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Instructions to Authors

The Journal of Breast Health accepts research articles, case reports, reviews and technical reports on the condition that they have not been published or submitted for publication elsewhere. All articles undergo evaluation by the editors for style and by at least two independent referees scientifically. The publication language is both in English and in Turkish. Submission of scientific papers can be both either in English or Turkish. The translation of accepted Turkish manuscripts will be provided by our journal.

PREPARATION OF MANUSCRIPTS

All articles should include the following parts:

The title should express the content of the article clearly.

Names and affiliations of the authors should not be stated in the main document. This information will be added in the submission process. All authors are expected to have contributed to the article. All authors will be identified by their initials and last names. At least one author should take the responsibility for all parts of the manuscript that influence the main conclusion. The first author will be held .responsible for conclusions. unless otherwise stated. All authors should sign a COPYRIGHT FORM and send it to the postal address of the journal for acceptance of the manuscript.

Abstract: All manuscripts in Turkish or English should include a Turkish and English abstract containing no less than 100 and no more than 250 words. The English summary should also include the title of the article in English. Summaries must include the aim, basic methods and applications, results, statistical significance and conclusions. Please write the research abstracts in the systematic format presented below. Case report, review and technical article abstracts can be submitted in plain format.

Keywords (2 keywords in both Turkish and English, compatible with Türkiye Bilim Terimleri - Medical Subject Headings, http://www.bilimterimleri.com)

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Introduction: The aim of the article should be clearly stated and briefly justified.

Materials and Methods: Please state the selection criteria of the study group and objects clearly. Methods used in the research should include reproducible detailed definitions. References must be given for specific and known methods and the reason for the selection of a specific method and its limitations must be explained. Generic names, doses and administration routes for all drugs and chemical agents must be indicated. The statistical methods used should be clearly stated and should be reproducible by others. Sampling methods and treatment complications should be defined; numbers as well as percentages should be given and the software used for statistical analysis should be included. At the time of submission, you are expected to present the ethical committee approval for experimental research in humans. Please do not use items displaying identities such as names, initials, and protocol numbers of patients and hospital names, particularly in the legends of photographs.

Results: The results of the research must be presented in the text, in tables or figures in a reasonable sequential manner. Results presented in tables and figures should not be repeated in the text; only the major findings can be underscored.

Discussion and Conclusions: Only novel and significant conclusions drawn from the data obtained in the study should be discussed. Conclusions must be associated with the aims. Please avoid stating conclusions unsupported by the study data or presenting imprecise results.

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

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Abbreviations and Symbols: Please use only the accepted standard abbreviations and avoid using abbreviations in the title and abstract. Abbreviations should be defined in the text where they are first mentioned.

Acknowledgements: Authors may write a short note of acknowledgment to persons or institutions, which have contributed to the preparation of the manuscript, made methodological contributions, supplied materials or given financial support.

Ethics: Manuscripts reporting the results of experimental studies on human subjects must include a statement that informed consent was obtained after the nature of the procedure(s) had been fully explained. Manuscripts describing investigations in animals must clearly indicate the steps taken to eliminate pain and suffering. Authors are advised to comply with internationally accepted guidelines, stating such compliance in their manuscripts and to include the approval by the local institutional human research committee.

The Journal of Breast Health

Contents

The Journal of Breast Health

From the Editor

Dear Readers,

We are pleased to present The Journal of Breast Health with innovations. In this issue of our magazine, a total of 11 articles including 6 original research articles are published and reaches to thousands of regular readers. The trend of submitting increased number of articles both from Turkey and abroad not only makes us happy but also enables us to progress towards becoming a perfect and accepted journal in all related centers.

On behalf of the Editorial Board of The Journal of Breast Health, I would like to share a very important advancement. As of April 2014, all of our issues will be published both in Turkish and in English. As you know, our previous issues have mostly contained the summary in English and the full text in Turkish. This important modification was carried out since English is a universal language and in order to be able to enter PubMed Central/PubMed. The articles you will submit with only the summary in English will be fully translated into English and will be sent to you for final control.

I would like to thank the Federation of Turkish Breast Diseases Association Board of Directors for their approval, which made this change possible, and Dr. Didem Öncel Yakar who helps us with the translations with an intense effort.

Sincerely,

Prof. Vahit Özmen
Editor
The Journal of Breast Health

Review

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Breast Cancer and Posttraumatic Growth

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ABSTRACT

The current methods for early diagnosis and increased treatment options have improved survival rates in breast cancer. Breast cancer diagnosis effects individuals in physical, psychological and social dimensions either positively or negatively. In the literature, usually the negative effects encountered in the period after the diagnosis of breast cancer are mostly described, with limited data on the positive effects. Nevertheless, the identification of positive changes and defining its determinants is important in supporting and strengthening posttraumatic growth in this group. The objective of this review is to explain posttraumatic growth and its determinants in breast cancer during the post-treatment period in accordance with the relevant literature. In our evaluation, it was noticed that breast cancer survivors experience posttraumatic growth in the post-treatment period, but the literature is limited in explaining the nature of posttraumatic growth and its determinants. Both qualitative and quantitative research that will provide in-depth information on the subject, explaining culture-specific posttraumatic growth and related factors, are required.

Key words: Breast cancer, survivors, posttraumatic, growth

Breast cancer, is the most common type of cancer among women worldwide, and a disease that affects a woman's daily life during diagnosis, treatment and post-treatment periods in physical and psychosocial dimensions (1). Currently, with early diagnosis and improved treatment options for breast cancer, survival rates are increasing and disclosure of survivor's experience after treatment is gaining importance (2, 3). At this point first the concept of "survival " needs to be clarified. In biomedical medicine cancer survival is defined as the population that is disease-free at least for five years after treatment. However, in psychosocial definition survival is accepted as a process that begins with the time the patient is diagnosed and is defined in three stages. ***1. Acute survival stage***: It is the period beginning at the time the patient is diagnosed. ***2. Extended survival stage***: It is the period beginning after termination of treatment, when the patient enters the healing process and experience the fear of recurrence. ***3. Permanent survival stage***: It is the period when a possible risk of recurrence is minimized (4). In this review, the concept of survivor is used for breast cancer patients who have completed the treatment process.

Breast cancer survival effects individuals in positive and negative way, in physical, psychological and social dimensions. In the literature the negatively affected survivors from breast cancer are often described, and efforts to explain the positive effect seem to be limited (5). Nevertheless, the identification of positive changes and defining its determinants is important in supporting and strengthening posttraumatic growth in this group. Based on this fact, this study was conducted in order to explain the posttraumatic growth and its determinants, in the aftermath of treatment for breast cancer. In addition, it is expected that this study will contribute to diagnosis of posttraumatic growth in breast cancer survivors.

The Concept of Posttraumatic Growth and Breast Cancer

Following life events containing high levels of stress and resulting in crisis most people not only experience negative changes but also positive changes at the same time. In the literature, the positive changes are discussed under the headings of "benefit finding", "posttraumatic growth" and "stress-related development" (6). At this point, the terminology that is used to express the positive changes should be clarified. Benefit finding and posttraumatic growth overlap conceptually, but they represent a number of structural differences (7). Benefit finding refers to a positive change in relationships, priorities in life and accepting life after a stressful experience. Posttraumatic growth, is a term used to describe positive psychological changes experienced as a result of an individual's efforts to cope with life crisis that exert high levels of stress, such as breast cancer (8). The differences between these two concepts are not clear, but "benefit finding "might begin at the time of diagnosis and is more focused on finding benefit from strength. On the other hand, posttraumatic growth may begin in weeks, months

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or even years following injury and is focused on the changes occurring in their own capacity during the fight with trauma and is a restructuring process. Posttraumatic growth defines both a process and a result. Posttraumatic growth is the experience after a traumatic (highly stress -forming) incident, and it does not express the stress encountered during life and growth. Therefore, stress-related growth terminology is accepted as a limited expression and the more inclusive statement of post traumatic changes is described as "trauma after development" (8, 9). In this study, the term "Posttraumatic Growth" is used to express the positive changes experienced by breast cancer survivors.

In order to clarify the terminology of posttraumatic growth "traumatic life events" should be disclosed. Traumatic life events refer to stressful experiences that threatens mental and physical well-being of individuals, and complicates one's functionality and compatibility. This kind of experiences is often accompanied by helplessness, weakness, anger, anxiety and fear (8). Breast cancer is a life crisis that creates intense stress during diagnosis, treatment and post-treatment period, and threatens the physical and psychological integrity of a woman and is a traumatic experience that influences women in all aspects of life by disrupting harmony. In addition, it is described as a mortal, painful, intimidating and scary disease and at the same time causes death and realization of one's own mortality. Facing the reality of death, leads to questioning of individuals' lives, with the realization that routines, habits and values have lost their importance, therefore it can provide creation of new meanings in an individual's life (10). Due to these features, crisis are turning points that include positive results and are experiences that help people to gain insight to sustain life in a more meaningful experience (11, 12).

Posttraumatic Growth Areas in Breast Cancer

Posttraumatic growth is grouped under three headings including changes of the individual in self-perception, relationships and life philosophy (spiritual, existential) (8). **Changes in self-perception** may be in the form of a sense of personal empowerment, autonomy, self-esteem development, flexibility and being able to see and to create new opportunities (13). In two studies conducted with a quantitative method, the second area that breast cancer patients reported improvement in is personal empowerment (7, 14). In another study conducted with long-term survivors of breast cancer, it has been determined that 79.2% of the survivors gained at least one benefit from cancer experience and one of the benefit area is in personal characteristics (7). In other studies conducted on the subject, the property of personal empowerment defined by survivors are described as: the ability to express oneself, self-improvement, awareness of positive personality traits and personal power, self-confidence, flexibility, confidence in their body, development of problem solving and positive thinking skills (7, 15, 16). However, the limited number of studies describing personal empowerment and the application of quantitative method in majority of these studies mandate further research on defining the nature of personal empowerment.

Another posttraumatic growth area is the change in interpersonal relationships. **The development of interpersonal relationship** is in the form of increased sense of compassion, improvement in the ability of empathy, increasing desire to help individuals with similar experience and increased sense of intimacy in relationships (8, 13). In two studies conducted with a quantitative method, the first area that breast cancer survivors reported personal improvement in is the development in interpersonal relationships (7, 14). After treatment, women defined finding meaning in their existing relationships with other women and deepening of their relationship as positive changes (17). In the literature, the effort to combat a traumatic event, such as cancer, is stated to strengthen the bond between spouses (18). In a review that compiled quality of life studies on breast cancer survivors by Russell et al. (19), the desire to help newly diagnosed breast cancer patients and supporting women for early diagnostic activities are examples of development in this field. The social support to the individual provided by her environment acts as a buffer against stress life and is known to support coping. In addition, social support is described as an important factor in survivors who experience the long term negative impact of cancer and its treatment and social support is reported to be an important determinant of the improvement in quality of life (20). At this point, supporting the strengthening of interpersonal relationships is important in coping with the post-treatment period.

Posttraumatic growth may involve the philosophy of life. **Changes in philosophy of life** includes being thankful they live, spiritual and existential development (13). In studies conducted with breast cancer survivors, change in the philosophy of life and development in spiritual matters are described (16, 21). In these studies, survivors reported that they gained features such as changes in life perspective, increased appreciation of life, in the spiritual dimension feeling closer to god, trust in god, forgiveness, patience, gratitude and sacrifice as change in philosophy of life, that they confronted the fact that life is actually an opportunity offered to people and stated that they made changes in their lifestyles. The lifestyle changes described are nutrition alterations, regular exercise and stress management. In the study, it is described that positive gains in breast cancer survivors improve both the quality and the quantity of life (7, 15, 16). Similarly, Bower et al. (22), showed changes in the process of posttraumatic growth in time and approximately 75% of breast cancer survivors experience a change in their approach to life, and in their life priorities and gain healthy living habits. Spirituality is one of the frequently studied subject area, which is related to development in philosophy of life in breast cancer.

Spirituality is the endeavor to question and accept the individual herself and her relationships with other people, her place in the universe, the meaning of life, the meaning of experience, awareness, values, and purpose in life. At the same time, it is a result of the information gained in a lifetime and contains elements that form the purpose of life, and are meaningful to the individual (23). Increase in religious rituals and beliefs are noted as spiritual development (8). The studies conducted in breast cancer survivors regarding spirituality state that spirituality is a multidimensional concept (21) and these dimensions are described as; maintenance, belief, coping and support (21, 24). Another spiritual change after breast cancer is described as convergence to god and deepening of faith in god (21). In our country, a study conducted in a group that completed treatment could not be reached. In a qualitative study conducted in women with breast cancer during chemotherapy, the patients defined the disease as coming from god and they state an increase in their faith in god after diagnosis (25). In another study from our country conducted in cancer patients, 80 % of patients expressed an increase in belief in God (26). Spirituality is an important psychological resource to cope, adapt and increase in quality of life (27). Beliefs as a spiritual dimension, may contribute to psychological well-being and harmony of an individual in the aftermath of treatment of breast cancer by providing hope, stamina and support, and by reducing the feeling of helplessness. At this point, the efficacy of praying on the psychological well-being of breast cancer survivors is emphasized (28, 29). In another study, breast cancer survivors have described religious beliefs and spirituality as sources of help in coping (30).

In addition, in the post-treatment period, spirituality was found to be associated with quality of life, distress, social support and benefit finding (28). As a result, in studies regarding spirituality in breast cancer patients and survivors, the positive effects on coping, patient compliance, mental health status and quality of life are expressed. It is stated that the spiritual dimension should not be ignored during different stages of management of breast cancer patients (31-33). In conclusion, supporting all aspects of spiritual development and change in the philosophy of life in survivors developing psychosocial adjustment is important in the post-treatment period.

Determinants of Posttraumatic Growth

The identification of factors associated with posttraumatic growth is important in increasing the effectiveness of treatment. In a review that examined posttraumatic growth in cancer survivors, personal factors (demographic characteristics, etc.), event related factors (incident clinical features, etc.), environmental factors (social support, etc.), cancer, and mismatch between one's perception of herself and the world, emotions and behaviors (such as avoidance) , coping (cognitive and emotional processes, positive reinterpretation, etc.) are determined as factors influencing posttraumatic growth (34). In a study conducted in patients with breast cancer in our country, social support and using problem-oriented methods in coping were associated with a higher level of development. In the same study, the income level was negatively correlated with development of depression (12). In a study conducted with breast cancer survivors (1 to 5.5 years after diagnosis) and their spouses, breast cancer was defined to result in the same level of stress in both women and their spouses. It has also been shown that women experienced more spiritual development than their spouses (14). In another study conducted with long-term (10 years) breast cancer survivors by Mols (7), posttraumatic growth was negatively correlated with radiotherapy. The cross-sectional nature of the study, and the fact that majority of the samples (72%) have received radiotherapy were stated as a limitation in the generalization of these results. In another study, tumor size, number of positive lymph nodes, mastectomy and endocrine treatment were positively correlated with posttraumatic growth (35). In a study regarding the type of treatment, a greater growth was disclosed in patients receiving chemotherapy. This relationship is described as being associated with the perception of severity due to treatment-induced stress, side effects, and losses (36). In another prospective study examining posttraumatic growth, it was determined that the growth patients experience increases over time and the determinants of growth are associated with younger age, expression of emotion and intellectual processes (oriented to the cause of cancer) (16). In another study conducted with long-term survivors of breast cancer, posttraumatic growth was found to be associated with mental health dimension of quality of life and happiness. In the study, the nature of mental health was especially associated with the level of personal empowerment and strengthening of relationships with others. Also in this study, positive affect and adaptive coping strategies (active, positive, relationship, religion, and denial) were associated with improvement in the positive direction. These findings are described in two ways. First, the effect of coping strategies over positive changes perceived according to cancer experience continues on the long-term. Another explanation is the finding that coping describes 25% of the variance in posttraumatic growth in analysis after controlling for personality traits. As a result, the study described post-traumatic growth to be associated with positive personality traits and the experiences during diagnosis and treatment process (36). In a qualitative study including breast cancer survivors who have completed treatment, sense of hope and achieving vital aims were reported to aid in the development of posttraumatic growth (15). In another study evaluating growth in breast cancer survivors who have completed treatment for at least six months ago and who have never experienced any stressful situation, higher posttraumatic growth was defined in women who have experienced breast cancer. It has been stated that a stressful life event should be lived for the development of posttraumatic growth, but that the development was independent of whether the incident was perceived as a traumatic experience or not. In the same study, the development of posttraumatic growth was found to be associated with better psychosocial quality of life and decrease in depression (37).

In conclusion, women do not experience only negative effects after breast cancer treatment but also go through psychosocial empowerment. Studies on the evaluation of this aspect defined as posttraumatic growth are required. In the survey, it was found that in most studies posttraumatic growth was assessed using the quantitative method, the posttraumatic growth scale (PTGI) developed in 1996 by Tedeschi and Calhoun (38). The development of both strategies to help medical staff in measuring and diagnosing growth, and evaluation tools are required. Also in this area, qualitative and quantitative research that compares the size of growth can be made to provide in-depth knowledge of culture-specific properties. The identification of positive changes that occur in women in especially the field of self-perception in posttraumatic growth, and the determinants of these changes experienced in three dimensions will provide important data for the empowerment and support of women in the post-treatment period. Another area to be investigated is the effects of personality traits of survivors, their methods of coping and their experiences during the diagnosis and treatment periods, on the development of growth during the post-treatment period.

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Review

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Guideline for Antimicrobial Prophylaxis in Breast Surgery

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ABSTRACT

The American Society of Health-System Pharmacists (ASHP) published the 2012/2013 edition of the book entitled "Best Practices for Hospital & Health-System Pharmacy: Position and Guidance Documents of ASHP" with Bruce Hawkins as the editor. (ISSN: 15558975). Pages 582-667 of this book contain the section:"Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery". This section includes current clinical developments, evidence and recommendations on the application of standard and effective antimicrobial prophylaxis in adult and pediatric patients, and has significant differences compared to the previous 1999 edition. On pages 632-633, antimicrobial prophylaxis in breast and plastic surgery practice is addressed in detail. This article contains a summary of the recommendations made in ASHP 2012/2013 Report regarding the antimicrobial prophylaxis in breast and plastic surgery applications.

Key words: Breast, antibiotic prophylaxis, surgery

Introduction

Currently breast surgery has a wide range of procedures including plastic surgery operations. The risk of wound infection is below 5% in surgical procedures including breast reduction and reconstruction surgery, in a patient without additional risk factors for infection (1-12). In addition to patient specific conditions that are known to increase the risk of infection in all kinds of surgical wounds in general, the use of implants in breast surgery (13) and preoperative radiotherapy application (14, 15) further increase the risk of wound infection.

Antimicrobial prophylaxis should be applied in clean wounds at high risk of wound infection, clean-contaminated wounds and contaminated wounds. In clean wounds without a risk, there is no indication for prophylaxis (16). In dirty-infected wounds treatment is planned, not infection prophylaxis.

Factors Increasing the Risk of Surgical Wound Infection

Antimicrobial prophylaxis has an important role in reducing surgical wound infection rates. Besides prophylaxis; basic infection control mechanisms implemented in the clinic (17), the surgeon's experience and technique, duration of operation, hospital and operating room conditions, instrumentation, preoperative preparation including body-washing, skin antisepsis and shaving, peri-operative management of temperature and blood glucose regulation, and the patient's existing co-morbidities all play an important role (16, 18). Patient-related risk factors for surgical wound infections are advanced age, negative nutritional status, obesity, diabetes mellitus, cigarette smoking, presence of infection, immunodeficiency or immunosuppressive use, steroid use, recent surgery, long preoperative hospitalization and colonization with microorganisms.

Microorganisms

In breast and plastic surgery procedures, usually S. aureus is responsible for the wound infection (2, 6, 7, 10, 11, 15, 19, 20). In axillary region procedures, obese patients prone to maceration, procedures at sweating areas P. aeruginosa, Serratia marcescens, Enterobacteriaceae including E. coli and gram-negatives like Klebsiella can be isolated (20, 21).

