head and neck cancer. In addition to side effects such as cardiotoxicity, neutropenia, arthralgia, and myalgia, they may also cause alopecia, urticaria, mucositis, acral erythema, pustular dermatitis, erythema multiforme, and scleroderma-like mucocutaneous lesions. Scleroderma is among the uncommon side effects of taxane antineoplastic agents. As was the case in few cases in literature, it usually begins with edematous changes in the proximal aspect of the extremities, and subsequently, sclerosis is developed in the skin. Scleroderma, which usually regresses with the discontinuation of the drug and with steroid therapy, may lead to severe contractions that require physical therapy and rehabilitation in some patients. In this paper, we presented a 60-year-old female patient in whom scleroderma developed because docetaxel chemotherapy for breast cancer because it is encountered rarely.

Keywords: Taxoids, scleroderma, breast cancer

Introduction

Paclitaxel and docetaxel are antineoplastic agents of the taxane family and act by inhibiting mitosis. They are used in the treatment of solid tumors in ovarian cancer, breast cancer, small cell lung cancer, and head and neck cancers. In many recent studies on adjuvant therapy of breast cancer, it has been demonstrated that chemotherapy regimens including taxane improve survival and decrease recurrence compared with standard FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) chemotherapy (1, 2). Nevertheless, in addition to side effects such as neutropenia, arthralgia, and cardiotoxicity, they may cause acral erythema, pustular dermatitis, erythema multiforme, and scleroderma-like mucocutaneous lesions (3). Scleroderma is an autoimmune disease of connective tissue with an unknown etiology and courses with increase in connective tissue and fibrosis. Scleroderma-like mucocutaneous lesions are rare adverse events encountered because of docetaxel, and we think that this should be kept in mind during the follow-up of breast cancer patients.

Case Presentation

A 59-year-old female patient underwent modified right radical mastectomy and axillary dissection due to multicentric invasive ductal carcinoma of the right breast. The pathology report revealed that the tumor consisted of numerous millimetric multiple foci, the largest being 3.5 cm in diameter. In addition to extensive lymphovascular tumor emboli and millimetric satellite foci in all quadrants, there were tumor emboli in the lymphatics of the areola and breast skin. Furthermore, the tumor showed extensive perineural invasion. The immunohistochemical examination demonstrated that estrogen and progesterone receptors were diffuse nuclear (-) and CerbB-2 was (-). Invasive ductal carcinoma metastasis and extracapsular adipose tissue invasion were detected in 6 of 14 lymph nodes obtained from the axillary specimen. Chemotherapy, radiotherapy, and hormonal therapy were decided to be initiated for the patient. A chemotherapy regimen consisting of docetaxel, doxorubicin, and cyclophosphamide (TAC) was started. After the second cure of docetaxel, the patient developed redness and edema followed by induration on the skin of the left lower extremity first, and after a while, the same lesion appeared on the right arm, and the photos of the lesions were taken after the patient provided informed consent (Figure 1-3). Dermatology and rheumatology consultations performed for this reason suggested that these lesions were due to a connective tissue disease. Drug eruptions, urticaria, eczema, local dystrophy, and other diseases with Raynaud's phenomenon were also observed in the differential diagnosis, and then various diagnostic tests were performed. On blood analysis, ANA (antinuclear antibody-centromere antibody) was positive (1/320). Anticardiolipin, antiphospholipid, ANCA, ENA, CCP antibodies, and other rheumatological parameters were found to be negative. Based on all clinical and laboratory findings and the 2013 ACR/EULAR Classification Criteria for Scleroderma, the patient was diagnosed with

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Figure 1. Cutaneous fibrosis in the dorsum of the right hand and arm



Figure 2. Cutaneous fibrosis in the palms of the right hand and arm

scleroderma. Skin biopsy was not performed because the patient was receiving chemotherapy and because of the probability of poor wound healing. Cyclophosphamide and prednisolone were commenced. Five thousand centigray radiotherapy was delivered in 25 fractions to the right chest wall and axillary fossa at the radiation oncology unit. However, femara was commenced at a single dose daily. Approximately a year later, the lesion on her left leg completely disappeared, but the one on her right arm partially regressed.

Discussion and Conclusions

Taxanes are antineoplastic agents derived from the yew tree, *Taxus brevifolia*, and they act by inhibiting mitosis. They are used in the treatment of ovarian cancer, breast cancer, small cell lung cancer, and head and neck cancers. Recently, numerous studies were performed on taxane-based chemotherapies. Multicenter studies such as BCIRG 001 and GEICAM/2003-02 demonstrated that chemotherapy regimens including taxane improve survival and reduce recurrence rates compared with the standard FAC chemotherapy (1, 2). Taxanes, as well as other antineoplastic agents, have many toxic effects. In addition to side effects such as cardiotoxicity, mucositis, neutropenia, arthralgia, and myalgia, they may also lead to some mucocutaneous lesions. Although hypersensitivity lesions such as urticaria are more common, there are patients in literature who developed erythematous and edematous skin reactions, erythema multiforme, and systemic lupus erythematosus after taxoid administration (3-6). Scleroderma-like skin lesions following docetaxel have rarely been reported in literature (7-10). There is no case reported from Turkey. Battafarano et al. (7) presented three