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Efficiency

In retrospective placebo-controlled trials it has been shown that antimicrobial prophylaxis did not significantly reduce rate of infection in surgical applications with clean wounds such as augmentation mammoplasty (9), reduction mammoplasty, lumpectomy, mastectomy, and axillary lymph node dissection (19, 22-24). However, a Cochrane review evaluating 7 randomized controlled trials and including 1984 patients with primary non-reconstructive breast surgery and axillary dissection due to breast cancer (25), showed that there was a significant reduction in infection rates with prophylaxis when groups with (995 patients) or without (989 patients) prophylaxis were compared (8% versus 10.5%, RR 0.72, 95% CI: 0.53-0.97). In this study, it

Table 1. Recommended doses and dose interval for antimicrobial agents frequently used in surgical prophylaxis

Antimicrobial	Recommended dose		Half-life in adults with normal renal functions h (19)	Recommended 2.Dose administration interval (The preoperative dose accepted as the first dose) h (c)
	Adult (a)	Pediatric (b)		
Ampicillin-Sulbactam	3g (ampicillin 2 g/ sulbactam 1 g)	50 mg/kg of Ampicillin component	0.8-1.3	2
Ampicillin	2 g	50 mg/kg	1-1.9	2
Aztreonam	2 g	30 mg/kg	1.3-2.4	4
Cefazolin	2 g, 3 g for patients more than 120 kg	30 mg/kg	1.2-2.2	4
Cefuroxime	1,5 g	50 mg/kg	1-2	4
Cefotaxime	1 g (d)	50 mg/kg	0.9-1.7	3
Cefoxitin	2 g	40 mg/kg	0.7-1.1	2
Cefotetan	2 g	40 mg/kg	2.8-4.6	6
Ceftriaxone	2 g (e)	50-75 mg/kg	5.4-10.9	NA
Ciprofloxacin (f)	400 mg	10 mg/kg	3-7	NA
Clindamycin	900 mg	10 mg/kg	2-4	6
Ertapenem	1 g	15 mg/kg	3-5	NA
Fluconazole	400 mg	6 mg/kg	30	NA
Gentamicin (g)	5 mg/kg (tek doz)	2.5 mg/kg	2-3	NA
Levofloxacin (f)	500 mg	10 mg/kg	6-8	NA
Metronidazole	500 mg	15 mg/kg Single 7.5 mg/kg dose for newborns <1200 g	6-8	NA
Moxifloxacin (f)	400 mg	10 mg/kg	8-15	NA
Piperacillin-Tazobactam	3.375 g	80 mg/kg of piperacilin component in 2-9 months infant; 100 mg/kg of piperacilin component for infants older than 9 months and less than 40 kg	0.7-1.2	NA
Vancomycin	15 mg/kg	15 mg/kg	4-8	NA
Oral antibiotics used for prophylaxis in colorectal surgery (for mechanical bowel preparation)	1 g	20 mg/kg	0.8-3	NA
Erythromycin				
Metronidazole	1 g	15 mg/kg	6-10	NA
Neomycin	1 g	15 mg/kg	2-3 (3% absorbed in the normal GI tract)	NA

h: Hour

(a) Adult doses are those stated for every system. In case of discrepancy, an experienced senior was consulted to determine the recommendation dose.

(b) The maximum pediatric dose should not exceed the adult dose.

(c) Antimicrobials with short half-life (cefazolin, cefoxitin etc.) should be applied prior to the surgical procedure, and should be repeated during the operation according to their half-life in patients with normal renal function. Reccommended interval stated as NA (not applicable) depends on the length of the procedure and repetition may be required in very long surgeries. (d) Although the FDA approved label states 1g, experts recommend 2g for obese patients.

(e) In colorectal procedures when used as a single dose in combination with metronidazol

(f) Although floroquinolons increase the risk of tendinitis/tenosynovitis in all ages, single dose administration is safe.

(g) In general, use of gentamicin in surgical prophylaxis is limited to preoperative single dose. Dose is adjusted according to the patient's weight. If the patient's weight is 20% more than his ideal body weight (IBW), the dose (D) is calculated with this formulation: D = IBW + 0.4 (actual weight - IBW)

was concluded that in order to reduce the risk of wound infection, antimicrobial prophylaxis should be used in breast cancer patients undergoing non-reconstructive surgery.

Antibiotic Choice

There is no consensus about the choice of antibiotics for antimicrobial prophylaxis in clean wounds with risk factors, and clean contaminated wounds in breast and plastic surgery procedures (12, 26). The general application is selecting the antibiotic that will cover gram positive organisms and common gram-negatives according to the surgical area. In most cases, cefazolin or ampicillin-sulbactam is sufficient. In case of beta-lactam allergy, clindamycin and vancomycin are alternatives. If vancomycin or clindamycin is being used and gram-negative organisms are suspected then aztreonam or gentamicin or the addition of a single dose fluoroquinolone is suggested. There isn't any high-level evidence for oral antimicrobial prophylaxis or different applications in methicillin-resistant Staphylococcus aureus (MRSA) infection (2, 3, 11, 27).

Dose Adjustment

Data regarding dose adjustment according to weight in overweight patients and dose repetition in long surgeries have been updated. Obesity poses a high risk for surgical wound infection. The pharmacokinetics of the drug may vary in obese patients. That is why, dose should be adjusted according to body weight in these patients. If the procedure continues 2 times longer than the half-life of the drug, or if there is a considerable amount of blood loss during the procedure, intraoperative dose repetition is required in all patients, to make sure that the serum and tissue concentrations of the drug are sufficient (Table 1).

Timing of Preoperative Dose

The best time for preoperative medication is 60 minutes before surgical incision. This is a more specific timeframe then the previous suggestion of application 'during induction of anesthesia'. Some agents, such as fluoroquinolones and vancomycin need to be applied 1-2 hours prior to the operation. Therefore, these agents should be initiated 120 minutes before the surgical incision.

Duration of Prophylaxis

In order to prevent the development of side effects and resistance, antimicrobial prophylaxis should be discontinued as soon as possible even if drains, catheters or implants have been used in breast and plastic surgery operations (4, 5, 11, 16, 19, 28). In breast surgery, any significant differences were not found between single dose antimicrobial prophylaxis regimens and extended protocols in terms of wound infection (5, 11, 19). In addition, side effects such as nausea, diarrhea, itching and skin rash were reported more in the group with more than a single dose of prophylaxis.

Summary Recommendations

- Unless there are no factors increasing the risk, antimicrobial prophylaxis is not required in clean wounds.
- Although no significant antimicrobial activity has been shown in studies, antimicrobial prophylaxis should be applied in clean wounds with risk factors based on expert opinion.
- In clean contaminated wounds, antimicrobial prophylaxis should be administered in breast cancer patients.
- The antimicrobial prophylaxis should be done with single-dose cefazolin or ampicillin-sulbactam, or in the presence of beta-lactam allergy, clindamycin or vancomycin.
- If there is risk of Gram-negative microorganisms, prophylaxis should be done with cefazolin, or in the presence of allergy with gentamicin or aztreonam or fluoroquinolone.
- The post-operative prophylaxis period should be kept less than 24 hours regardless of the presence of catheters, drains, or implants.

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Original Article

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Comparison of Different Techniques in Breast Cancer Radiotherapy Planning

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ABSTRACT

Objective: This study aimed to minimize the radiation dose to organs other than the target tissue during adjuvant therapy applied for breast cancer, by using different planning methods.

Materials and Methods: 30 women with T1-2 N1-3 M0 breast cancer were included in the study. Planning was performed using four different methods to the supraclavicular area, internal, and external tangential fields. All planning was done in a virtual environment by and the requested data was obtained. All patients were treated by the 1st method. Method 1: Different isocenter, complete supraclavicular area, breast half beam. Method 2: Different isocenter, half supraclavicular area, breast half beam. Method 3: Single isocenter, half supraclavicular area, breast half beam. Method 4: Different isocenter, supraclavicular area full beam, breast full beam.

Results: Evaluation of PTV values showed a statistically significant reduction in D-max, 110% and 115% values by method III. Lower doses in other parameters were not statistically significant.

Conclusion: Based on these results, the application of single isocenter, 3D radiotherapy in breast cancer provides significant advantages especially in PTV and pulmonary dosages.

Key words: Breast cancer, radiotherapy, toxicity

Introduction

Breast cancer constitutes approximately 26% of all cancers in women. In the United States, 209 thousand new cases were detected in 2010 (1). Breast cancer incidence increases at a rate of 1-2% throughout the world and each year approximately one million new cases are diagnosed (1-3). Lifetime risk of developing breast cancer is calculated as 36% for women living in some western societies (3).

Since the 1990s, breast cancer incidence is increasing while breast cancer mortality rate in all cancers decreased from 36% to 25% (1, 2, 4). One of the most important reasons is that the methods used for diagnosis and screening are more efficient as well as the increasing effectiveness of treatment. With the published randomized controlled trials in the 1990s and their long- term results, radiotherapy has become an integral part of treatment for breast cancer. However, following the article stating that breast radiotherapy resulted in increased myocardial infarcts and caused related mortality in 1994, not only effective treatment with radiotherapy but also reducing its toxicity was taken into account (5). The effective use of both the devices and the newly developed planning techniques provide a great advantage in this regard.

This study aimed to minimize the radiation dose to organs other than the target tissue during adjuvant therapy applied for breast cancer, by using different planning methods.

Materials and Methods

30 patients who received radiotherapy with a diagnosis of breast cancer in our hospital's Department of Radiation Oncology between 2009 and 2011 were included in the study. Patients enrolled in the study had T1-2, N1 -3, M0 disease and breast-conserving surgery (BCS) was applied to all patients. With a standard dose of 50 Gy to the supraclavicular, internal and external tangential areas, Boost therapy was applied to the tumor location as 16 Gy if the distance to surgical margin was less than 0.5 cm, and as 10 Gy if it was over 0.5 cm. The treatment was applied at a dose of 2 Gy per day, five days a week and on weekdays. Radiotherapy was applied after chemotherapy in patients undergoing chemotherapy, while in other patients it was given following surgery. Hormonal therapy was started according to

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menopausal status in hormone receptor positive patients. Tamoxifen was given to hormone-responsive premenopausal patients and postmenopausal patients were started on an aromatase inhibitor.

All drawings and planning were made by a single physician. According to 50th and 62_{nd} reports issued by ICRU (The International Commission on Radiation Units and Measurements) the breast tissue was entered as clinical tumor volume (CTV) and the planned target volume (PTV) PTV margin was given as 1 cm, and the skin margin as 0.5 cm (6, 7). Planning was made by using four different methods to supraclavicular area, internal and external tangential fields. Planning was entirely performed in a virtual environment with acquisition of the requested data. All patients were treated by the 1st method.

Technique I
Different isocenter, supraclavicular area full, breast half beam: Planning was set as supraclavicular area full beam, and tangential field half beam with different isocenter. In the supraclavicular area, the gantry angles required for extraction of oesophagus out of the field were added. To ensure the tangential and supraclavicular area overlap table and collimator angles were added. To protect the humerus, larynx and the skin, personalized supraclavicular blocks were inserted; for those patients localized in the left breast and come up with high heart doses, heart block was used.

Technique II
Different isocenter, supraclavicular area half, breast half beam: Planning was set as supraclavicular area half beam, and tangential field half beam with different isocenter. The gantry angle was provided to extract the oesophagus out of the field and to ensure the tangential and supraclavicular area overlap table and collimator angles were added. In patients with location in the left breast and with high heart doses a heart block was used and for protection of the humerus and the skin personalized blocks were applied to the supraclavicular area.

Technique III
Single isocenter, supraclavicular area half, breast half beam: Planning was set as supraclavicular area half beam, and tangential field half beam with single isocenter. Table and collimator angles were not added to provide field overlap. The gantry angle was provided to extract the oesophagus out of the field. In patients with location in the left breast and with high heart doses a heart block was used and for protection of the humerus and the skin personalized blocks were used to the supraclavicular area.

Technique IV
Different isocenter, supraclavicular area full beam, breast full beam: Planning was set as supraclavicular area full beam, and tangential field full beam with different isocenter. The gantry angle was provided to extract the oesophagus out of the field, and to ensure the tangential and supraclavicular area overlap table and collimator angles were added. In patients with location in the left breast and with high heart doses a heart block was used and for protection of the humerus and the skin personalized blocks were applied to the supraclavicular area.

Demographic data of all patients, the pathologic and immune histochemical parameters of the specimens were recorded. Then chemotherapy and radiation therapy doses were recorded. For each of the four methods; PTV (maximum dose, minimum dose, mean dose, 110% field volume and 115% Gy field volume), lung (maximum dose, minimum dose, mean dose, 5 Gy field volume, 20 Gy field volume and 25 Gy field volume), heart (maximum dose, minimum dose, mean dose, 5 Gy field volume and 25 Gy field volume and mean dose while left breast was unblocked), the left coronary artery (maximum, minimum and mean doses), brachial plexus (maximum, minimum, mean doses and 60 Gy field volume), oesophagus (maximum, minimum, mean doses and 50 and 60 Gy field volumes), as well as mean doses for supraclavicular, level 1, level 2 and level 3 were calculated.

Statistical Analysis
The data were entered into an electronic database. Statistical software package was used for data analysis (SPSS 18.0). Descriptive analyzes were stated as mean, standard deviation, minimum and maximum values and descriptive tables were created. In further analysis, for the significance of the difference between means the two-way analysis of variance (ANOVA) was performed. Bonferroni test was used for confirmatory analysis. $p<0.05$ was considered significant.

Results

The youngest patient was 23 and the oldest 71 years old, the mean age was 49 years. Only one patient (3.3%) was premenopausal, whereas 15 (50%) patients had a natural menopause and 14 (46.3%) had chemotherapy induced menopause. The general demographic characteristics of the patients are shown in Table 1.

60% of patients (n=18) underwent axillary dissection. Sentinel lymph node biopsy was performed in the remaining 12 patients and in seven and axillary lymph node dissection was added.

The tumor was adjacent to the surgical margin in one patient. The farthest surgical margin was 2 cm. The mean surgical margin distance was 0.53 cm. The smallest tumor diameter was 0.5 cm and the largest was 3.5 cm, with a mean of 2 cm. The mean number of dissected nodes was 14 (3-33) and the mean number of metastatic nodes was 2 (0-10). The pathological examination revealed invasive ductal carcinoma in the majority of patients (n=17).

All patients received chest wall irradiation together with the supraclavicular area. 50 Gy radiotherapy was applied in all patients, in one patient 47 Gy was given with increase in boost dose. Boost dose was applied to all patients except one patient. The boost dose was 10 Gy in 15 patients, 13 Gy in 16 patients and 17 Gy in one patient who is mentioned above.

It was shown that the significant difference obtained by the Benforroni approach was caused by method III. On evaluation of the PTV values, D- max ($p=0.006$), 110% ($p<0.0001$) and 115% ($p<0.0001$) values had a statistically significant reduction in method III. The lowest dose values regarding other parameters (PTV min, mean PTV) were also obtained by method III, although this difference did not reach statistical significance. Regarding pulmonary doses, there was also a statisti-

Table 1. Patient demographics

Feature	Minimum	Maximum	Mean	Standard deviation
Age (year)	23	71	48.9	11.4
Weight (kg)	46	106	73.7	12.2
Height (cm)	145	168	157.6	2.9
BMI (kg/m2)	19.4	40.4	29.9	5.2

BMI: Body mass index

cally significant decrease in V5 (p=0.005). However, although lower values in favor of method III were obtained in V25, V20, D- mean and D-min, the highest value for Dmax was also obtained in this method. The evaluated cardiac values of V25, V5, D- max, and D- min have also decreased in a similar manner in favor of method III. Nevertheless, the highest D-min value was observed in method III. The evaluation of LAD showed a reduction in D-max and D-mean doses in method III, although not statistically significant, while the D-min value did not show superiority over other methods. The V60 value calculated for the brachial plexus was equal to zero in all methods. D-max, D-min and D- mean values showed very small non-significant differences. The V60 value calculated for the esophagus was equal to zero in all methods. The V50, D-max, D-min and D- mean values were found to be lower in favor of method III, although not statistically significant. The evaluation for conformity index showed no significant difference, in fact the obtained values were very close to each other. Similarly, significant difference was not detected in dose assessments of the supraclavicular area, level I, II and III.

During radiotherapy in patients with left breast cancer, cardiac doses was reduced almost by half by use of lead alloy blocks to protect the heart.

Discussion and Conclusions

Frequently encountered in women, breast cancer is still a serious problem due to both incidence and mortality rates. It has been shown that radiotherapy, which is accepted as an integral part of breast-conserving surgery, improves survival by reducing local recurrence in locally advanced breast cancer (8).

Although radiation therapy is applied with success nowadays, especially in recent years, adverse effects and side effects of radiotherapy are being discussed frequently (9). The aim is to both irradiate the targeted area with the appropriate amount of radiation and protect other organs from radiation, and if possible not receive any dose at all.

While planning radiotherapy after BCS, the remaining breast tissue, chest wall, and incision area are included in the irradiation field (10). Depending on the patient's lymph node metastasis, the axilla or supraclavicular area is included in the area to be irradiated (11, 12). The total dose applied to the breast should be 45-50 Gy in 5-6 weeks. In our patients after 50 Gy whole breast irradiation, all patients received an additional dose of 16 Gy if the closest surgical margin was less than 0.5 cm and 10 Gy if more distant.

Various methods such as 2D planning, 3D planning, IMRT, IGRT, Field in Field, have been described to be applied in breast cancer radiotherapy planning with developing technological infrastructure and software programs (13, 14, 15). Among these combinations with methods like single isocenter, multiple isocenter, half- beam, or full beam are generated (16, 17). Although application methods continuously improve with developments in technology, there is not an accepted standard method (18, 19, 20). The most commonly used methods are 3D planning and IMRT planning (21, 22). By these two commonly used methods better dose homogenisation is provided with significant reduction in especially skin toxicity and minimizing the dose received by normal organs. However, there is insufficient data on long-term results. In our clinic, 3D supraclavicular area full beam, tangential areas half beam, two-isocentric treatment is applied. A significant problem with treatment using different isocenters is undesirably increased doses due to overlapping of fields. At this point, the use of a single isocenter seems to be a suitable solution. However, in the literature we did not find a study comparing one and two- isocenter 3D planning. By simple logic, the most practical and precise way of eliminating intersection of two areas is to decrease two fields to one. The PTV values in our study support this conclusion. The PTV max and PTV mean values obtained by single isocenter use were very close to the planned values and overdose was minimal. The advantage in PTV max was statistically significant (p=0.006). Single isocenter use resulted in more than half reduction in PTV 110% and PTV 115% values as compared to multiple isocenter (regardless of full beam or half beam status) planning and this reduction was statistically significant (p<0.0001).

Lungs are one of the first organs to receive radiation beam and to be protected during breast radiation (23). The pulmonary damage ranges from simple edema to severe pneumonia and fibrosis. The severity of symptoms is often directly proportional with the disease (23, 24). 3D and IMRT planning provides significant advantages in the prevention radiation pneumonitis (25). The values obtained in our study in 3D planning were similar to the literature, although the superiority of single isocenter use could not be clearly demonstrated (24). However, statistically significant reduction of V5 was detected (0.005). There was a decrease in V20, V25, and D- mean values but they did not reach statistical significance. Nevertheless, the relative surplus in D- max and D-min values as compared to other methods precludes a final judgment. Still, the positive results obtained in other doses are promising.

Another important organ affected during breast radiation is the heart. Although the exact mechanism is not clear, the dose of radiation exposure causes significant cardiac toxic effects (26) and results in significant mortality (27). These risks are increased especially during radiotherapy for the left breast (26, 27). Patient related factors like gender, age, diabetes, smoking habits, hypertension, obesity, and hypercholesterolemia contribute significantly to these risks, still the most important factor is the dose received by the heart (26, 27). The most important study on cardiac dose affecting the heart was published by Shultz-Hector (28). In this study conducted in 2007, it has been reported that doses as low as 1-2 Gy may cause acute effects and cardiac mortality could be observed at a dose of approximately 10Gy. The emerging devices and new contouring techniques are highly effective in better cardiac dose calculation and reduction (26, 27). In recent studies, IMRT and 3D planning radiation therapy is reported to provide for the lowest cardiac dose (29). There is not any study stating the cardiac dose caused by treatments using different isocenters, as in the lung. In our study, the doses obtained were generally similar to the literature, single isocenter application resulted in significant reduction, although not statistically significant. There was an approximately 25% decrease in V25, V5, D- mean, D-min and D- max values as compared to the other methods that use multiple isocenters, although it was not statistically significant. Similar results were obtained from the measurements for the left coronary artery.

During radiotherapy planning for breast cancer, another area to be considered and protected as much as possible is the brachial area. As the dose administered increases, the risk of damage also increases (30). Some patients may require surgical decompression and in unnoticed or untreated cases, permanent damage may occur (30). In the literature brachial plexus injury is mentioned in most studies, however we were unable to find a detailed study regarding the results of dose measurements specific to this field. In our study, doses corresponding to this area in each of the four methods did not show a statistical difference, in fact, the doses were almost equal. Similarly, in a study with single isocenter 3D planning, a slight decrease in dose has been reported that

did not reach significance (31). In parallel, any significant difference between the calculated values for the close located supraclavicular area was also not found.

Another organ to be taken into account during planning and dose calculation is the esophagus. The doses obtained in each of the four methods, including the maximal doses, are well below the recommended tolerance dose by Emami (32). Although it has been reported that the maximum dose received by the esophagus is decreased 50% by using the single isocenter 3D planning, in our study, a marked difference in V50 could only be achieved in planning that use complete bundle (31). When half beam was used, in both the supraclavicular and tangential field, almost the same results were obtained even if different isocenters were taken into account. Moreover, the difference detected with other methods was not statistically significant. The D- mean, D- max and D- min values were nearly equal.

The conformity index was first published by the RTOG in ICRU 62 in 1993 (7). After the publication of this report, conformity index was considered more often in radiotherapy planning. In our study, the conformity index in each of the four methods did not show a significant difference.

In our study, it has been detected that the advantages obtained in PTV max and the reduction in PTV 110% and PTV 115% values in single isocenter application are statistically significant ($p<0.0001$). On evaluation of pulmonary doses, there was a statistically significant reduction in V5. In addition, although not reaching statistical significance, a marked decrease was achieved in lung V20, V25, D-mean doses and doses received by the heart. Similar results were obtained from measurements for the left coronary artery. No significant differences were found in brachial plexus, esophagus and supraclavicular area doses.

Based on these results, the application of single isocenter, 3D radiotherapy planning in breast cancer provides significant advantages especially in PTV and pulmonary doses.

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Original Article

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Efficacy of Methylene Blue in Sentinel Lymph Node Biopsy for Early Breast Cancer

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ABSTRACT

Objective: Sentinel lymph node biopsy is the recommended approach in the evaluation of axilla during breast cancer surgery. In this study, results of patients who underwent methylene blue sentinel lymph node biopsy were evaluated.

Materials and Methods: The study included 32 female patients with T1 and T2 tumors. 5 ml of 1% methylene blue was injected into the peritumoral area or around the cavity. The axillary sentinel lymph node was found and removed, and then axillary dissection was performed. The sentinel lymph node and axillary dissection specimen were histopathologically examined and the results were compared.

Results: The sentinel lymph node was found in 30 (94%) patients. Lymph node metastasis was not observed in 17 patients in both the sentinel lymph node and axilla. Two patients had metastasis in the axilla although this was not detected in sentinel lymph node. Eleven patients had metastasis both in the sentinel lymph node and in the axilla . The accuracy rate was 93%, and the false negativity rate was identified as 15%.

Conclusion: Sentinel lymph node biopsy by methylene blue is a method that can be applied with high accuracy. Methylene blue can be considered as an alternative to isosulphane blue in sentinel lymph node biopsy.

Key words: Breast cancer, sentinel lymph node, methylene blue

Introduction

The evaluation of axillary lymph node metastases in breast cancer is important to determine prognosis, and to plan treatment after surgery. The standard approach recommended for the evaluation of axillary lymph node status is sentinel lymph node biopsy (1). Sentinel lymph node is the first lymph node receiving lymphatic drainage from a tumor. If there is a tumor spread to the lymph nodes, it will first be in the sentinel lymph node. Then it spreads to other lymph nodes. If there are not any metastases in sentinel lymph node it is assumed that there are no metastasis in other lymph nodes (2).

Giuliano and colleagues first applied sentinel lymph node biopsy in breast cancer in 1994 (3). They were able to find the sentinel lymph node in 114 of 174 patients (65.5%) and showed that the sentinel lymph node provided accurate information about axillary involvement in 109 (95.6%) patients. In subsequent studies, the false-negative rate was shown to be decreased to 0% (4).

In order to locate the sentinel lymph node, methylene blue, isosulphane blue and radioisotopes have been used. These methods may also be used in combination. Methylene blue is cheaper and more easily accessible than isosulphane blue and radioisotope applications. Its side effects are less serious than isosulphane blue. Studies have found similar efficacy as compared to other methods. In this study, we aimed to evaluate our results of sentinel lymph node biopsy (SLNB) with methylene blue in patients with early-stage breast cancer.

Materials and Methods

The Akdeniz University Ethics Committee approved the study. Thirty-two women with T1 and T2 tumors and without clinical axillary lymph node metastases from Akdeniz University Faculty of Medicine, Department of General Surgery were included in the study. Pre-operative ultrasonographic evaluation of the breast and axilla and mammography were obtained in all patients. Core biopsy or excisional biopsy was performed for palpable tumors and wire-guided biopsy for non- palpable breast tumors for histopathological diagnosis.

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Patients with clinically palpable axillary metastatic lymph nodes, patients with a history of previous axillary surgery, and patients who received breast radiotherapy were excluded.

Informed consent was obtained in all patients. Different surgeons performed the surgical procedures. A single person who would follow-up all patients was involved in the operation during sentinel lymph node biopsy. One % methylene blue was used to locate the sentinel lymph node. Five mL of sterile methylene blue was administered in the peritumoral area in four- quadrants, and if the patient underwent excisional biopsy the injections were applied into the parenchyma around the cavity in four quadrants. The tumor or excised tumor cavity was massaged for 5 minutes towards the axilla. Afterwards, either modified radical mastectomy or breast conserving surgery was performed as scheduled. During axillary dissection, the sentinel lymph nodes were found and removed. Then standard axillary dissection was completed. The extracted sentinel lymph nodes were evaluated with frozen section examination, then the sentinel lymph node and axillary dissection specimen were histopathologically evaluated and metastasis rates were compared.

Results

A total of 32 patients were included into the study. Patient's age varied between 25-82 years (mean: 50). Twenty-eight (87.5%) patients underwent modified radical mastectomy, and 4 (12.5%) underwent breast conserving surgery. Tumor locations are shown in Table 1.

The sentinel lymph node was not found in two (6%) patients. In 30 patients, 1-2 (mean: 1.69) sentinel lymph nodes were removed. In 18 of these patients, only one sentinel lymph node was found. In 17 patients, metastasis was not detected in both sentinel lymph node and the axilla. Two patients had metastasis in the axilla, although it was not detected in the sentinel lymph node. Eleven patients had metastasis in both the sentinel lymph node and the axilla (Table 2). In our study the rates of accuracy, sensitivity, specificity, positive predictive value, negative predictive value and false negativity were calculated as 93%, 85%, 100%, 100%, 90% and 15%, respectively (Table 3).

When patients were evaluated according to tumor location, in the two patients who had false-negativity the tumor was located in the upper outer quadrant. Considering the number of sentinel lymph nodes removed, false-negativity was not an issue in patients with removal of 1 and 3 lymph nodes, whereas both of the false-negative sentinel lymph node patients had 2 lymph nodes removed. According to TNM stage, one N1 and one N3 patient had false-negative results. When evaluated according to tumor size, a patient with T1 and another with T2 stage had false negative findings.

Discussion and Conclusions

The axillary dissection applied in breast cancer surgery has complications such as lymphedema, pain, numbness, loss of sensation, limitation of shoulder movement, seroma, nerve and vascular injuries (5). According to tumor size, axillary lymph node metastasis is not detected in 95-97% of T1, and 52-77% of T2 patients. Therefore, these patients will undergo unnecessary axillary dissection and face these complications. With the use of sentinel lymph node biopsy, unnecessary axillary dissection can be avoided in patients without lymph node metastasis (6).

There are two methods to perform sentinel lymph node biopsy. In the first method, isosulphane blue or methylene blue is injected. In the other method, radioactive material is injected first and the sentinel lymph node is found with a gamma probe. These two methods can be used in combination (5, 7).

Either isosulphane blue or methylene blue can be used as a dye in sentinel lymph node biopsy. Methylene blue is cheaper, more easily obtainable, and is a dye with fewer complications as compared to isosulphane blue. Considering our country, it gives the opportunity of performing SLNB even in clinics away from the city center. Hypersensitivity reactions which may also be fatal are reported at a rate of 0.6 to 2.5 % following isosulphane blue injection (8). Skin necrosis, fat necrosis, and fibrosis are among complications of methylene blue. However, in our study, no complications related to methylene blue was encountered. In studies conducted in our country isosulphane blue was often preferred (9-11). In the literature, there are many studies showing that methylene blue can be used safely and with high success as an alternative to isosulphane blue (12-15). Simmons and colleagues (16) have identified the sentinel lymph node in 104 of 112 patients by using methylene blue and reported that sentinel lymph node represented axillary status in 96.9% of patients. Bleesing et al. (17) compared isosulphane blue and methylene blue, and found the accuracy rate as 88.5 % with isosulphane blue and as 92.7% with methylene blue.

Core biopsy is the gold standard in the diagnosis of breast cancer, although there are physicians who prefer excisional biopsy. Some of our patients were referred to our clinic with a diagnosis and we chose to include the patients in whom excisional biopsy was previously performed into the study. The rate of modified radical mastectomy in our study seems

Table 1. Tumor location

Left breast	23 (72%)
Right breast	9 (18%)
Upper outer quadrant	24 (75%)
Upper inner quadrant	5 (16%)
Lower inner quadrant	2 (6%)
Central zone	1 (3%)

Table 2. Comparison of SLNB results and axillary lymph node status

		Axillary metastasis		
		Yes	No	Total
Sentinel	Yes	11	0	11
Lymph Node	No	2	17	19
Metastasis	Total	13	17	30

SLNB: Sentinel lymph node biopsy

Table 3. Sensitivity, specifity, negative predictive value, positive predictive value, accuracy rates

	n	%
Sensitivity	11/13	85
Specifity	17/17	100
Negative Predictive Value	11/11	100
Positive Predictive Value	17/19	90
Accuracy	28/30	93

very high, especially considering that they were used for early stage breast cancer. This rate should have been much lower. The operative strategy is a joint decision by the patient and the surgeon. However, when looking at the results, it is believed that breast-conserving surgery should have been encouraged more. In our study, peritumoral injection of methylene blue was preferred. This application is a commonly used route in the use of methylene blue . besides peritumoral area, the dye might also be injected intradermal, subdermal, or subareolar area. Similar success rates can be achieved by using different injection methods (18).

The spread of breast cancer is generally from level 1 to level 3. The rate of skip metastasis is about 2 to 4% (19). The false negative rate of sentinel lymph node is 0-10%. Especially in patients with tumors near the axilla and a history of previous axillary surgery, the false-negative rate is high (20). In our study, the two patients with false negative results had their tumor localized in the upper outer quadrant near the axilla.

During the learning process of sentinel lymph node biopsy, axillary dissection should be performed after identification of the sentinel lymph node. The results of sentinel node biopsy should be compared with axillary dissection results. at least 90% sentinel lymph node detection rate and less than 5% false-negative rate indicates that only sentinel lymph node biopsy without axillary dissection can be made. Tafra et al. (21) reported that 30 cases are adequate for the learning phase. In the ALMANAC study, it has been reported that at least 40 patients are required (22). In our first study of 30 cases, the sentinel lymph node detection rate was over 90% even though the false-negative rate was above 5%. We believe that as the number of patients increase, the false negativity rate will decrease to the desired level. These rates prove that we need to continue with axillary dissection after sentinel lymph node biopsy, and that we were unable to reach ideal results yet.

In conclusion, sentinel lymph node biopsy using methylene blue demonstrated axillary involvement with high accuracy. In patients scheduled for sentinel lymph node biopsy, use of methylene blue may be considered as an alternative to isosulphane blue.

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Original Article

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Frequency of Early-Stage Lymphedema and Risk Factors in Postoperative Patients with Breast Cancer

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ABSTRACT

Objective: Lymphedema is a chronic major complication that is seen frequently post-operatively and has negative effects on quality of life. In our study, determining the early-stage postoperative lymphedema frequency and specifying the risk factors in its development has been aimed.

Materials and Methods: One hundred one cases that were operated on for breast cancer were evaluated regarding the 12-month control of their clinical specifications, histopathological specifications, and specifications related with the surgical intervention retrospectively. The data related to the parameters envisioned as risk factors were evaluated.

Results: Lymphedema development was found in 7 (6.9%) out of 101 cases constituting the study group. No significant difference ($p>0.05$) in terms of lymphedema development was determined among age, body mass index (BMI), chemotherapy (CT), postoperative seroma or infection, mastectomy with the dominant arm, and breast-conserving surgery (BCS), which were evaluated as risk factors. There was a significance ($p<0.05$) between the other risk factors, which were axillary dissection (AD), number of positive lymph nodes (LN), radiotherapy (RT), the tumor size (T), and lymphedema existence. In every case in which lymphedema was determined, it was seen that there was axillary LN involvement and 15≤LN were ablated in the dissection ($p<0.05$).

Conclusion: It is seen that AD, RT applied to the breast cancer patients, and T are important risk factors in early-stage lymphedema development. No early-stage lymphedema development was determined in any of the patients to whom sentinel lymph node dissection (SLND) was applied.

Key words: Lymphedema, breast cancer, risk factors, incidence

Introduction

The increase in the survival time of breast cancer cases in the last 2 decades has brought health problems in the long term relating to treatment (1). Lymphedema development, which affects the quality of life negatively, is defined as interstitial tissue effusion rich in protein as a result of failure in the lymphatic system in patients who undergo surgical treatment and radiotherapy (RT) for breast cancer (2). Even though the lymphedema development rates are given as 30% in the literature, there are many studies which that it in a large range of 2%-83% (3-5). This large range difference is thought to depend on the technique of lymphedema measurement, differences in description, and the timing of the assessment. Lymphedema development is frequently seen during the first 18 months but sometimes weeks or years after the treatment (6, 7). As the presence of lymphedema prevents daily activities, it affects the patient psychologically, socially, and economically, as well (8). Lymphedema is considered to be an important complication of breast cancer surgery that comes into prominence, as information towards preventing its development is limited; its treatment is difficult, it is progressive, and it affects a patient's quality of life negatively. Many risk factors are mentioned in the development of lymphedema. Determining these parameters will help the determination of high-risk case groups, thus providing the preventive precautions to be applied. There are 3 basic subjects that are envisioned as risk factors in lymphedema development; these are the factors relating to the treatment, the disease, and the patient (9-11). The factors relating to the disease are the stage of the tumor (T), the number of lymph nodes (LN) dissected, and the localization of the T. The factors relating to the treatment include the type of the applied surgical treatment and other treatment combinations applied together with RT and chemotherapy (CT). The factors relating to the patient are age, body mass index (BMI), wound site infection, and excessive use of extremity. Even though the factors that might be related to arm lymphedema development in patients with breast cancer have been assessed in many studies, its etiology has not been fully understood yet.

In our study, we aimed to determine the rate of lymphedema development in cases to whom surgical intervention was applied in our clinic due to breast cancer to assess the risk factors and differentiate the case groups with high risk of lymphedema development.

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Materials and Methods

One hundred one female patients diagnosed with one-sided breast cancer who had surgical intervention to the breast and axilla between January 2010-March 2011 were included in the study. In the routine follow-up of the cases, the clinical and histopathological data and the data relating to the surgical procedure assessed at the 12th month were examined retrospectively, and arm measurements were made for lymphedema evaluation. Among the factors relating to the patient envisioned as risk factors, age (<50 or ≥50), BMI (<25 kg/m^2, ≥25 kg/m^2), smoking status, arm dominance (present or not), the surgery of breast [mastectomy/breast-conserving surgery (BCS) and axilla (axillary dissection (AD)/sentinel lymph node dissection (SLND)] applied, dissected number of LN, LN positivity, postoperative seroma and infection development (present or not), CT or RT treatment, grade (1, 2, 3) relating to the T, size (T_1, T_2, T_3), and parameters of histopathological type were evaluated (Table 1).

Arm Lymphedema Measurement Method

The circumferential measurement method was used. Circumferential measurements were made in four regions of both upper extremities: the metacarpophalangeal joint, wrist, and 10 cm distal and 15 cm proximal to the lateral epicondyle. A diameter difference of more than 2 cm in the measurements made at the four regions compared to the healthy side was evaluated as lymphedema presence (12).

All of the cases were informed of lymphedema and protective measures after the clinical evaluation. The cases in which lymphedema development was determined were taken into a treatment program by the Physical Treatment and Rehabilitation Clinic, and written informed consent was obtained from patients who participated in this study.

Statistical Analysis

The SPSS-17.0 statistical software package was used. Statistical evaluation of the data was performed using Pearson chi-square test and Mann-Whitney test. $p<0.05$ was considered statistically significant. Age and BMI values of the cases were shown as mean±SD (minimum-maximum).

Results

Age, BMI, smoking status, and arm dominance, which were considered as the risk factors of the cases, were examined: the mean age of 101 cases was 52±10 (32-76), whereas it was 51±12.9 (38-68) in 7 cases (6.9%) where lymphedema was found. Lymphedema was found in 4 out of 50 cases aged under 50 and 3 out of 51 cases aged over 50 (p:0.706). BMI evaluation of all cases showed a mean value of 28.9±4 (20.9-42.5); 17 cases had a BMI value under 25, and 84 cases had a value of 25 and over. Lymphedema was found in 1 case whose BMI value was under 25 and in 6 cases whose BMI values were over 25 (p:1.000). In the whole study group, 5 cases (4.9%) were smokers, but none of the 7 cases in which lymphedema development was found was a smoker. Arm dominance was present in 3 out of 7 cases (42.9%) (p:0.699).

When the factors relating to the applied treatment, such as the surgery of the breast (mastectomy/BCS) and axilla (AD/SLND), dissected number of LN, number of positive LN, postoperative seroma or infection development, and RT and CT treatments, were examined, lymphedema development was found in 4 (57.1%) cases to which mastectomy was applied and in 3 cases (42.9%) to which BCS was applied (p:0.102). It was seen that AD was performed in every case in which lymphedema development was found (p:0.040) and that there was no lymphedema development in patients to whom SLND was applied (p:0.014). In every case to which AD was applied and lymphedema development was found, it was seen that the number of LN excited was ≥15 (p:0.013). The number of LN dissected in every case to which AD was applied was 15 (9-24) and 28 (22-34) in the cases in which lymphedema was found (p:0.069). When the positivity of the dissected LN was evaluated, the positive LN number in the whole case group was 1 (0-5) but 8 (7-26) in the lymphedema group (p: 0.019). Lymphedema development was found in 3 (9%) out of 33 (32.7%) cases in which postoperative seroma developed (p:0.680) and 1 (16.6%) out of 6 (5.9%) cases in which infection developed (p:1.000). It was seen that every case in which lymphedema was seen had RT (p:0.041) and CT (p:1.000) treatment.

When the factors relating to the disease, such as the T grade, T value, and parameters of T histopathology, were assessed as the risk factors relating to the disease, it was seen that the T grade was 2 in all cases in the lymphedema group. T_1 was determined in 2 (28.6%), T_2 was determined in 3 (42.9%), and T_3 was determined in 2 (28.6%) of the cases in which lymphedema was found (p:0.025). As for T histopathology, invasive ductal carcinoma was seen in 6 (85.7%) and inflammatory carcinoma was seen in 1 (14.3%) case in the group with lymphedema.

Discussion and Conclusions

Breast cancer is among the most frequent cancer types seen in women, and its frequency has shown an upward inclination in recent years (13, 14). When cancer data of the Ministry of Health in Turkey were examined, it was seen that the frequency of breast cancer in 2006 was 37.6 per 100,000, while it became 38.5 in 2007 and 41.6 in 2008 (15). Besides the increasing frequency of breast cancer, the survival time has lengthened significantly through the current early diagnosis methods for breast cancer and multidisciplinary treatment approaches, while the problems affecting the quality of life negatively have been encountered more frequently. Of these problems, lymphedema differs from others, as it is seen frequently in the long term during the postoperative period.

The most important reason of such a large range of lymphedema incidence is the timing differences in detection and evaluation (16). In the evaluation of lymphedema, volumetric measurement, circumferential measurement, tissue tonometer, or imaging techniques are used. While it is known that volumetric measurement techniques give more accurate results, the circumferential measurement technique is used more frequently because of its higher practicability (17). For this reason, we used the circumferential measurement technique in our study. The 6th postoperative month is envisioned as the best time for the evaluation, when the adjuvant CT and RT are usually completed and the lymphedema symptoms became measurable (18). In our study, lymphedema development was found in 7 (6.9%) cases at the assessment at the 12th month.

When the risk factors were assessed in patients with lymphedema development, no statistically significant difference was found between the cases aged over 50 and under 50 in terms of lymphedema development (p: 0.706). Geller et al. (9) reported a significant increase in lymphedema development risk in women aged under 50. In many studies where age is assessed in the literature, similar to the results we obtained, this factor did not show a significant effect on lymphedema development (5, 7, 9, 11, 19).

When BMI was assessed as a risk factor, it was seen that there was no statistically significant difference between the BMI values of >25 or ≤25 on lymphedema development (p:1.000). In the studies, lymphedema development risk shows a 2-fold increase in cases where BMI is over 30. Even though its etiology is unclear, it is thought to occur because of increased fat and the subcutaneous tissue's role as a lymphatic fluid resource or the increase in lymphatic damage as a result of the need for more ecartation in axillary intervention (20).