Figure 3. Scleroderma affecting the right hand and arm. Improvement in erythema, dyspigmentation, and skin thickness demonstrated over a 3-month period

patients who developed sclerotic skin lesions in the lower extremities following docetaxel administration. Cleveland (8) reported extensive edema followed by fibrosis after docetaxel in a metastatic breast cancer patient in whom the signs were rapidly improved when the drug was discontinued. Likewise, Hassett (9) also identified scleroderma-like skin lesions due to docetaxel in a breast cancer patient. In their study that included 5 patients with metastatic breast cancer who developed scleroderma following taxane administration, Itoh et al. (11) reported edema in the distal aspect of the extremities followed by sclerosis in the skin. While all these patients received steroid therapy, three required rehabilitation. It is known that similar skin lesions also develop with paclitaxel, another taxane agent (12-15). Tanaka et al. (16) also presented a patient with metastatic breast cancer who developed cystoid macular edema due to paclitaxel and emphasized the importance of mucocutaneous lesions as a rarely seen side effect that could substantially affect the quality of life. Sclerotic skin lesions may either be limited to a certain region of the body or be extensive (8, 9). In the present case, extensive sclerotic skin lesions appeared in the lower left and upper right extremities after docetaxel administration. Restriction occurred in the hand, arm, and foot movements of the patient. This condition quite unfavorably influenced the patient's quality of life. The lesions began to regress after the chemotherapy was ended and steroid therapy was commenced.

Taxoid antineoplastic agents, which are being increasingly used in the adjuvant therapy of breast cancer, have mucocutaneous adverse events in addition to their many toxic effects. Although scleroderma is rarely encountered, it should always be kept in mind that it may develop after docetaxel administration. Moreover, a systemic approach is needed in the diagnosis and treatment of these cutaneous lesions.

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Modified Radical Mastectomy under Local Anesthesia in High-Risk Male Breast Cancer

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ABSTRACT

Carcinoma of the male breast is responsible for less than 1% of all malignancies in men, but the prognosis is poor. Being diagnosed at an older age and advanced stage both affect the prognosis. Surgical treatment of elderly patients with co-morbid diseases is challenging. Unfortunately, these patients do not receive chemotherapy due to poor overall status. Mastectomy with local anesthesia may be an option for these patients. We aimed to present an elderly male patient who underwent successful mastectomy and axillary dissection under local anesthesia.

Keywords: Breast cancer, mastectomy, local anesthesia

Introduction

Breast cancer is the most common type of cancer in women, while constituting less than 1% of all malignancies in men (1). Its incidence is 1 in 100,000 men (2). Male patients are diagnosed at advanced stages and at an older age than women (2-5). Surgery and chemotherapy can result in serious problems in elderly patients with co-morbid diseases. Herein we presented a male breast cancer patient who underwent modified radical mastectomy (MRM) with local anesthesia since he was not suitable for general anesthesia due to chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF).

Case Presentation

An 82-year-old patient who was being followed-up by the urology clinic due to hematuria was consulted with surgery due to a right sided breast lump. The patient stated that he noticed the lump about 2 years ago, that it enlarged in size, and that he noticed skin redness and discharge over the mass a week ago. He underwent TUR with spinal anesthesia due to prostate hyperplasia three years ago, and was being followed-up by the urology clinic with complaints of intermittent hematuria. He had COPD for thirty years, and CHF for 5 years, and was receiving doxazosin mesylate (Cardura XL®) 8 mg 2×1, fexofenadine (Fexofen®) 120 mg 1×1, valsartan hidrochlorothiazid (Premium Plus®) 160/12.5 mg ×1, budesonid formoterol (Foradil combi®) 400 mcg 2×1, tiotropium bromide inhaler (Spirava®) 18 mcg 1×1. He was unable to walk due to impaired exercise capacity. He had central obesity, dyspnea, and pitting edema of the lower extremity. On physical examination he had arrhythmic heart sounds, tachycardia, and disseminated rhonchus in both lungs. A malignant lesion, 5×4 cm in size was observed in his right breast that infiltrated the skin. He had right axillary lymphadenopathies, the largest being 3×3 cm in size. His laboratory results revealed; leukocyte count: 9790 / mm³ (H), hemoglobin 10.2 g/dL (L), hematocrit: 35% (L), fasting blood glucose 116 mg/dL (H), calcium 8.3 mg/dL (L), aspartate aminotransferase: 50 U / L (H), carcinoembryonic antigen: 7.96 ng/mL (H), prostate specific antigen (PSA): 5.94 ng/mL (H), and free PSA: 1.1 ng/mL. Other routine biochemical parameters and CA 15-3 were normal. The chest X-ray showed prominent aortic arch, with an increased cardiothoracic index. The breast ultrasound showed a 50×40 mm in size heterogeneous solid mass in the right breast retroareolar area, with lobulated contours and vascularization. There were a few lymph nodes with a diameter of 30 mm and thick cortex in the right axilla. The tru-cut biopsy revealed an invasive ductal carcinoma (grade II/III, Bloom-Richardson). The immunohistochemical study showed staining of 90% tumor cells as ER (+++), PR (+++), and c-erbB2 (-). Ki-67 was positive in 10%. The whole body positron emission tomography showed pathological FDG accumulation in the right breast lesion of 54×36 mm size, with an increase in prostate size and pathological FDG accumulation in the prostate. The patient was consulted with medical oncologist for neoadjuvant chemotherapy (CT). However, the patient was not eligible for CT due to advanced age and co-morbid diseases. After preoperative evaluation for surgery, the patient was classified as ASA IV. Thereupon, MRM with local anesthesia was considered. Upon obtaining patient informed consent, 2 mg intravenous benzodiazepine (Dormicum®) was used to provide sedation. Local