In many studies present in the literature where smoking status and arm dominance are assessed, they are not found to be potent risk factors in lymphedema development, similar to our findings (7, 21, 22).

Table 1. The distribution of parameters in the case groups

Risk Factors	All case groups (n:101) %	Lymphedema (+) group (n:7) %	p value
Age	52±10 (32-76)	51±12.9 (38-68)	
• 50>	50 (49.5%)	4 (57.1%)	0.756
• 50≤	51 (505%)	3 (42.9%)	
BMI	28.9±4 (20.9-42.5)	30.4±5 (24.21-35.98)	
• 25>	17 (16.8%)	1 (14.3%)	1.000
• 25≤	84 (83.2%)	6 (85.7%)	
Smoking status	5 (4.9%)	0	
Arm dominance	55 (54.5%)	3 (42.9%)	0.699
Mastectomy/BCS			
• Mastectomy	29 (28.7%)	4 (57.1%)	
• BCS	72 (71.3%)	3 (42.9%)	0.102
AD/SLND			
• AD	54 (53.5%)	7 (100%)	**0.040**
• SLND	47 (46.5%)	0	**0.014**
The number of LN dissected in cases to whom AD has been applied	15 (9-24)	28 (22-34)	0.069
LN positivity	1(0-5)	8 (7-26)	**0.019**
Cases with 15≤LN dissection	51 (50.5%)	7 (100%)	**0.013**
Seroma development	33 (32.7%)	3(42.9%)	0.680
Infection development	6 (5.9%)	1 (14.3%)	1.000
RT treatment (+)	62 (61.4%)	7 (100%)	**0.041**
CT treatment (+)	92 (91.1%)	7 (100%)	1.000
Tumor			
• Grade			
1	5 (4.9%)		
2	89 (88.1%)	7 (100%)	
3	7 (6.9%)		
• Size (T)			
T1	25 (24.8%)	2 (28.6%)	
T2	71 (70.3%)	3 (42.9%)	**0.025**
T3	5 (4.9%)	2 (28.6%)	
• Histopathological type			
• Invasive ductal carcinoma	85 (84.1%)	6 (85.7%)	
Tubular carcinoma	3 (2.9%)	0	
Papillary carcinoma	3 (2.9%)	0	
Medullary carcinoma	2 (1.9%)	0	
İnvasive lobular carcinoma	2 (1.9%)	0	
Apocrine carcinoma	3 (2.9%)	0	
Inflammatory carcinoma	2 (1.9%)	1 (14.3%)	

BMI: Body mass index; BCS: breast-conserving surgery; AD: axillary dissection; SLND: sentinel lymph node dissection; LN: lymph node; RT: radiotherapy; CT: chemotherapy

Table 2. Studies reporting the prevalence of lymphedema following different surgical interventions in the literature

Study	Applied Surgical Procedure	Lymphedema Definition	Follow-up Period (month)	Number of cases	Incidence of lymphedema (%)
Kissin et al. (30)	Unidentified	≥2 cm	9	200	25.5
Werner et al. (20)	AD, RT	≥2.5 cm	37	282	19.5
Lin et al. (31)	RM, MRM, SM + AD, and RT	≥2 cm	24	283	16
Keramopoulos et al. (32)	SM/MRM + AD	≥2 cm	6	104	17
Deutsch et al. (33)	RM/Mastectomy+ RT Only Mastectomy	≥2 cm	36	1665	46.3
Clark et al. (5)	Mastectomy/SM	PVD ≥20% $aPVD_{change}$ ≥5%	36	188	20.7
Wilke (29)	SLND	>2 cm	6	2904	7
Lucci (35)	SLND	≥2 cm	12	411	6
Langer (34)	SLND	>2 cm	31 (average)	431	3,5
McLaughlin et al. (36)	SLND	>2 cm	60 (average)	600	5

MRM: Modified radical mastectomy; PVD: volume difference ratio; RM: radical mastectomy; RT: radiotherapy; SM: segmental mastectomy; AD: axillary dissection; SLND: sentinel lymph node dissection

It is reported that the range of surgery of the breast and axilla and adjuvant treatments, such as RT, may increase the risk of lymphedema (23). Schunemann and Willich et al. (24) reported lymphedema development rates after radical mastectomy without postoperative RT, modified radical mastectomy (MRM), and BCS of 22.3%, 19.1%, and 6.7%, respectively. In most of the studies in the literature, it is reported that there is a relation between AD range and lymphedema incidence. Siegel et al. (25) reported that the lymphedema incidence of 37% with level I, II, and III dissection reduces to 8% when only level I and II dissection is applied. Moreover, in a study where BCS was applied, the lymphedema rate of 15% in the cases in which lumpectomy and AD were performed reduced to 3% in cases with only lumpectomy (26). In many studies, the LN number dissected was found to increase the lymphedema risk (18, 27, 28). It is reported that the lymphedema frequency is 5-7 times less in SLND, which is recommended to be performed in axilla-negative cases today compared to AD (29-36).

When different procedures for breast cancer, such as mastectomy, RT, and axillary procedures (AD/SLND), were assessed in terms of lymphedema development, it was seen that lymphedema rates varied between 16% and 46.3% during a follow-up period of 6 to 37 months, but in the last few years, it has also been seen in studies examining the cases to which SLND is applied that the lymphedema incidence is far lower, such as 3.5%-7% (Table 2). In our study, even though no statistically significant difference was seen between the cases to which mastectomy and BCS were applied (p:0.102), it was found that AD was applied to every case where lymphedema had developed, and no lymphedema development was found in any case in the early-stage cases (p:0.014). When the dissected LN number in the cases to which AD was applied was assessed, it was seen that the lymphedema incidence increased with increasing LN number dissected (p:0.069) and LN positivity (p:0.019).

In our study, RT treatment seemed to be one of the major factors that increased the lymphedema incidence (p:0.041). In the literature, even cases without surgical intervention with RT to the axilla showed increased lymphedema incidence; moreover, with the combination of AD, it is reported to increase the lymphedema risk even more by showing a synergistic effect (37). In similar studies, the lymphedema incidence in patients to whom RT was applied in addition to surgery was 41%, while this ratio was 17% in patients in whom surgery was performed alone (38, 39).

It is reported in the literature that infection and seroma development with adjuvant CT treatment do not increase the lymphedema incidence. No significant difference in these parameters in terms of lymphedema development was found in our study (p>0.05).

In all 7 (6.9%) cases in which lymphedema development was found, the T grade was 2. T histopathology revealed invasive ductal carcinoma in 6 (85.7%) cases and inflammatory carcinoma in 1 (14.3%) case.

When the relationship between the T value and lymphedema incidence was assessed, T_1 was seen in 2 (28.6%), T_2 was determined in 3 (42.9%), and T_3 was determined in 2 (28.6%) cases. When compared to the whole case group, a significant difference was determined between T size and lymphedema incidence (p: 0.025). In many studies, T diameter was found to be a potent factor in lymphedema development (7, 40, 41).

As a result, a statistically significant relationship has been determined with the range of the AD (15≤ LN), dissected positive LN number, RT, and T and early-stage lymphedema incidence (p<0.05). The widespread prevalence of cases with early-stage breast cancer diagnosis, small T sizes, and absence of application of RT to the axilla (as the axillary involvement is lower), as well as the routine preference of SLND in cases where the axilla is clinically negative, are the basic reasons of the low lymphedema rates in our study group.

We do not have enough of a sample size to compare the groups based on the variables and no preoperative baseline measurements.

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Original Article

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Breast Cancer in Turkey: Clinical and Histopathological Characteristics (Analysis of 13.240 Patients)

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ABSTRACT

Objective: Breast cancer is the most common type of cancer and the leading cause of cancer related deaths in women in Turkey, as elsewhere around the world. However, detailed and systematic demographics, data on clinical and pathological characteristics, and treatment were largely unavailable in Turkey until now. This paper is intended to provide an analysis of clinical and pathological data on women registered in the National Breast Cancer Database (Ulusal Meme Kanseri Veri Tabanı [UMKVT]), established within Turkish Federation of Breast Diseases Societies (TMHDF) and available for use in Turkey since 2005.

Materials and Methods: Clinical and pathological data on breast cancer patients registered online in the database from May 01, 2005 to May 01, 2011 were investigated. Parameters examined in patients included age, menopausal status, distribution of clinical and pathological stage, histological type, tumor diameter, histological grades, regional lymphatic stage, estrogen (ER), progesterone (PR), HER-2 receptors and molecular subtypes. Analysis results of these parameters were compared with literature data and discussed.

Results: A total of 13,240 patients with breast cancer since April 07, 1992 were included in the study, and 99% of them were female. Female breast cancer patients whose requisite parameters had been completely entered in the database were included in the analysis. The mean age was 51.6 years (±12.6; range 12-97), 17% of them were younger than 40 years of age, and 45% were premenopausal. According to an analysis of age groups at diagnosis, the frequency of cancer peaked at the 45 - 49 age group with 16.7%, declining to 7.6% in the 65-69 age group, and then rose again. Most of the patients (78.7%) had invasive ductal, 7.8% were invasive lobular cancers, 9.8% were invasive mixed cancers (invasive ductal + invasive lobular), and 4% were other histological types (e.g. inflammatory, intracystic papillary, mucinous, etc.), respectively. Half of them (50%) had grade III histology. According to an analysis of pathological stages of all breast cancers (stage 0 - IV), 5% were stage 0, 27% were stage I, 44% were stage II, 21% were stage III, and 3% were stage IV breast cancer, respectively. The mean tumor diameter was 2.5 cm (±1.6; range 0.1-20 cm). The rates of lymphatic stages were pN0 50%, pN1 28%, pN2 15%, and pN3 7%, respectively. ER, PR, and HER-2 receptors were positive in 70%, 59%, and 23% of patients. A subtype analysis of tumors showed that 62% were type luminal A. This was followed by subtypes luminal B (15%), triple negative (15%), and HER-2 positive (8.5%).

Conclusion: As a conclusion patients with breast cancer in our breast cancer registry program were younger, and had more advanced disease, and worse prognostic factors than patients in developed countries.

Key words: Turkey, breast cancer, stages, pathology, molecular subtypes, hormone receptors, prognostic factors

Introduction

One of the most important points in cancer is keeping accurate and complete records. The development of national health policies, the preparation of strategic plans, and the use of limited resources cannot be prioritized or be decided upon, unless reliable data is obtained and statistically evaluated.

The oldest and modern cancer registry program has been established in Hamburg in 1929 (1). In this program, it is indicated that not only medical and scientific issues, but also public health and economic aspects should be taken into consideration for cancer control. A population-based cancer registry program was initiated in the US, in 1935 (2). The SEER Program (The Surveillance, Epidemiology, and End Results) is affiliated to the NCI (National Cancer Institute), collecting and publishing cancer related data on approximately 28% of the US population. The Danish Cancer Registry is a program established in 1942 by the Danish Cancer Society, covering not only a city but also the entire country's population with excellent function (2).

The World Health Organization (WHO) founded a dedicated cancer research center the IARC (International Agency for Research on Cancer) in 1965, and the International Association of Cancer Registries (IACR) in 1966 (3). This organization, in collaboration with IARC, is intended to help creating cancer registries and evaluate cancer incidence and treatment outcomes. Currently, there are approximately 200 population -based registry programs throughout the world and they are all monitored.

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In our country, studies on cancer registry have started quite late (4, 5). Cancer has been accepted as a notifiable disease in 1982, and in 1983, the KSDB (Kanserle Savaş Dairesi Başkanlığı- Cancer Control Department) was established to keep and oversee records. One of the main tasks of the KSDB, which is responsible for cancer control, is to collect reliable and accurate data in a cancer registry that is of high quality.

On March 13, 1993, Cancer Monitoring and Control Center [Kanser İzlem ve Denetim Merkezi (KİDEM)] was established within the Izmir Provincial Health Directorate, and was assigned to coordinate study projects. KİDEM was accepted as a member of WHO, IARC and the IACR in 1995, and the European Network of Cancer Registries (ENCR) in 1997 (4). KSDB has included 12 cities after Izmir (Edirne, Trabzon, Samsun, Erzurum, Eskişehir, Ankara, Antalya, Izmir, Kayseri, Ankara, Adana and Bursa) in the active cancer registry program. Currently, Kocaeli (Dilovası area ranks first in cancer-related deaths) and Van (as a representative of the eastern region) have been added and the number reached to 14 cities. The cancer registry program continues to be implemented in these regions.

One of the ongoing major projects led by the Turkish Federation of Breast Diseases Societites [Türkiye Meme Hastalıkları Dernekleri Federasyonu (TMHDF)] is National Breast Cancer Database [Ulusal Meme Kanseri Veri Tabanı (UMKVT)]. The Federation Board decided to embark on this project in December 2004, and a professional software company was assigned for writing and implementation of the program. Data recording into the software program started in May 1, 2005 and as of August 2013, data on more than 20,000 patients were registered.

This study aimed to evaluate the clinical and histopathologic features of our patients registered into the program, identify the standard prognostic factors and compare them with data from other developed or developing countries.

Materials and Methods

The database is designed as computer software containing 576 parameters and has been implemented on May 1, 2005. It is composed of sections on identity, medical history, clinical data, histological diagnosis, surgical treatment, pathology, adjuvant treatment and follow-up. In this article, the data of 13,240 patients who were registered from May 1 2005 to May 1 2011 was analyzed.

Data Entrance and Clearance

The centers that were linked to TMHDF were asked to enter information to the central database in either a prospective (online) or retrospective (offline) manner, the entered data was reviewed, and duplications, incompatible and non-eligible data were excluded from the analysis.

In this study, patients' gender, age, clinical and pathologic stage, tumor size, histological type and grade, pathologic stage, estrogen receptor (ER), progesterone receptor (PR), and HER-2 receptors and breast cancer subtype distributions were analyzed. ER / PR value of ≥1% was considered positive, and for HER-2, a 3 + result or in suspected cases a positive SISH or CISH were accepted as positive.

Invasive cancer histological types were classified according to the World Health Organization's proposed classification, the staging according to the American Joint Committee on Cancer (AJCC) TNM 2002 version, and the histological grade according to the modified Scarff Bloom-Richardson classification (6, 7). Another classification was performed separately as Hormone receptor (HoR) positive (at least one of ER or PR positive) or HoR negative (both ER and PR negative) patients.

Molecular subtypes were divided into 4 groups as luminal A (ER or PR positive + HER-2 negative), luminal B (ER or PR positive, HER 2 +), triple negative (ER, PR and HER-2 negative) and HER-2-positive (HER -2 group, ER and PR negative, HER-2 +) and were analyzed accordingly (8).

Statistical Analysis

The mean, median, mode, minimum, maximum and standard deviation were calculated for continuous variables. Kolmogorov-Smirnov test was performed to evaluate the distribution of variables. Mann-Whitney U test was used to compare the average of two independent groups, and Kruskal-Wallis test was applied to compare the average of more than two independent groups. When required, continuous variables were re-assessed in groups according to a standard cut-off point. The relationship between categorical variables was evaluated by chi-square test. The level of significance was accepted as 0.05 in Pearson's chi-square test.

Results

A total of 13,420 breast cancer cases were recorded between 1 May 2005 and 1 May 2011 from 24 different health units (Table 1). After data cleaning, 11,542 cases with valid data were detected. Only patients with sufficient data for each parameter were included.

11,385 of the patients (99%) were female, with a mean age of 51.6 years (±12.6; 12-97). 48% of them were younger than 50 years of age, and 17% were under the age of 40. It is found that, in our country, breast cancer incidence significantly increased up to the age of 50 and this increase reached its peak in the age group of 45-49 years (17%), and then gradually decreased down to 7.6% in the age of 65 to 69 years, with another increase after 70 years of age to 10% (Chart 1). 45% of the patients were pre-menopausal.

The histologic types of invasive breast cancer were as follows: 79% of invasive ductal cancers (IDC), 7.4% of invasive lobular cancers (ILC), 9.8% of mixed types of cancer (IMC, ILC + IDC), and the remaining 3.8% of other types (Table 2). While 52% of the patients with IDC were pN0, 41% of patients diagnosed as ILC and IMC were found to be pN0 (p=0.0001). The rate of patients with early-stage (stage I, II) disease was 76.5 % in IDC patients, while this proportion was 68.5% in cases with ILC and IMC (p=0.0001).

The clinical stages were as: Stage 0 (Ductal Carcinoma in Situ (DCIS)) 3%, stage I 26%, stage II 54%, stage III 14% and stage IV %3. Stage III breast cancer rate in women under 40 years of age was 19%, while this rate was 12.7% in those between 60-69 years of age (p<0.001). The incidence of Stage III disease decreased with increasing age, with an increase after 70 years. Early stage breast cancer rate was lower in pre-menopausal patients than in menopausal patients, but this difference was not significant (p>0.05, Table 2).

The patients were divided into two groups according to age, as ≥40 and <40 years of age and pathologic tumor size distribution were examined in these groups. The rate of T1 tumors was 43% in women under the age of 40, while this rate was 50% in women aged ≥40 years (p=0.0001). Accordingly, T2 and T3 tumors were significantly higher in women <40 years of age (p=0.0001). pT1 was detected in 47%

Table 1. Centers providing data input and number of registered breast cancer patients

Center providing the data	Number of patients	%	Date of first data entry
1. Ege University	4076	30.8	07.05.2005
2. IU Istanbul MF	3775	28.5	29.03.2007
3. Uludağ University	1423	10.7	28.06.2005
4. MAMER Surgery Center	1308	9.8	18.06.2009
5. Ankara Dışkapı TH	611	4.6	12.04.2007
6. Vahit Özmen, M.D.	530	4.0	09.07.2009
7. Kocaeli University	300	2.3	22.03.2006
8. Savaş Koçak, M.D.	267	2.0	10.04.2006
9. IU Cerrahpaşa MF	236	1.8	25.06.2009
10. Marmara University MF	167	1.3	28.10.2005
11. A.Menderes University MF	164	1.2	13.05.2009
12. Ankara University MF	163	1.2	21.02.2007
13. Dicle University MF	66	0.5	18.06.2009
14. Cumhuriyet University MF	60	0.4	31.10.2005
15. Maltepe University MF	39	0.3	29.04.2009
16. Southeastern Anatolia BS	24	0.2	10.03.2008
17. Çukurova University MF	13	0.1	16.04.2009
18. Others	18	0.12	14.12.2007
TOTAL	**13.420**	**100**	

IU: Istanbul University; MF: Medical Faculty; MAMER: Breast Diseases Research Center; TH: Teaching Hospital; BS: Breast Society

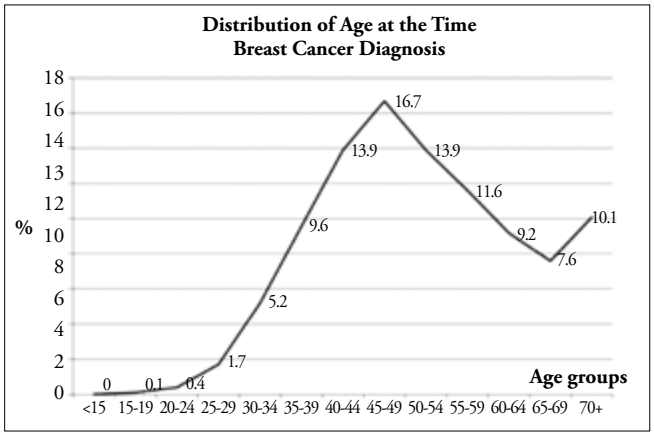

Figure 1. Breast cancer frequency according to age at diagnosis (%)

of premenopausal women, and in 49% of postmenopausal women (p=0.059, Table 3).

Pathological lymphatic stages were found as 50% pN0, 28% pN1, 15% pN2, and 7% pN3. pN0 patients were mostly in the ≥70 years group. It was observed that as age at diagnosis increased regional lymphatic involvement decreased therefore resulting in decreased lymphatic stage (p=0.0001). While 44% of women diagnosed with invasive cancer under the age of 40 were pN0, 51% of women aged ≥40 years were staged as pN0 (p=0.001). 47% of premenopausal women, and 53% of menopausal women were pN0 (p=0.018).

pN0 rate in pathologic T1 patients was 61%, whereas this rate was significantly lower in pT2-3 tumors (42% vs. 18%, respectively) (p=0.0001).

The rates of pathologic stage were: 4.9% Stage 0, 27% stage I, 45% stage II, 21% stage III, 3% stage IV. With increasing age at diagnosis, pathologic stage is decreased, and this difference was statistically significant (p=0.011).

The patients aged ≥40 years and <40 years of age were divided into two groups and were classified according to pathologic stage in these groups (Table 3). Early stage (stage 0, I, II) breast cancer in women under the age of 40 was 71.5%, while the rate of advanced stage (ever III, IV) was 28.5%. In cases over 40 years of age early and advanced stage disease rates were 77.5% and 22.5%, respectively (p=0.005).

The histological grades (HG) were found as HG I 5%, HG II 45%, and HG III 50%. HG III tumors were detected in half of the cases, whereas HG decreased with advancing age (p=0.0001). Sixty percent of tumors detected in patients younger than 40 years, while this rate was 48% in patients ≥ 40 years (p=0.0001). In patients with pT1 44.5% were HG III, as tumor size increased the rate of HG III increased, up to 57% in T2, and 61% in pT3 (p=0.0001).

51% of pN0 cases, and 71% of pN3 patients were HG III (p=0.0001). Lymphatic involvement was seen in only 30% of HG I patients. As HG increased, regional lymphatic involvement rate increased significantly (p=0.0001).

In 69% of patients, ER was positive. This rate decreased to 61% in patients <40 years of age, and increased to 71% in patients ≥40 years (p=0.0001). ER was positive in 66% of pre-menopausal, and 73% of menopausal women (p=0.0001).

Progesterone receptor positivity rate was 58%, when patients were divided into two groups of ≥40 years and <40 years of age; 57%

Table 2. Demographic Characteristics of patients

Patient and Tumor Characteristics	Number (%)
Number of patients	11.542 (100%)
Male	157 (1%)
Female	11.385 (99%)
Median age	51.6 (12-97 age)
<40 age number of patients	1.950 (17%)
≥40 age number of patients	9.435 (83%)
Number of patients, menopausal status known	5.471 (100%)
Number of premenopausal patients	2.440 (45%)
Number of menopausal patients	3.031 (55%)
Number of patients , histopathology known	4.510 (100%)
Ductal carcinoma in situ (DCIS%)	223 (4.9%)
Invasive cancer	4.287 (95.1%)
Histopathologic type	
Invasive ductal cancer	3.387 (79%)
Invasive lobular cancer	317 (7.4%)
Mixed type	425 (9.8%)
Others	18 (3.8%)
Number of patients, histologic grade known	6.336 (100%)
I	317 (5%)
II	2.851 (45%)
III	3.168 (50%)
Resceptor Positivity	
ER	2383/3442 (69%)
PR	1867/3199 (58%)
HoR	2522/3328 (75.8%)
HER- 2	391/1703 (23%)
Pathologic Stage at Diagnosis	
Stage 0	184/3780 (4.9%)
Stage I	1007/3780 (26.6%)
Stage II	1696/3780 (44.9%)
Stage III	787/3780 (20.8%)
Stage IV	106/3780 (2.8%)

ER: Estrogen; PR: progesterone; DCIS: ductal carcinoma in situ; HoR: hormone receptor

of patients <40 years and 59% of patients ≥40 years were positive (p>0.05, Table 3).

Hormone receptor (HoR) positivity (at least one positive hormone receptor) was found as 76%. HoR positivity was significantly higher in patients over 40 years of age as compared to those <40 years (77% vs 71%, respectively, p=0.005). HoR was positive in 79% of pT1 cases. However, HoR positivity rate was reduced as tumor diameter increased (p=0.0001). HoR positivity was 77% in patients with pN0, and 69 % in pN3 (p<0.029). HoR was positive in 94% of HGI patients. As HG increased HoR positivity rate was reduced (p=0.0001).

In 23% of patients, HER-2 expression was positive according to results of immunohistochemical analysis (FISH or SISH test). This rate was higher in young (<40 years) patients and pre-menopausal women, although the difference was not significant (p>0.05). HER-2 positivity was detected in 24.5% of patients with IDC histopathology, and 14% in ILC and IMC cases (p=0.0001). ER positivity rate was 70% in all patients, 68% in patients diagnosed with IDC, and 78% in those diagnosed with ILC-IMC (p=0.0001).

HER-2 positivity did not show any significant difference according to tumor size, however it significantly increased as lymphatic involvement and HG increased. HER-2 positivity rate was 20% in pN0 and 26.5% in pN+ patients (p=0.002); and 10% in HG1 and 28% in HGIII cases (p=0.0001).

Molecular subtype distribution among cases was as follows: Luminal A 62%, Luminal B 15%, HER-2 Group 8.5% and Triple Negative 15%. As patient age increased the likelihood of the tumor being Luminal A molecular subtype also increased (p=0.006).

On analysis of the distribution of molecular subtypes according to age, it was found that 64% of Luminal A subtype was detected in patients ≥40 age. However, Luminal B and triple negative group (TNG) tumors were found at higher rates in patients below 40 years of age (p=0.044). Out of all the pT1 cases, 66% were Luminal A, 15% were Luminal B, 6% were HER-2 positive and 12% were in the TNG group. As tumor size increased the rate of patients with Luminal A and B molecular subtypes decreased while rate of HER-2 positivity and TNG patients increased (p=0.0001).

Out of all the pN0 patients, 64% was in Luminal A, 13.5% in Luminal B, 6% in HER-2 positive and 17% in TNG group. When the molecular subtype variables were independently evaluated, it was determined that with increasing lymphatic involvement stage the incidence of Luminal A type tumors decreased, while HER-2 positive tumor rates increased. These findings were also statistically significant (p=0.001). However, no significant relationship between lymphatic involvement and Luminal B and TNG subtypes was revealed.

Among HGI cases, 87% were Luminal A, 10% were Luminal B, 3% were in the TNG molecular subtype. With increase in HG, Luminal A subtype incidence decreased while the rates of Luminal B, HER-2 positive and TNG tumors increased (p=0.0001).

Discussion and Conclusions

Breast cancer incidence displays a rapid increase in Turkey. Breast cancer incidence had been previously calculated as 24.1/100,000 in 1993, and it is estimated that by 2010 the same rate raised to 50/100,000. These results show a two-fold increase in breast cancer incidence in Turkey over the last 20 years (9-12).

In the USA, 6.6% of women diagnosed with breast cancer are under the age of 40, while 33% are above 65 years (13). The median age is 61 years, with 25% premenopausal patients (13, 14). In our study, the rate of younger patients is high: 17% of all cases were ≤40, 18% were above 65 years with a median age of 51 years. In other words, the median age was 10 years younger in our patients than those in the USA. Furthermore, premenopausal breast cancer cases constituted 45% of our cases.

The incidence of young aged (≤40) breast cancer was shown to be high in Asian and African countries reaching up to 30% (15). This is due to the general population' being younger in Turkey and other develop-

Table 3. Characteristics according to age groups (<40 years x≥40 years)

Patient characteristic	Total Number	<40 years (%)	≥40 years (%)	p value
Number of patients	11.385	17%	83%	
Pathologic T1 (<2 cm)	3.167	43%	50%	p=0.0001
Pathologic N0	2.599	44%	51%	p=0.001
Pathologic Stage 0, 1, 2	2.841	71.5%	77.5%	p=0.005
Histologic Grade 3	3.212	60%	48%	p=0.0001
Receptor positivity				
ER	3.442	61%	71%	p=0.0001
PR	3.199	57%	59%	p>0.05
HoR	3.328	77%	71%	p=0.005
HER-2	1.703	26.5%	22.2%	p<0.05
Molecular subtype	1.692	17%	83%	
Luminal A	1.054	56%	64%	p<0.05
Luminal B	247	19%	14%	p<0.05
HER-2 Positive	144	8%	8%	NS
Triple Negative	247	17%	14%	NS

ER: Estrogen; PR: progesterone; DCIS: ductal carcinoma in situ; HoR: hormone receptor

ing countries, and a higher young/old population ratio. According to the data acquired from the Turkish Institution for Statistics (Türkiye İstatistik Kurumu [TÜİK]), women under 40 years of age represent 68% of total female population in Turkey (16). In the USA, the rate of women under 40 years of age is only 45% (14). This difference shows a relative over-population in the younger subgroup and a relative increase in breast cancer in the younger age.

The identification of advanced staged breast cancer in younger women at the time of diagnosis is thought to be related to lack of screening programs among this subpopulation and the relatively higher rate of false negativity due to higher density of the breast tissue (17). The rates of clinical stage I and III breast cancer in patients under 40 years of age is 21% and 19%, while these rates are 29 and 13% in the 50-59 aged subgroup, respectively. Another surprising result was detected in patients above 70 years of age. In this group, the rate of clinical stage I disease at first presentation was higher (26%) than that of the group under 40 years, but lower than that of the 50-59 years of age group. The general disregard of diseases in the advanced age group and their usually painless manifestation results in delay in diagnosis. There is a general misbelief among our population that a painless mass is harmless.

Similarly, the mean tumor size was 2.8 cm among those under 40 years of age, while it decreased to 2.4 cm in the 40-69 year aged subgroup. Evaluation of age groups according to pathological tumor stages revealed the following distribution: pathological stage I breast cancer was detected in 22% of patients under 40 years and in 30% of those aged 50-59, and pathological stage III cancer was detected in 26 and 19% of the same age groups, respectively.

In addition to the data above, in younger breast cancer patients the rate of axilla positivity and HG were higher, ER and PR positivity were lower and HER-2 positivity was also higher (17-20). In our database, in patients under 40 years of age pN0 was 44%, HGIII rate was 60%, ER positivity was 61%, PR positivity was 57%, and HER-2 positivity was 26.5%, while in the more advanced aged group pN0 was 60%, HG3 rate was 44%, ER positivity was 71%, PR positivity was 59%, and HER-2 positivity was 23%.

The relatively dense breast tissue in premenopausal patients results in the diagnosis of the disease at a more advanced stage (21, 22). Clinical stage I and pN0 state breast cancer rates in premenopausal patients were 24.5 and 47% while these rates were 27.2 and 53% in menopausal patients, respectively. In this particular group, ER positivity was lower (66% vs. 73%) and PR positivity was a slightly higher (61% vs. 58%) as compared to the menopausal group. The comparison between the two groups concerning molecular subtypes, Luminal A and B breast cancer rates were similar, while HER-2 positivity (10% vs. 7%) and triple negative (16% vs. 13%) breast cancer rates were higher in the premenopausal group.

The extensive application of population based screening programs enables frequent detection of in situ breast cancers. Before the introduction of mammography into routine screening, DCIS was only diagnosed when it became palpable and accounted for only 1% of all breast cancers (23). Currently, DCIS is generally diagnosed as non-palpable lesions and constitutes around 20-25% of newly diagnosed breast cancer cases (23). Due to lack of fully organized population based screening in our country, in our database DCIS represents around 5% of all breast cancers. It is expected that the rate of detection of DCIS will soon rise due to the newly implemented fully organized population based mammographic screening program in Bahçeşehir, once gains wider spread and popularity. Indeed, in our program that screened 6500 women between 2009-2012, 21% of patients diagnosed with breast cancer had DCIS and 61% of them were stage I patients (24). Moreover, the fact that 48% of breast cancer cases detected in this prospective clinical study were in the 40-49 years age group, the KSDB (Cancer Control Department) adjusted the existing age limit for screening from 50-69 years to 40-69 years of age as of 2012.

"Invasive ductal carcinoma" is the most common histological type of breast cancer, constituting 49 to 75% of invasive breast cancer according to various studies (25-28). According to our study, histological types of breast cancer were as follows: 79% IDC, 7% ILC, 10% IMC and 4% other rare forms. Positive expression of ER and PR was higher in ILC's than in IDC cases (25-28). It is thought that hormone replacement therapy results in increase of tumors of especially ILC histology due to this increase in expression of hormone receptors (29). Similar to the mentioned studies, in our database, rates of ER positivity in ILC and IMC (78%) were significantly higher than in IDC (68%) (p=0.0001).

The pN0 rates in our patients with newly diagnosed IDC were 52%, while it was 41% for those with ILC and IMC, similar to the literature (30). The pathological stage of cases in our study was also more advanced in ILC+IMC cases. The rate of stage I and II breast cancer was 76.5% for IDC and 68% for ILC+IMC.

It is known that HER-2 positivity that is present in 20-30% of invasive breast cancers is associated with decrease in overall and disease-free survival along with reduction in chemotherapy response rates (31). Various studies report ILC cases to be ER/PR positive, HER-2 negative, bcl-2 positive and p53 negative (32). Similar to the aforementioned reports in our study, among all cases with HER-2 expression, the rate of tumors with IDC histopathology was found to be approximately 9-fold higher than tumors with ILC and IMC histopathology (p=0.0001). HER-2 positivity was seen in 24.5% of patients with IDC, and in 14% of cases with ILC and IMC (p=0.0001).

In developed countries, the mean tumor size is around 10 mm, and the incidence of non-palpable breast cancer is 50% (33). According to our database, the mean tumor size was 25 mm, and the tumor was ≤1 cm in 9.5%, ≤2 cm in 48%, between 2-5 cm in 46%, and >5 cm in 6% of all patients. pT1 tumors were detected in 43% of women under 40 years and in 50% above 40 years of age. With increasing tumor size, axillary lymph node involvement incidence was also increasing. Nemoto et al. (34) reported the rate of pN0 patients according to tumor size as 75% in tumors of 0.6-1.0 cm size, 66% in 1.1-2.0 cm size, 50% in 3.1-4.0 cm size and 35.5% in those >5 cm. In our study, the pN0 rates in patients with pT1, 2 and 3 tumors were 61%, 42% and 18%, respectively. There was a parallel correlation between tumor size and HG, as tumor size increased the HG increased. HGIII rate was 44% in pT1 patients, and 61% in pT3 patients.

Studies focused on the correlation of tumor size and hormone receptor revealed that there is a negative correlation between tumor size and hormone receptor expression (35, 36). Similarly, in our patients, hormone receptor positivity decreased as tumor size increased. The rate of at least one receptor positivity was 79% in patients with tumor size ≤ 2 cm, whereas this rate was 73% in pT2, and 68% in pT3 patients.

A few studies assessing the relationship between tumor size and HER-2 expression reported that HER-2 positivity rate was increasing with growing tumor size (35, 36). In a study by Kong et al. (35), high levels of serum HER-2 was found to be correlated with tumor size of ≥2 cm, age (<35), menopausal status, stage III breast cancer, lymph node involvement and ER/PR negativity in univariate analysis, and multivariate analysis showed that as HER-2 serum levels increased overall and disease-free survival was decreased. Our study partially supports these data. HER-2 positivity was determined as 21.5% in pT1 and elevated to 25% in pT2 cancers.

It is known that in developing countries breast cancer is seen in younger ages, is diagnosed in more advanced stages, and the rate of HGIII and triple negative cancers are higher (9, 10, 15, 36, 37). In our National Breast Cancer Database, the rate of HGI was 5%, HGII 45%, and HGIII approximately 50%. Thus, in half of the patients HG rates were as high as African/American race (37). The distribution of cases according to age was similar to the general trend presented in the literature; younger patients had a higher HG (13, 38-40). The rate of HGI in patients less than 40 years of age were half the rate in the group of 60-69 years, and the rate of HGIII (60%) was 16% higher than the rate in the group of 60-69 years. If patients are stratified as age <40 and ≥40 years, the rate of HGI was 2.6% and HGIII was 60% in patients younger than 40, and 5% and 48% respectively in patients aged ≥40 years.

Various studies show that there is a direct correlation between HG and HER-2 positivity; as HG increases HER-2 positivity significantly increases (41-43). In a clinical study by Hoff et al. (43), HER-2 positivity rate in HGI patients was found to be <1%. In addition, in our study, out of all the HER-2 positive patients only 2% were HGI, 28% were HGII and 70% were HGIII.

It is determined that rates of HR positivity of breast cancer patients in developed countries are higher than the rates of patients in developing countries. Indeed, in a USA based evaluation of 360,933 cases, ER positivity was found in 79% of Caucasian, 72% of Asian and 63% of African patients (37). Progesterone receptor positivity was also similar; 68% in Caucasian, 62% in Asian and 53% in African descent patients. In 70% of our patients, ER was positive while PR positivity was 58%, which is lower than the rate in Caucasians, similar to the rate in Asian descent and higher than the rate in African descent patients.

Luminal A, B, HER-2 and TNG molecular subtypes in our database were 62%, 15%, 8% and 15%, respectively. When these rates were compared with western rates, the HER-2 and TNG molecular subtypes are found to be lower in our patients (44). In our younger patients (≤40 years), Luminal A, B, HER-2 and TNG breast cancer rates were 56%, 18.5%, 8% and 17%, respectively. In the older subpopulation (50-59 years of age), these rates were 63%, 15%, 10% and 12%, respectively. These results reveal that molecular subtypes indicating worse prognosis were significantly higher in younger patients. This difference was more prominent in the group aged >70 years, with HER-2 positivity rate of 7.5% and TNG rate of 8.8%.

Evaluation of HG level according to molecular subtypes, show that triple negative and HER-2 positive breast cancers have higher levels of HG (44, 45). In a clinical study, the rate of HG3 according to molecular subtypes was reported as 76% in TNG breast cancer, 67% in HER-2 positive group, 15% in Luminal A and 47.5% in Luminal B patients (45). According to our database 87% of patients with HGI were Luminal A, 10% were Luminal B, and 3% were TNG subtype, while none of the patients with HGI revealed to be HER-2 positive. The rate of breast cancer patients with HG3 were; 83.5% in the triple negative group, 82% in HER-2 positive group, 43% in Luminal A and 61% in Luminal B. Although the list of HGIII rates were similar to the results of Spitale et al. (45), it was observed that our HGIII rates in all molecular subtype groups were higher than the rates in developed countries. These findings, as was emphasized earlier, support the statement that breast cancer has higher histological grade and worse prognosis in developing countries.

In another study evaluating molecular subtypes, Luminal A group was shown to have a smaller tumor size, and less multifocality, lymph node involvement and lymphovascular invasion (45). Spitale et al. (45) compared molecular subtypes among 1214 patients, and found that the mean tumor size was 19.6 mm in Luminal A and B, 22.6 mm in HER-2 positive group and 26 mm in TN group, with the differences showing statistical significance. In our patients, the rate of pT1 was 51% in Luminal A, 50% in Luminal B, 41% in TNG and 37.5% in HER-2 group. As tumor size increases the rate of Luminal A and B decreases, while HER-2 and TNG rates increase. In pT3 tumors, HER-2 and TNG molecular subtypes showed a nearly 100% increase, which is parallel to the findings of other studies stating that patients with smaller size tumors have a better prognosis (44, 45). The pN0 rate in our patients were 55% in Luminal A, 49.7% in Luminal B, 39.6% in HER-2+ and 59.7% in triple negative group. This finding shows that the risk of local spread is higher in the HER-2 positive group as compared to TNG.

Triple Negative (TN) breast cancer incidence is higher in premenopausal women (43-45). In a study, 37% of TN breast cancers were detected in premenopausal women, and 13% of HER-2 positive patients and 23% of Luminal A cases were premenopausal (45). In our study, no statistically significant difference was found between Luminal A, B and HER-2 positive groups and menopausal status, although TN cancer rate was found to be 16.3% in premenopausal and 13.2% in menopausal women.

The tumor proliferation is high in the HER-2+ molecular subgroup, 75% of these patients is high grade, and more than 40% display p53 gene mutation (44, 45). It represents nearly 5-10% of all breast cancers. In our study, 8.5% of the patient population was HER-2 positive. The greater tumor size and higher axillary involvement rate results in worse prognosis in this group (44, 45). In our study population, the increase in tumor size increased the number of patients in HER-2 positive group. 6.4% of pT1 patients, 10% of pT2 patients and 11.2% of pT3 patients were found to be in this group. Similarly, in HER-2 group 6% of cases were pN0 whereas the rate of pN3 cases was threefold higher (18%).

Approximately 7-30% of patients are in the triple negative molecular subtype, and the rate of TNG is higher in younger (<40 years of age), premenopausal and Asian/African descent women (43-45). The rate of patients in the TNG group was 14.6% in our patients and this rate was lower than the rate in Asian and African descent races but higher than the rate in some developed countries. The rate of TN breast cancer patients was 17.4% in the younger subgroup (≤40 years) while the same rate was less than half of this rate in women over 70 years of age (8.6%).

According to evaluation of our database, it can be concluded that our patients are younger, have more advanced stage breast cancers and worse prognostic factors than those patients in developed countries.

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Original Article

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Comparison of Chest Wall and Lymphatic Radiotherapy Techniques in Patients with Left Breast Carcinoma

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ABSTRACT

Objective: The aim of this study was to find the most appropriate technique for postmastectomy chest wall (CW) and lymphatic irradiation.

Materials and Methods: Partially wide tangent, 30/70 photon/electron mix, 20/80 photon/electron mix and CW and internal mammary en face electron field, were studied on computerized tomography (CT) scans of 10 left breast carcinoma patients and dosimetric calculations have been studied. Dose volume histograms (DVH) obtained from treatment planning system (TPS) were used for minimal, maximal and mean doses received by the clinical target volumes and critical structures.