Figure 1. Applying local anesthesia on localization of Stewart incision



Figure 2. Appearance of 3 months after surgery

anesthesia with 1 mg/kg prilocaine (Citanest® 2%) was performed to the skin, subcutaneous tissue and fascial planes related to a right-sided Stewart incision (Figure 1). A right modified radical mastectomy was performed. The axillary drainage on postoperative day 1 through 4 were 150 cc, 100 cc, 50 cc and 30 cc. The surgical drain was withdrawn on the 4th postoperative day, and the patient was transferred to urology clinic due to hematuria. There was drainage through the incision two days later, wound cultures were obtained that did not reveal any pathogen. He was receiving oral ciprofloxacin 500 mg (Cipro®) bid due to urinary tract infection, and the wound drainage regressed. He was discharged on the 10th postoperative day, and sutures were withdrawn on the 15th day. Pathologic examination revealed grade II / III (modified Bloom-Richardson) infiltrating ductal carcinoma. The tumor size was 5×4 cm, and the surgical margins were clear. Three out of 13 axillary lymph nodes were metastatic. There was lymphovascular invasion, without perineural invasion. The largest metastatic lymph node was 1 cm in diameter, without extranodal spread. The patient did not receive adjuvant chemotherapy, he was started on oral tamoxifen 10 mg (Tadex®) 1×1. He did not have any problems related to mastectomy on his 3rd month outpatient follow-up (Figure 2).

Discussion and Conclusions

Routine breast examinations and screening programs are not implemented in male patients due to its low incidence. Being diagnosed at an older age and more advanced stages than female patients affect the prognosis of the disease. Giordano et al. (2) showed that tumor size and lymph node involvement affect survival in male breast cancer patients. Lorfida et al. (6) reported shorter disease-free survival rates in male patients (The 10-year disease-free survival rate was 51.7% vs. 66.5%; hazard ratio [HR], 1.79; 95% CI, 1.19-2.68; P=.004). Madden et al. (7) showed that advanced age, advanced tumor stage and hormone receptor negativity impacted prognosis, in their study of 1337 male breast cancer patients.

Definitive treatment of breast cancer in male patients is surgery, as in women. Regional anesthesia can be used in patients who are not candidates for general anesthesia due to advanced age or co-morbid diseases. For this purpose, high thoracic epidural anesthesia, cervical epidural anesthesia and paravertebral block can be used (8). However, in patients with high cardiac risk even regional anesthesia may pose a risk. Hypotension, bradycardia and cardiac arrest can be observed due to Sympathetic block following epidural anesthesia (9). Pollard et al. (10) stated that male gender, basal heart beat <60/min, ASA III or IV, beta-blocker therapy, sensory block above T6, patients younger than 50 years of age, prolonged PR interval were risk factors for cardiac arrest during epidural anesthesia.

Local anesthesia does not have serious side effects other than the rare methemoglobinemia and allergic reactions. MRM can be implemented with local anesthesia in high-risk and elderly patients with advanced breast cancer; however, the data on this issue is limited. Most of the reported studies included patients who underwent early-stage breast conserving surgery and sentinel lymph node biopsy (11, 12). Carlson (13) treated four female patients with stage 4 disease by total mastectomy under local anesthesia. However, these patients had advanced disease and did not undergo axillary dissection. Similarly, Oakley et al. (14) performed simple mastectomy with local anesthesia in 36 high-risk patients. A male patient with advanced stage breast who underwent mastectomy and axillary dissection was not included in these series. This case report will contribute to the literature in this regard.

In conclusion, MRM under local anesthesia is feasible in elderly patients with advanced disease who are not candidates for general surgery and this option should be kept in mind especially in male patients with breast cancer.

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