Results: Partially wide tangent field resulted in the most homogeneous dose distribution for the CW and a significantly lower lung and heart doses compared with all other techniques. However, right breast dose was significantly higher for partially wide tangent technique than that each of the other techniques. Approximately 0.6-7.9% differences were found between thermoluminescent dosimeter (TLD) and treatment planning system (TPS). The daily surface doses calculating using Gafchromic® external beam therapy (EBT) dosimetry films were 161.8±2.7 cGy for the naked, 241.0±1.5 cGy when 0.5 cm bolus was used and 255.3±2.7 cGy when 1 cm bolus was used.

Conclusion: As a result of this study, partially wide tangent field was found to be the most appropriate technique in terms of the dose distribution, treatment planning and set-up procedure. The main disadvantage of this technique was the higher dose to the contralateral breast comparing the other techniques.

Key words: Breast cancer, treatment, techniques, dosimetry, radiation

Introduction

Chest wall (CW) and lymphatic irradiation in postmastectomy radiotherapy constitute one of the most challenging treatments in radiation oncology. Different target volumes in different planes and the close proximity of the critical structures, such as lung, heart, and spinal cord, make the treatment highly complicated in terms of planning and administration. Several studies with various treatment planning techniques showed the importance of conformal therapy planning (1-6). Three-dimensional (3D) treatment planning allows estimation of the dose distribution of target tissues and normal structures. To evaluate the actual doses of target volumes and critical structures, a thermoluminescent dosimeter (TLD) and Gafchromic™ external beam treatment (EBT) dosimetry films (international specialty products manufacturer) are used.

In this study, 3D planning is used to compare four different techniques for CW and lymphatic irradiation with respect to target volumes and doses in critical structures in patients with left-sided breast carcinoma. All techniques were also simulated on Alderson rando® phantom using the computed tomography (CT) scans of the phantom. In addition, a certain number of TLDs and Gafchromic™ EBT dosimetry films were placed to the points defined by the treatment planning system (TPS) on Alderson rando® phantom. The primary goal of this study was to define the ideal treatment plan according to the TPS and the dosimetric analysis.

Materials and Methods

The CT scans of 10 patients with left-sided breast carcinoma treated by postmastectomy radiotherapy were used for this study. The target volume [CW, supraclavicular fossa (SCF), level I-II-III axilla, and internal mammary lymphatics] and the normal structures (heart, lung, brachial plexus, spinal cord, right breast, and esophagus) were contoured on the CT scans by a single radiation oncologist (F.Y.), and 3D conformal treatment planning for four treatment techniques (partially wide tangent, 30/70 photon/electron mix, 20/80 photon/electron mix, and CW and internal mammary en face electron field) was planned for each patient (3-6). The partially wide tangential technique uses unique tangential fields that cover both CW and internal mammary lymphatics. In the mixed 30/70 photon and electron beam

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technique, CW is irradiated with photons by separate tangential fields, and internal mammary lymphatics are irradiated with parallel photon beams in 30% of the treatment and electron beams with the appropriate energy in 70% of the treatment. The mixed 20/80 photon and electron beam technique is the same as the 30/70 photon/electron mix technique, apart from their different percentages of combination (20% photon and 80% electron). In the en face CW and internal mammary electron field technique, the CW and internal mammary chain are irradiated with only electron fields. All dose-volume histograms (DVHs) obtained from different treatment techniques were evaluated for target volumes (CW, internal mammary, SCF, level I, level II, and level III) and critical structures (heart, lung, right breast) separately. When electrons were used for treatment, the appropriate energy was chosen as the 90% isodose surface that reached the anterior pleural surface.

Pursuant to the treatment planning used in the TPS, an individual simulation was done in Alderson rando^{R} phantom for each technique. Field borders were defined, and CT markers were placed to delineate margins. The CT scans of Alderson rando^{R} phantom were transferred to the TPS, and treatments were planned with 4 different techniques. After the determination of treatment fields in rando phantom, TLDs thought to represent the SCF, axilla, and internal mammary were put on certain depths. Additionally, the TLDs were several points that were thought to represent the right breast, CW, lung, and heart. In order to determine surface doses, Gafchromic^{TM} EBT dosimetry films were placed on the CW and right breast with either 0.5 or 1 cm tissue equivalent bolus material or as naked. In this way, three different measurements were taken for each plan. Precise, version 2.15 was used for this study (Elekta Oncology Systems Ltd, Crawley, UK). TLD and Gafchromic^{TM} EBT dosimetry films were calibrated before treatment.

Statistical Analysis

All statistical analysis was performed using SPSS, version 15.0 (SPSS, Chicago, Illinois). Plan evaluation parameters were chosen for each structure, and the same parameters were used to evaluate all plans. Forty different DVHs were calculated for all target volumes, including the CW, SCF, axilla, and internal mammary chain and normal structures. For evaluating the homogeneity of dose distribution, DVHs were calculated for each target volume and critical structures in all plans. The minimal dose, maximal dose, and mean doses were obtained, and standard deviations were defined. Friedman test was used for comparison. P-value <0.05 was considered significant. The mean values obtained from the TLD and Gafchromic^{TM} EBT dosimetry films and standard deviations were compared to the doses of the same points in the TPS.

Results

The minimal, maximal, and mean doses ± standard deviations in target volume obtained from different treatment plans were specified and are presented in Table 1. No differences could be observed among the four techniques for mean and maximal doses of CW. However, the CW and internal mammary en face electron field technique resulted in a significantly lower minimal dose compared to other techniques (p=0.002). Again, this technique was inadequate for delivering effective doses to the internal mammary and axillary lymphatics (Table 1). Partially wide tangent fields provided significantly lower maximal dose to the internal mammary chain compared to the other three techniques (p=0.001). Similarly, dose homogeneity for the partially wide tangential technique was significantly better than all the other techniques (p=0.005). Again, no differences could be observed in dose distribution of SCF lymph nodes among the different techniques.

Table 1. The minimal, maximal, and mean doses ± standard deviations in target volume obtained from different treatment plans

Techniques	CW min. dose	CW max. dose	CW mean dose	IM min. dose	IM max. dose	IM mean dose	Level 1 min. dose	Level 1 max. dose	Level 1 mean dose	Level 2 min. dose	Level 2 max. dose	Level 2 mean dose	Level 3 min. dose	Level 3 max. dose	Level 3 mean dose
	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD	cGy± SD
Partially wide tangent	4557.8± 107.3	5881.9± 241.4	5124.7± 132.7	4653.1± 193.6	5427.9± 192.9	5093.7± 141.1	4553.6± 58.8	5736.0± 299.9	5077.7± 161.6	4587.8± 58.4	5464.7± 322.3	5007.2± 167.8	4652.0± 110.0	5507.4± 231.4	5039.0± 139.5
30/70 photon/electron mix	4502.6± 83.1	6214.2± 347.4	5189.6± 104.5	4520.0± 45.7	6159.3± 186.2	5502.6± 129.2	4628.1± 71.8	5814.3± 154.0	5103.9± 101.1	4723.1± 104.2	5562.9± 107.2	5054.6± 87.4	4745.8± 132.2	5552.8± 240.7	5065.0± 90.2
20/80 photon/electron mix	4429.6± 128.9	6094.2± 120.0	5138.6± 121.9	4536.0± 21.7	6217.3± 383.5	5516.7± 246.5	4664.0± 114.1	5837.7± 214.5	5120.0± 115.6	4754. 3±88.4	5574.4± 132.9	5092.0± 90.2	4767.8± 85.3	5514.1± 208.9	5099.0± 89.4
CW-IM only electron	4085.3± 491.0	6026.6± 783.7	5340.0± 403.4	3809.3± 733.7	6199.9± 401.2	5364.2± 386.4	3118.8± 1367.9	6437.8± 393.1	5033.0± 316.8	3400.1± 1470.7	6151.2± 413.0	4943.3± 395.4	4047.0± 946.9	6092.0± 354.0	5100.7± 206.2
p value	0.002	0.163	0.62	0.01	0.001	0.002	0.003	0.017	1	0.006	0.001	0.782	0.056	0.003	0.696

CW: Chest wall; IM: internal mammary; min.: minimum; max.: maximum; SD: standard deviation

When comparing techniques for heart doses, it was observed that the heart dose in partially wide tangent fields was significantly lower than in the other techniques (Table 2). This difference was highly significant when compared with the 20/80 photon/electron mix and CW and internal mammary en face electron field.

The partially wide tangent field technique resulted in lower mean lung dose, the percentage lung volume receiving more than 20 Gy (V20), and mean left lung dose compared with the other techniques (Table 3). Partially wide tangent fields resulted in the lowest mean dose (919.8±84.6 cGy), and CW and internal mammary en face electron field resulted in the highest (1209±128 cGy) mean dose for whole lungs. Similarly, partially wide tangent fields resulted in the lowest mean dose (1831±176 cGy), and the en face CW and internal mammary electron field technique resulted in the highest (2374±298 cGy) mean dose for left lung.

As shown in Table 4, partially wide tangent fields produced significantly higher right breast doses than all other techniques ($p<0.001$).

Thermoluminescent dosimeter dose calculations in certain points representing the SCF, axilla, internal mammaria, CW, and critical normal structures were compared with the dose calculations obtained from TPS. In the partially wide tangential technique, the difference between TLD and TPS was 0.1%-6.4%. The corresponding comparisons for the 30/70, 20/80, and en face CW and internal mammaria electron field techniques were 0.5%-5.9%, 0.4%-7.9%, and 0.1%-6.1, respectively. The surface doses in the partially wide tangential technique found by EBT films were 161.8±2.7, 241.0±1.5, and 255.3±2.7 cGy with no bolus, with 0.5 cm bolus, and with 1 cm bolus, respectively.

When we compared the treatment planning and set-up periods for each technique, the partially wide tangent field and CW and internal mammary en face electron fields techniques took 30-45 minutes for planning and approximately 15 minutes for set-up procedures. The treatment planning time of the 30/70 and 20/80 photon/electron mix technique took 4-5 hours, and the set-up time took 30-45 minutes.

Discussion and Conclusions

The aim of this study was to evaluate the best treatment technique in patients with left breast carcinoma in the 3D conformal radiotherapy era. For left CW and lymphatic irradiation, 4 different techniques were chosen and compared according to DVH analysis obtained by TPS and dosimetric analysis using Gafchoromic™ EBT dosimetry films and TLDs.

The description of homogenous dose distribution was announced within the limits of between -5% and +7% according to the International Commission on Radiation Units and Measurements (ICRU) 50 report (7). However, in breast cancer radiotherapy, contour irregularity of CW and clinical target volumes on different depths and planes can frequently cause difficulties in reaching homogeneous dose distribution, as indicated in the ICRU 50 report. Generally, a minimum dose of 4,500 cGy to target volumes is believed to be acceptable. The maximum dose, on the other hand, is observed to be in the range of ≤120%. In our study, all the techniques except en face electron field to CW and internal mammaria achieved the goal of delivering a minimum of 4,500 cGy to the CW and internal mammaria, and the best homogenous dose distribution of CW was achieved by the partially wide tangent field technique. Similar to our study, Pierce et al. (8) confirmed that the partially wide tangent field was the most suitable technique, providing better coverage of the target volume and sparing the critical structures for CW and internal mammary radiotherapy.

Table 2. V_{10}, V_{30}, and mean doses for heart ± standard deviations and p values

Techniques	Heart V_{10}(%)± SD	Heart V_{30}(%)± SD	Heart Mean Dose (cGy)±SD
Partially wide tangent	11.0±6.3	6.7±5.5	534.7±250.7
30/70 photon/electron mix	20.9±10.2	9.6±4.4	853.7±304.3
20/80 photon/electron mix	31.4±9.3	8.4±4.3	972.8±256.6
CW-IM only electron	30.9±10.2	12.3±7.1	1054.7±369.5
p value	<0.001	0.088	<0.001

CW: Chest wall; IM: internal mammary; SD: standard deviation

Table 4. V_5 and mean doses for right breast ± standard deviations and p values

Techniques	Right Breast Mean Dose cGy±SD	Right Breast V_5 (%) ±SD
Partially wide tangent	126.2±44.4	1.2±1.8
30/70 photon/electron mix	78.6±23.0	0.1±0.3
20/80 photon/electron mix	68.5±24.6	0.1±0.4
CW-IM only electron	27.4±18.5	0.2±0.7
p value	<0.001	0.019

CW: Chest wall; IM: internal mammary; SD: standard deviation

Table 3. V_{20} and mean doses for whole, left, and right lung ± standard deviations and p values

Techniques	Lung V_{20}(%) ±SD	Mean Lung Dose cGy±SD	Mean Left Lung Dose cGy±SD	Mean Right Lung Dose cGy±SD
Partially wide tangent	16.7±1.5	919.8±84.6	1830.9±175.8	101.7±18.7
30/70 photon/electron mix	21.2±2.8	1113.6±138.6	2202.7±291.5	86.8±24.4
20/80 photon/electron mix	18.2±2.4	1019.3±110.3	1991.4±220.5	85.9±28.7
CW-IM only electron	23.4±1.9	1209.6±128.1	2374.2±298.4	128.0±70.3
p value	<0.001	<0.001	<0.001	0.026

CW: Chest wall; IM: internal mammary; SD: standard deviation

Chest wall and internal mammary en face electron field uses electron beams with appropriate energy for CW, internal mammary, and axillary region irradiation. Homogenous dose distribution and optimum coverage of the CW could not be obtained with this technique, since the depth of each volume showed considerable variations with respect to human anatomy. When the energy is selected according to the maximum depth, heart and lung doses become critical. In the literature, it was shown that the differences of beam obliquity and skin-source distance (SSD) resulted in low CW and internal mammary doses (6). The missing dose on the lateral CW is caused by this distance effect. Although a boost dose is suggested by some authors, no recurrence was observed in some reports when the boost dose was not applied to this region (6). In addition, hot dose spots are frequently defined with this technique. It was reported that homogenous and sufficient dose distribution could be obtained for internal mammary and CW because of the absence of axillary lymph nodes in the target volume (6). However, our data showed that both high-dose regions and unacceptable low-dose regions were observed in the CW, axilla, and internal mammary, and the dose distribution was very heterogeneous when en face electron beam fields were used for the CW and internal mammaria. This technique was assumed to be useful when axillary lymph nodes were not irradiated, and the literature showed that it could be as effective as photon beams for CW radiotherapy (9, 10).

The minimal dose of the internal mammary was less than 45 Gy with the CW and internal mammary en face electron field technique, despite the other 3 techniques. On the contrary, it was equal or greater than 45 Gy for the other three techniques. The reason for this difference can be attributed to the deeper localization of the internal mammary chain in some patients. Increasing the electron energy to reach an adequate dose on internal mammary lymph nodes, on the other hand, raised the doses of other target volumes and critical structures, which constituted a disadvantage of this technique. Kirova et al. (6) reported that a more homogenous dose distribution was observed with one unique electron field that included both the CW and the internal mammary chain compared to the standard technique; however, in that special manuscript, the internal mammary lymphatics were irradiated separately with different energies. In this particular study, only 5 CT slices were used, and minimal doses were not given. In our study, on the other hand, CT slices with 0.5-cm intervals covering the whole neck and thorax were used, and axillary lymphatics were also included in the treatment field. The most homogenous dose distribution in our study was provided with the partially wide tangent field for internal mammary chain.

In patients with breast carcinoma, one of the most important points for radiotherapy is minimizing the irradiated heart volume. It is observed that the risk of cardiac morbidity is severely increased when the median heart dose is greater than 35 Gy (11). It is indicated that if the percentage heart volume receiving more than 25 Gy (V25) is less than 10%, cardiac mortality ~15 years after radiotherapy would be seen as less than 1% (12). When the percentage heart volume receiving more than 10 Gy (V10), 30 Gy (V30), and mean heart dose was evaluated, our data demonstrated that the use of the partially wide tangent field resulted in the lowest cardiac exposure. The mean heart dose was found to be 534.7±250.7 cGy, which is significantly lower than the other three techniques. The heart V10 was significantly higher for the 20/80 photon/electron mix and CW and en face electron field technique. On the other hand, another important point for radiotherapy is the decreasing the risk of pneumonia. Pneumonia was rarely seen when lung V20 was less than 30% of the ipsilateral lung (13, 14). In our study, calculated lung V20, mean left lung dose, mean right lung dose, and mean total lung dose were obtained for each technique. The lung V20 and mean left lung dose were lower for the 20/80 photon/electron mix and partially wide tangent field when compared to the other techniques. The highest doses on lung were observed with the CW and internal mammary en face electron field. All our results are consistent with similar studies in the literature (8, 15, 16).

The probability of contralateral breast cancer is higher in patients with breast cancer after breast-conserving surgery than normal counterparts (17). It is important to minimize the contralateral breast dose in order not to increase the secondary carcinoma risk and not to cause side effects, like fibrosis, in healthy breast tissue. The CW and internal mammary en face electron field resulted in the lowest mean dose for the right breast in our study. The percentage of right breast volume receiving more than 5 Gy (V5) was significantly higher for the partially wide tangent field technique and lower for the 30/70 photon/electron mix technique. The main disadvantage of the partially wide tangent field is the higher right breast doses than all other methods. If the right breast is closer to the midline, other techniques rather than the partially wide tangent field are recommended or the right breast should be taken away from the treatment field by some daily immobilization method.

There is a significant correlation between tumor recurrence risk and tumor size, invasion at surrounding tissues, and positive axillary lymph nodes in breast carcinoma (18, 19). Recurrence after modified radical mastectomy is mostly observed at the CW with a frequency of 50% and then at the SCF region after postmastectomy radiotherapy (20, 21). The aim of CW irradiation is to minimize the risk of CW recurrence due to microscopically residual disease and to treat subcutaneous, interpectoral, and intercostal lymphatics sufficiently. In modern radiotherapy, recurrence is generally observed at the superficial part of the CW due to the skin-sparing effect of megavoltage radiotherapy (11, 22, 23). According to a study using photon energy of 6 MV, the surface dose is 15%-40% lower than the prescription dose (24). The surface doses of CW need to be known during the treatment planning process. However, none of the TPSs can estimate the surface dose correctly. Due to the high spatial resolution and low spectral sensitivity, Gafchromic™ EBT dosimetry films are used as an ideal detector for surface dose measurements (24). In our study, surface doses without bolus after the partially wide tangent field were 84%±2.7% by using Gafchromic™ EBT dosimetry films for 6 MV photon beams. It resulted in 120% ± 1.5% and 128%±2.7% with the use of 0.5 and 1 cm tissue equivalent bolus, respectively. In our department, the 7, 11, and 7 technique is used for CW irradiation with 6 MV photon beams: open field for the first 7 days, all CW with 1 cm bolus for the following 11 days, and around the incision scar with 1 cm bolus for the last 7 days. With this technique, the CW skin and scar surroundings receive 50 and 57 Gy, respectively. Thus, dose escalation could be done at the regions with high recurrence risk.

In all techniques, the planned and applied treatments were attempted to be validated after comparing the dose from the TPS and the measurements from the TLD-100H put on the phantom. With the partially wide tangent field for the CW and internal mammary irradiation, the difference between TPS and dosimetric measurements was a maximum of 6.4%. It was determined to be 7.9% with the techniques using a photon/electron mix.

The applicability of the treatment plan becomes as important as providing the best dose homogeneity and sparing critical structures. Set-up

errors may cause terrible results, even if the treatment plan is perfectly prepared in the TPS. Additionally, treatment planning time is also important for busy departments. In our study, planning and set-up procedures were significantly shorter for the partially wide tangent field and en face CW and internal mammary electron field techniques. Considering the dose distribution and time required for the planning and set-up procedure, the partially wide tangent field technique is proven to be the best method, especially for the department with high patient load.

In our study, the partially wide tangent field was the most suitable technique for CW and lymphatic irradiation in view of providing homogenous dose distribution for clinical target volume and decreasing lung and heart doses. Compared to the other techniques, easier and quicker planning and set-up were other advantages of this technique. However, the main disadvantage of the partially wide tangent field is higher doses to the contralateral breast, especially when it is located closer to the midline. In these cases, other techniques, rather than the partially wide tangent field, are recommended, or the contralateral breast should be taken away from the treatment field by immobilization in order to prevent secondary carcinomas.

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Original Article

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Evaluation of Neoadjuvant Chemotherapy Response with Dynamic Contrast Enhanced Breast Magnetic Resonance Imaging in Locally Advanced Invasive Breast Cancer

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ABSTRACT

Objective: The reliability of traditional methods such as physical examination, ultrasonography (US) and mammography is limited in determining the type of treatment response in patients with neoadjuvant chemotherapy (NAC) application for locally advanced breast cancer (LABC). Dynamic contrast-enhanced magnetic resonance imaging (MRI) is gaining popularity in the evaluation of NAC response. This study aimed to compare NAC response as determined by dynamic contrast-enhanced breast MRI in patients with LABC to histopathology that is the gold standard; and evaluate the compatibility of MRI, mammography and US with response types.

Materials and Methods: The US, mammography and MRI findings of 38 patients who received NAC with a diagnosis of locally advanced breast cancer and surgical treatment were retrospectively analyzed and compared to histopathology results. Type of response to treatment was determined according to the "Criteria in Solid Tumors Response Evolution 1.1" by mammography, US and MRI criteria. The relationship between response types as defined by all three imaging modalities and histopathology were evaluated, and the correlation of response type as detected by MRI and pathological response and histopathological type of breast cancer was further determined. For statistical analysis, the chi-square, paired t test, correlation and kappa tests were used.

Results: There is a statistical moderate positive correlation between response type according to pathology and MRI (kappa: 0.63). There was a weak correlation between response type according to mammography or US and according to pathology (kappa: 0.2). When the distribution of treatment response by MRI is stratified according to histopathological types, partial response was higher in all histopathological types similar to the type of pathologic response. When compared with pathology MRI detected treatment response accurately in 84.2% of the patients.

Conclusion: Dynamic contrast-enhanced breast MRI appears to be a more effective method than mammography or US in the evaluation of response to neoadjuvant chemotherapy. MRI evaluation of LABC is accepted as the appropriate radiological approach.

Key words: Cancer, chemotherapy, breast, MRI, neoadjuvant, response

Introduction

Tumors with a diameter above 5 centimeters, skin and chest wall involvement, involvement of ipsilateral supraclavicular, infraclavicular, internal mammary or fixed axillary lymph nodes are defined as locally advanced breast cancer (LABC). These characteristics are compliant with stage 3A and B tumors in general. LABC can be classified as operable and inoperable. Neoadjuvant chemotherapy (NAC) is the standard method of treatment in patients with inoperable LABC and increases both disease-free and overall survival (1). In operable patients, it permits breast conserving surgery rather than mastectomy (2-7). In a meta-analysis consisting of 5500 patients, NAC and surgery combination was compared to surgery and adjuvant chemotherapy (4). Although survival was similar in both groups, the rate of mastectomy as well as the incidence of side effects was significantly lower in patients treated with the combination of NAC and surgery (4).

However, a pathological complete response to neoadjuvant chemotherapy cannot be achieved in all patients. The early detection of patients with complete or near-complete response is of great significance in the follow-up and survival of patients (2, 3). The timely identification of patients who are unresponsive to treatment is important for the planning of new treatment regimens with different chemotherapeutic agents as soon as possible, reducing toxicity and complications (1). Disease-free and overall survivals have a clear correlation with NAC response (8).

Physical examination, ultrasonography (US), mammography, magnetic resonance imaging (MRI) and molecular imaging can detect response to neoadjuvant therapy in the early period. The reliability of traditional methods such as physical examination, ultrasonography and mammography is limited, thus dynamic contrast-enhanced MRI is being increasingly used for the evaluation of response to treat-

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ment (9, 10). The MRI, unlike physical examination and mammography, is also able to distinguish between fibrosis and tumor tissue in dense breasts (3). It reflects tumor size more accurately and is more reliable than ultrasound, mammography or physical examination in predicting the size of residual disease after neoadjuvant chemotherapy. In patients receiving neoadjuvant chemotherapy, antiangiogenic effects of cytotoxic chemotherapy agents decrease tumor vasculature, thereby reducing contrast enhancement. Viable residual tumor tissue will show contrast enhancement on dynamic contrast-enhanced breast MRI, and can be distinguished more easily. The sensitivity of MRI in the evaluation of response to neoadjuvant chemotherapy is reported as 50% - 100% (2). This high sensitivity depends on the ability of MRI to distinguish between fibroglandular tissue and untreated hypervascular tumors within the breast tissue.

This study aimed to compare NAC response as determined by dynamic contrast-enhanced breast MRI in patients with LABC to histopathology that is the gold standard; and evaluate the compatibility of MRI, mammography and US with response types.

Materials and Methods

The radiology images of patients who were referred to Dokuz Eylül University Medical Faculty Hospital Radiology Department between January 2002 to October 2011 for evaluation of their treatment response after receiving NAC with a diagnosis of LABC have been retrospectively reviewed. Patients without an MRI either before or after NAC, who did not undergo surgery and without histopathological results were excluded from the study. The US, mammography and dynamic contrast-enhanced MRI investigations of the 38 included patients before and 1-3 months after NAC were evaluated and compared to histopathological results. The ethical permission was obtained from "Dokuz Eylul University Non-Interventional Research Ethics Board".

The chemotherapy regimens used combination of anthracycline and taxane group chemotherapeutic drugs and received 4 +4 cycles of treatment. In addition, in 8 patients with c-erb-B2 receptor-positivity, trastuzumab was added to the treatment.

The mammography examinations were conducted with a digital mammography device (Lorad Selenia; Hologic, Danbury, USA) with low kVp and high mAs protocol, in the routine craniocaudal and mediolateral-oblique positions. Additional positional views were added if needed. The breast US examinations were carried out with Philips HDI-11 SA ultrasound device (Koninklijke Philips Electronics, the Netherlands) using a high-resolution linear probe, simultaneously with the mammography examinations.

Dynamic contrast-enhanced breast MRI of all patients was performed in our department with a 1.5 Tesla MRI device (Gyroscan Achieva; Philips, Best, the Netherlands) with a SENSE- Breast coil, in the axial plane. In the reports of breast imaging, the classification by Breast Imaging Reporting and Data System (BIRADS) was used. As routine magnetic resonance parameters, the turbo spin echo (TSE) T1-weighted (repetition time (TR): 476 msn, echo time (TE): 8.0 msn, flip angle: 90, matrix: 288, field of view (FOV): 400, rectangular FOV: 100, slice thickness: 3 mm, gap: 0 mm, number of excitation (NEX): 2) and T2-weighted (TR: 5726 msn, TE: 120 msn, flip angle: 90 matriks: 448, FOV: 400, rectangular FOV: 100, slice thickness: 3 mm,gap 0 mm, NEX: 2), dynamic contrast-enhanced fat-suppressed THRIVE (TR/TE: 5.6/2.7, flip angle: 10, matriks: 448, FOV: 400, rectangular FOV: 100, slice thickness: 3 mm, NEX: 2) and post-contrast fat-suppressed T1-weighted axial sequences (TR: 550 msn, TE: 8.0 msn, flip angle: 90, matrix: 288, FOV: 400, rectangular FOV: 100, slice thickness: 3 mm, gap: 0 mm, number of excitation (NEX): 2) were applied in all patients. After obtaining pre-images for all sections, patients were injected gadopentetate dimeglumine at a dose of 0,1 mmol/kg via a venous access, and repetitive images with 30 sec intervals were obtained. Upon completion of imaging, subtraction images were created by using the Standard subtraction function of the device that subtracts early and late contrast-enhanced images from non-contrast images. The pharmacokinetic curves of the images were created by View Forum and recorded with the PACS system.

The tumor size determined by mammography and US before and after NAC, was compared to the measured tumor size by MRI. For the measurements, the largest single diameter, or the sum of the long axes of all target lesions in multifocal multicentric lesions were used according to "Response Criteria in Solid Tumors Evolution "(RECIST 1.1 criteria). When assessing magnetic resonance images, number and propagation of the mass, multicentricity, shape, contour features, presence of necrosis, time / intensity curve type (Type 1, 2, 3), enhancement pattern (homogeneous, heterogeneous, point, reticulated, branching, cobblestone, peripheral glossy - dark interior region) and enhancement speed (fast, medium and slow) were recorded. In addition, breast parenchyma type, accompanying signs (pectoral muscle invasion, microcalcifications, skin edema) and axillary lymph node status were evaluated. The tumor size in pathology reports has been accepted as the gold standard in the evaluation of residue after NAC, and was compared to tumor size as determined by each of the three methods (mammography, breast US, breast MRI) after the operation. The histopathological type of breast cancer was also recorded.

According to RECIST 1.1 criteria, the NAC response was grouped into complete response, partial response, stable disease and progressive disease. The absence of contrast-enhancing lesions on MRI, the complete disappearance of mass lesions on mammography and breast US examination were accepted as complete response. The absence of invasive focus on pathology evaluation was considered as pathological complete response. Table 1 summarizes NAC response types according to RECIST 1.1 criteria.

In the statistical evaluation, the tumor size detected by mammography and breast US prior to chemotherapy was compared to the size de-

Table 1. Type of response to neoadjuvant chemotherapy according to RECIST 1.1 criteria

Complete response	Disappearance of all target lesions
Partial response	30% and higher decrease in tumor longitudinal diameter
Progressive disease	20% and higher increase in tumor longitudinal diameter - 5 mm increase in tumor size – new lesion formation
Stable disease	Less than 25% increase or less than 30% decrease in tumor size

Table 2. Pre-post treatment tumor size detected by MRI / Mammography / US

	Pre-treatment tumor size (cm)		Post-treatment tumor size (cm)	
Method	Min/Max	Mean*	Min/Max	Mean *
Mammography	0/16	4.1±3.0	0/10	2.4±2.6
US	0/16	3.9±3.1	0/10	2.6±2.7
MRI	0.8/16	5.2±2.8	0/6	2.07±1.6

*Mean value ± Standard deviation
US: Ultrasonography; MRIG: magnetic resonance imaging; cm: centimeters; min: minimum; max: maximum

tected by breast MRI and after chemotherapy the tumor size detected radiologically was compared to the size stated in the pathology report and their correlation was assessed. The correlation of response types and mammography, breast US, and breast MRI were determined. The relation of response types detected with MRI and pathologic evaluation with histopathological type of breast cancer were also considered. Statistically, chi- square, paired t test, correlation and kappa tests were used. Data were reported as mean ± standard deviation (SD) or as percentages where appropriate. P value of <0.05 was considered statistically significant. Statistical analyzes were performed using SPSS (version 15.0, SPSS, Inc., Chicago, IL, USA).

Results

The mean age of 38 patients was 49.84 (SD 17.12) years and the breast parenchyma was classified as BIRADS 1 in 6, as BIRADS 2 in 14, as BIRADS 3 in 14, and as BIRADS 4 in 4 patients. All patients received tru-cut biopsy and dynamic contrast-enhanced breast MRI examinations prior to treatment. Two patients had no pre-treatment mammography and US evaluations.

According to pathology results, 10 cases had dominant invasive ductal carcinoma component, and in 12 patients the invasive lobular carcinoma component was evident. In five patients invasive ductal carcinoma+ invasive lobular carcinoma, in 3 patients medullary-like invasive ductal carcinoma, in 1 patient mixed invasive breast cancer and in 1 patient inflammatory breast cancer was observed. In six patients, the histopathologic type was reported as invasive breast carcinoma.

The properties of mass lesions viewed on MRI were as follows: 14 multicentric and heterogeneously enhancing, 4 diffuse growing and heterogeneously enhancing; 6 spicular edged and homogeneous enhancing, 3 irregular margined, 2 peripheral enhancing, 2 nodular enhancing, 4 compatible with inflammatory cancer (skin edema and mass lesions tendency to coalesce). Two patients had breast edema and regional enhancement findings. In one case, the lesion had irregular margins and central necrotic areas were observed. In two cases there was invasion of the skin and pectoral muscles.

The pre-treatment mean tumor diameter detected by mammography was 3 cm, the mean tumor diameter detected by US was 3.1 cm, and the mean tumor diameter detected by MRI was 5.2 cm. The mean tumor diameter detected by MRI, mammography and US after treatment were 1.6 cm, 2.6 cm and 2.7 cm, respectively. Table 2 summarizes pre-treatment and post-treatment tumor size detected by each of the three imaging modalities.

Mammography and US showed statistically high level of correlation in terms of lesion diameter by Pearson's correlation test (r=0.9, p<0.005), but mammography and MRI (r=0.7, p<0.005) and US (r:0.6, p<0.005) were moderately correlated. Tumors were measured by US as compared to MRI. US did not detect any tumor in two patients, and in four patients the tumor diameter was measured larger than MRI. Statistically, there was moderate correlation between MRI and pathology in terms of tumor size after treatment (r=0.4, p=0.007). MRI predicted residual tumor diameter correctly in 26 of 38 cases. There was no statistical correlation between mammography and pathology (r=0.2, p=0.1) or US and pathology (r=0.1, p=0.4).

On the pharmacokinetic evaluation before treatment, type 2 (44.7%) and type 3 (55.3%) curves were observed and after treatment the most common finding was type 2 curve (65.8%). In four cases (10.5%) type 1 benign curve was observed that was not detected before treatment and there was a significant decrease in the rate of type 3 curves. Most of the mass lesions showed heterogeneous (70%) and fast (60.5%) contrast enhancement prior to treatment, whereas the contrast enhancement rate significantly decreased after treatment and rapid enhancement was seen in only 10.5%. However, significant differences in enhancement pattern were not detected. In five cases, the MRI did not reveal a mass lesion due to complete response. In one patient, although there was not significant contrast enhancement, a mass lesion in the localization of the lesion was found in other sequences that were considered compatible with a partial response to treatment. Contrast enhancement pattern has not been evaluated in six cases. The dynamic contrast-enhanced MRI findings before and after NAC treatment are summarized in Table 3.

The cases were fairly homogenous in terms of the chemotherapy protocol. Anthracycline and taxane group chemotherapeutic drugs are used in combination and 4+4 cycles of treatment were given. Only one patient received 6 cycles of treatment. Eighteen out of 38 cases were c-erb-B2 receptor positive and trastuzumab was added to the treatment in 7 of them. Chemotherapy regimens are summarized in Table 4.

After NAC all 38 patients had a dynamic contrast-enhanced breast MRI, 22 had mammography and 19 underwent US examination. There was statistical high-level positive correlation between mammography or US and response type (kappa: 0.9). MRI type of response and mammography or US response type showed poor statistical compatibility (kappa: 0.1). The type of pathologic response after treatment with mammographic or US response type showed poor statistical compatibility with kappa test (kappa: 0.2). Figure 1-5 show radiological examinations of a case that was evaluated as "partial" NAC response type by mammography but was considered as "complete response" by MRI and histopathological evaluation.

The pathological complete response rate of 38 patients after treatment was 15.8%, and the complete response rate in MRI was 13.2%. MRI

Table 3. MRI findings pre- and post-neoadjuvant chemotherapy

		Pre-treatment	Post-treatment*
		n (%)	n (%)
Pharmacokinetics curve	Type 1	0 (0)	4 (10.5)
	Type 2	17 (44.7)	25 (65.8)
	Type 3	21 (55.3)	3 (7.9)
Contrast-enhancement pattern	Homogenous	9(23.7)	4 (10.5)
	Heterogeneous	27 (70)	26 (68.4)
	Peripheral	2 (5.3)	2 (5.3)
Contrast-enhancement speed	Slow	3 (7.9)	7 (18.4)
	Medium	12 (31.6)	21 (55.3)
	Fast	23 (60.5)	4 (10.5)

*Pharmacokinetic evaluation could not be performed in 6 cases in whom there were no focal lesions with contrast-enhancement on post-treatment images.
MRI: Magnetic resonance imaging

Table 4. Neoadjuvant chemotherapy protocols

Treatment (*)	Number	%
4 cycle FEC + 4 cycle D / P	23	60.5
4 cycle EC + 4 cycle D / P	8	21
4 cycle FEC + 4 cycle DT	6	16
6 cycle TAC	1	2.5
Total	38	100

*F: 5-Fluorourasil; E: epirubicin; C: cyclophosphamide; D: dosetaxel; P: paklitaxel; A: adriamisin

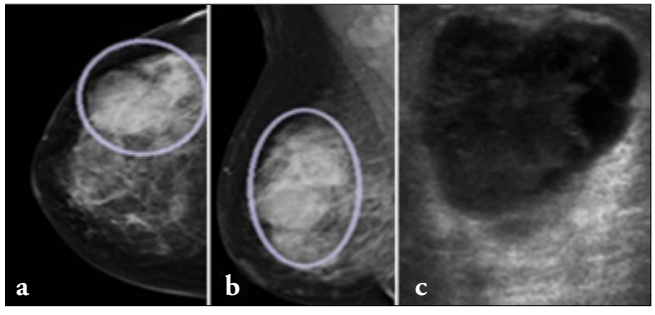

Figure 1. a-c. Pre-treatment mammography and US examinations of a 55-year-old patient (case 1) with a mass in the left breast. Mammographic craniocaudal and mediolateral oblique views of the left breast (a, b). US image of the left breast (c). Mass lesions located in the left breast UOQ-LOQ junction with extension to UOQ, showing cystic-solid components on US, with lobulated borders are visualized. There is left axillary lymphadenopathy. Results were interpreted as multicentric-multifocal breast tumor

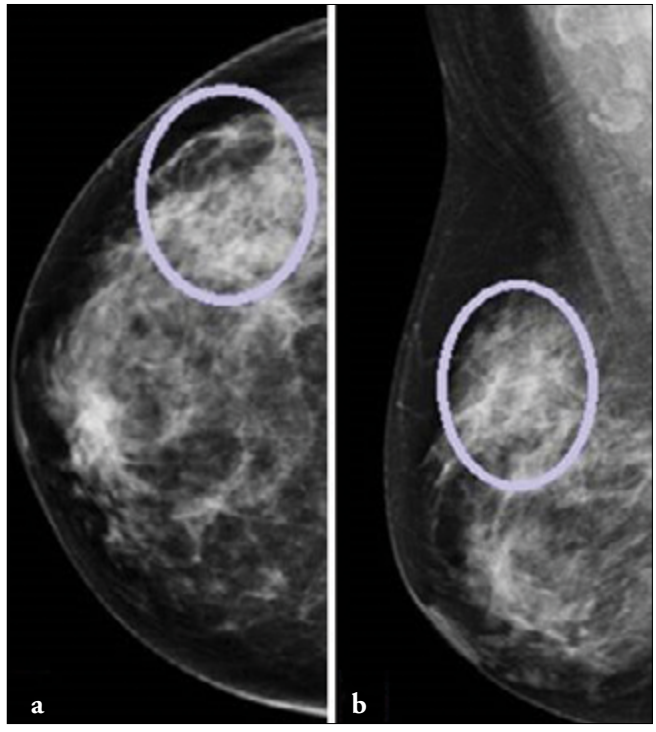

Figure 2. a, b. Mammographic craniocaudal and mediolateral oblique views of Case 1 after treatment. Compared to the previous views, a significant reduction in the size of the mass is observed (a, b). Mammography response type was evaluated as "partial response".

identified type of NAC response correctly in 32 (84.2%) of 38 patients as compared to pathology. Pathological response type and MRI response type showed a statistical moderate positive correlation with the kappa test (kappa: 0.63). Table 5 shows the type of NAC response detected by all three imaging methods and identified by pathology.

Following NAC, 17 of 38 cases underwent breast conserving surgery, 16 modified radical mastectomy (MRM) and 5 simple mastectomy. Patients who underwent breast-conserving surgery after NAC had less than 4cm of residual tumor as detected by MRI and their axillary lymph nodes disappeared after treatment. In 16 of these patients, the MRI response type was consistent with the type of pathologic response and the difference between residual tumor size between MRI and pathology were maximum 1 cm except two patients. Figures 6-10 show radiological examination of a patient who was evaluated as "stable disease" after NAC by MRI but had "partial response" on histopathological evaluation.

Complete response was detected in 25% of patients with invasive lobular carcinoma, in 7% of invasive ductal carcinoma, in 16% of invasive

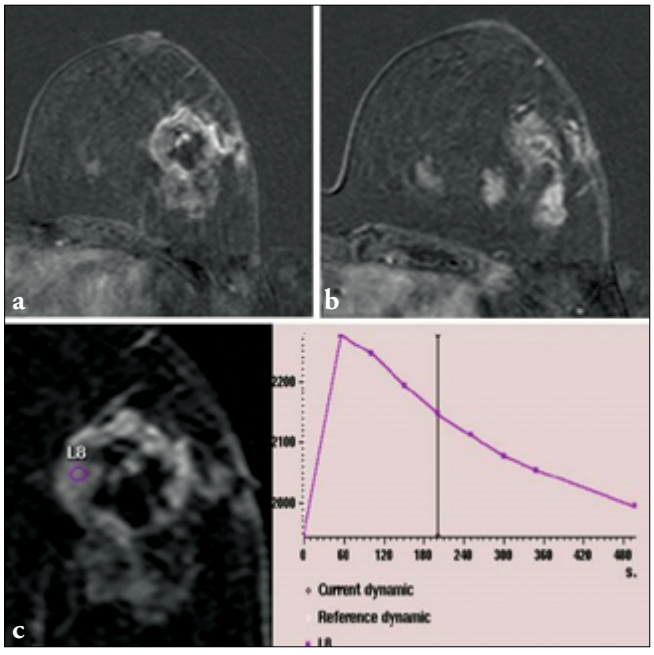

Figure 3. a-c. Dynamic contrast-enhanced MRI and pharmacokinetic curve of Case 1 before treatment. The subtraction image revealed a 6.5 cm, lobulated, irregularly contoured, necrotic mass lesion with skin invasion in the left breast outer quadrant (a, b). Various foci with similar morphologic and kinetic features, the largest reaching 2 cm in diameter, are detected (b). Pharmacokinetic evaluation is compatible with type 3 curve (c).

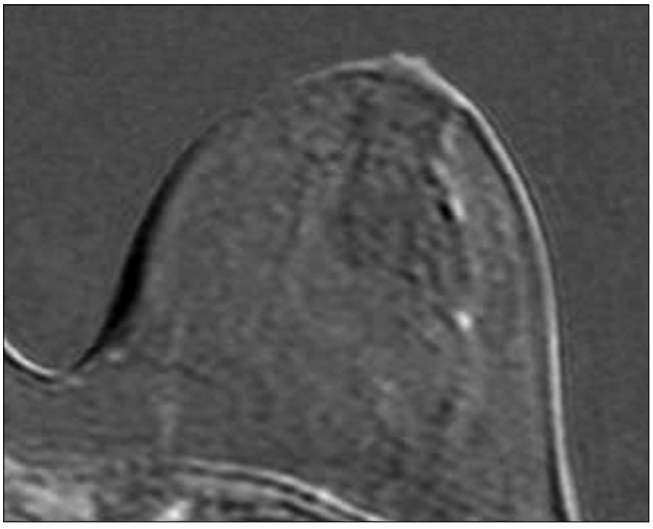

Figure 4. Post-treatment subtraction MRI images of Case 1 MRI not showing any pathological mass lesion or enhancement in the left breast. MRI response type was evaluated as "complete response"

ductal + invasive lobular carcinoma and in 7% of other pathological types. The histopathological distribution according to pathologic response types revealed that partial response was more frequent in all types, with a partial response in 73.7% of patients. One out of 14 patients with invasive ductal carcinoma had a pathological complete response. Three out of 12 patients with invasive lobular carcinoma had complete response. Out of the 12 patients who have been grouped as other types involved invasive breast cancer, invasive ductal + invasive lobular carcinoma, and inflammatory carcinoma, two patients showed

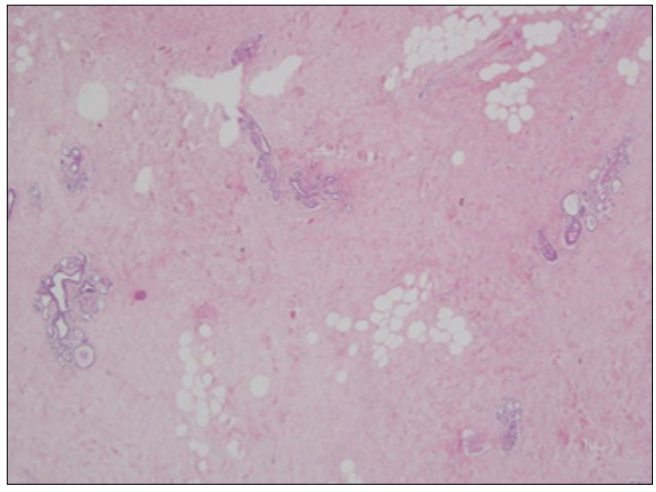

Figure 5. The histopathological examination of modified radical mastectomy specimen of Case 1 after NAC showed chemotherapy-induced changes, diffuse fibrosis, and lobular atrophy areas. Tumor cells were not detected with 'complete response'. Pathologic and MRI response types are compatible.

pathologic complete response. When the histopathological distribution according to MRI response type is evaluated, partial response is detected the most in all histopathological types similar to pathological response type.

Discussion and Conclusions

Currently NAC is the standard treatment of choice in LABC. The clinical and pathological response of the primary tumor to NAC has been reported as a prognostic factor that can be used as an indicator of long-term survival and disease management (11, 12). Early tumor response to chemotherapy during treatment can provide the opportunity of patient-specific treatment protocols (13). One of the major advantages of this treatment is the oppurtunity of BCS in patients who were initially unsuitable for BCS due to disappearance or shrinkage of the tumor in some selected cases (14). Singletary and colleagues (15) from MD Anderson Cancer Center reported that according to pathology results of mastectomy specimens of 143 LABC patients after neoadjuvant chemotherapy, 23% became suitable for BCS. Afterwards, Bonadonna and colleagues (16) showed that the rate of breast conserving surgery increases with neoadjuvant chemotherapy. In our study, 17 patients (44.7%) underwent breast conserving surgery after neoadjuvant chemotherapy.

In order to ensure negative surgical margins in breast-conserving surgery, proper detection of residual tumor size is crucial. However, there are limitations of mammography in the assessment of response to NAC. Dense breast parenchyma, increase in intensity due to edema, not being able to view the borders of diffuse growing lesions can be stated among these limitations. Similarly, due to edema the breast cannot be compressed at optimum quality and inability to obtain appropriate quality images are among the challenges. Based on all these reasons, physical examination and mammography cannot differentiate neoplastic tissue from fibrosis. In recent years studies are done in order to develop normograms that estimate the size of residual tumor after neoadjuvant chemotherapy and determine whether patients are eligible for breast conserving surgery or not (14, 17).

In our study, MRI correctly identified residual tumor size in 26 of 38 cases and the superiority of MRI over mammography or US in deter-

Table 5. Response type following neo-adjuvant treatment

	Complete response	Partial response	Stable disease	Progressive disease	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Pathology	6 (15.8)	28 (73.7)	3 (7.9)	1 (2.6)	38 (100)
MRI	5 (13.2)	28 (73.7)	4 (10.5)	1 (2.6)	38 (100)
Mammography	7 (18.4)	5 (13.2)	8 (21.1)	2 (5.3)	22 (58)
US	5 (13.2)	4 (10.5)	8 (21.1)	2 (5.3)	19 (50.1)

US: Ultrasonography; MRI: magnetic resonance imaging

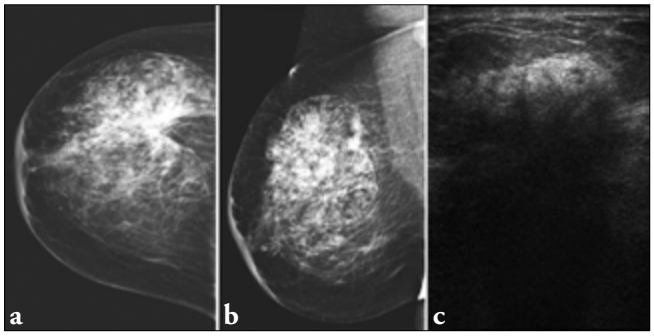

Figure 6. a-c. Mammographic craniocaudal and mediolateral oblique views of a 48-year-old patient (Case 2) with a left sided mass (a, b). US image of the left breast (c). A diffuse growing tumor with indistinguishable boundaries and that cannot be measured in size is located in the UOQ of the left breast, it cannot be clearly assessed by US, the hypoechoic heterogeneous mass lesion was evaluated as BIRADS -5

mining residual tumor size after NAC was shown by correlating with histopathology. The difference in maximum residual tumor diameter between MRI and pathology was 1 cm in 15 of 17 patients who underwent breast-conserving surgery. It should be kept in mind that pathology accepts the tumor size as the entire width of the lesion therefore, in patients with millimetric tumor foci pathology determines a larger tumor size than MRI. In some patients, there might be no contrast enhancement on MRI while a few invasive cells might be detected on pathology. In two of our cases, 1-2 mm of invasive tumor tissue type was detected in some foci, resulting in a mismatch between MRI and pathologic response.

The difference in the widest diameter is important by itself in evaluation of NAC response. However, only using diameter measurement for assessment of response to treatment with MRI has some limitations. It is difficult to determine the actual size of the tumor in lesions with originally multiple nodular contrast enhancements that show partial – patchy response after NAC. Also in lesions with necrosis, the size can appear larger in MRI although the residual viable tumor tissue has decreased. Parallel to the literature in our study, MRI was found to be superior to mammography and US in terms of tumor size after NAC, its statistical correlation with pathologic diameter was moderate. MRI was able to determine the residual tumor size accurately in only 26 of 38 cases. For all these reasons, there is a need for other parameters in evaluation of response to treatment. Total tumor volume, changes in signal enhancement pattern and changes in peak signal enhancement can be stated as such parameters (10).

It is reported that in cases with response to NAC, type 3 pharmacokinetic curves with wash-out either flatten (type 1) or form a plateau

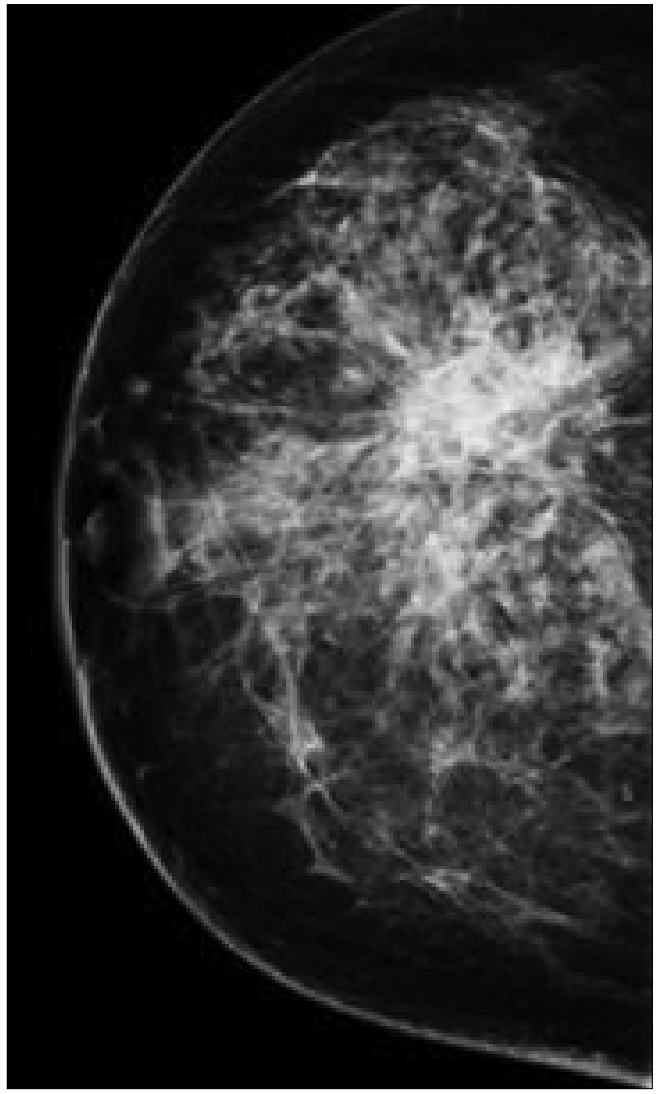

Figure 7. The histopathology result of tru-cut biopsy of Case 2 before treatment showed invasive lobular carcinoma, and 8 cycles of chemotherapy were administered. Treatment response type with mammography was considered as "stable disease"

(type 2) (18, 19). Balu Maestro and colleagues (20) accepted disappearance of early and initial contrast enhancement in the tumor after treatment as pathological complete response. Rieber et al. (18) determined that flattening or disappearance of the kinetic curve segment in the pharmacokinetic curve after the first course of chemotherapy or absence of enhancement after four cycles of chemotherapy indicate pathological complete response. In our patients, type 3 pharmacoki-

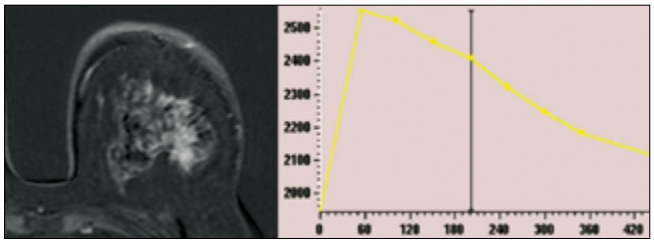

Figure 8. Pharmacokinetic curve of pre-treatment dynamic contrast-enhanced MRI of Case 2 before treatment. A 5x6 cm, diffusely growing mass mainly located in the middle and outer quadrant of the left breast, radiating from the lower to the upper quadrant was evaluated as BIRADS-5. The left breast skin is thick in appearance

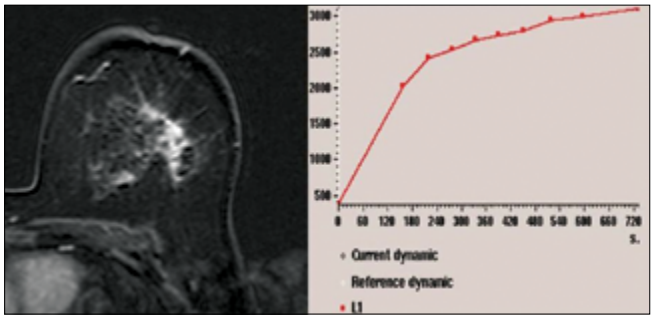

Figure 9. Pharmacokinetic curve of post-treatment dynamic contrast-enhanced MRI of Case 2. Mass lesion in the left breast showed approximately 40% reduction in dimension, the pharmacokinetic curve type shifted from type 3 to type 1. The MRI response type was considered as "partial response"

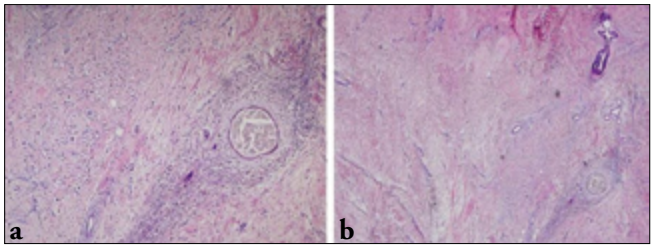

Figure 10. a, b. The histopathological examination of modified radical mastectomy specimen of Case 2 after neoadjuvant chemotherapy showed invasive lobular carcinoma and chemotherapy-induced changes (a low magnification, b: high magnification) are detected in histopathological examination. The pathological response type was evaluated as "partial response" and is compatible with the MRI results.

netic curve ratio decreased from 55.3% to 7.9% with treatment. In patients with partial response to treatment, type 1 and type 2 curves are in the majority. It was observed that mass lesions showing rapid enhancement pattern before treatment, show medium and slow enhancement after treatment and that contrast enhancement rates decrease.

It is reported that there is a strong correlation between MRI and pathology in determining tumor response to NAC in LABC patients (correlation coefficient: 0.75 to 0.93) (21). The accuracy rate of MRI in detecting response to neoadjuvant chemotherapy as compared to pathology have been reported as 63.3%, 69%, 94.8%, and 80% (10, 18, 20). These publications include 15 to 60 patients and their chemotherapy and MRI protocols are different. In our study, MRI detected response to treatment accurately in 84.21% of the patients, and it was superior to mammography and US.

One of the limitations of our study is the difficulty in assessing tumor diameter in patients with inflammatory breast cancer with diffuse growth. MRI has limitations in detecting scattered small tumors and in showing residual tumor with slight contrast enhancement. The pathologic residual tumor size was different from the residual tumor size detected by MRI in three of our patients who were clinically compatible with inflammatory breast cancer. In these cases, MRI detected the size of the tumor smaller than its actual size due to edema. Another limitation was that diffusion-weighted images could not be obtained for each patient during MRI and thus it could not be used as a parameter in the evaluation of NAC response. The limited number of cases included is another limitation of our study.

There are three main stages in the radiographic evaluation of LABC patients who underwent neoadjuvant CT. The first is to diagnose the tumor and to determine its extent , the second is to accurately evaluate response to treatment therefore enabling implementation of appropriate chemotherapy protocol, and the third is to detect residual tumor size and its extent for exact surgical planning, and if breast conserving surgery is to be made to ensure tumor free surgical margins.

Traditional methods may not be accurate in assessing the true extent of the disease because of chemotherapy-induced fibrosis. MRI is more advantageous in assessing the true extent of the disease by evaluation of tissue vascularization and the ability to distinguish viable tumor from fibrotic tissue. It reflects tumor size more accurately and is more reliable than mammography or US in predicting residual disease after NAC. Similarly in our study, when compared to histopathological findings, contrast-enhanced dynamic breast MRI was determined as a more effective method than either mammography or US in the evaluation of response to neoadjuvant chemotherapy. Evaluation of locally advanced breast cancer by MRI is appropriate due to its not being invasive, ability of performing re- measurements and guiding future treatment.

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

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

Peer-review: Externally peer-reviewed.

Informed Consent: Oral informed consent was taken from the patients who participated in this study.

Author Contributions: Concept - Ö.O., P.B.; Design - N.S.G., S.S.; Supervision - P.B.; Materials - S.S.; Data Collection and/or Processing - Ö.O.; Analysis and/or Interpretation - N.S.G., Ö.O.; Literature Review - N.S.G.; Writer - N.S.G., Ö.O.; Critical Review - M.G.D., B.D.

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Case Report

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A Rare Breast Tumor Confused with Ductal Carcinoma in Situ, Primary Solid Neuroendocrine Carcinoma

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ABSTRACT

The concept of pure neuroendocrine breast tumors was initially defined by Sapino et al. There are three sub-types of these tumors: solid, small cell/oat cell, and large cell neuroendocrine carcinomas. To diagnose neuroendocrine tumors, more than half of the tumor cells must have neuroendocrine differentiation. The possibility of metastatic neuroendocrine carcinoma must always be excluded in the differential diagnosis. In addition, it should be considered that solid neuroendocrine (NE) carcinomas can be confused with ductal carcinoma in situ due to their similar morphologic appearance. In this article, a patient with primary solid neuroendocrine breast cancer who had been diagnosed with ductal carcinoma in situ at another center was presented along with morphological and immunohistochemical features.

Key words: Neuroendocrine carcinoma, breast, solid

Introduction

Primary neuroendocrine (NE) breast carcinomas are rare tumors (1). These tumors were initially defined by Cubilla and Woodruff and have been categorized into a different group of primary NE breast tumors by the most recent breast cancer classification of the World Health Organization (2, 3). The diagnosis of these rare tumors, which have three sub-types (solid, small cell/oat cell, and large cell NE carcinomas), is made by finding NE differentiation in more than half of the tumor cells (3, 4). When considering primary NE breast carcinoma, the possibility of metastatic carcinoma must be excluded (3). Another condition that must be excluded is solid NE carcinoma and ductal carcinoma in situ (DCIS) cases due to their similar morphologic appearance. In this article, a patient with primary solid neuroendocrine breast cancer who had been misdiagnosed with DCIS at another center was presented along with morphological and immunohistochemical features.

Case Presentation

A 76-year-old female patient was identified with a lesion suspicious for malignancy following mammography and ultrasonography performed by the healthcare organization she was admitted to for the palpable mass in her right breast. The mass was evaluated by aspiration cytology. Because the outcome of aspiration cytology revealed a malignancy, the patient underwent a breast-conserving surgery without an additional diagnostic intervention. No sentinel lymph node biopsy was performed during the surgery. The outside evaluation of patient's pathology was reported to be DCIS. The diameter of the tumor was reported to be 1.5 cm by the pathology report of an outside center. The patient then presented at our hospital for oncologic treatment, and paraffin-embedded blocks were required to revise the pathologic diagnosis. Analysis of H&E sections made of paraffin-embedded blocks revealed a tumoral formation made of atypical cells with uniform appearance infiltrating the breast tissue in solid isles (Figure 1). We noticed that rosette-like structures were generated within the tumor cells and showed palizatic string on the periphery (Figure 2). Despite positive interior control, in immunohistochemical analysis performed with SMA and P63, no myoepithelial cells were found around tumor isles (Figure 3). Approximately 80% of the synaptophysin tumor cells strongly stained positively (Figure 4). Estrogen and progesterone were 90% and 80% positive, respectively. Cerb B2 stained negatively. The proliferation index was found to be 10% with Ki-67. There was no DCIS focus present. Neither non-breast primary focus nor metastasis was found during systematic scanning performed for metastatic disease. The case was reported to have primary solid NE breast carcinoma. Neither recurrence nor metastasis was present during the 12-month follow-up period with no additional treatment after surgery.

This case was presented as a poster at the 22th National Pathology Congress, 07 November-11 November 2012, Antalya, Turkey.

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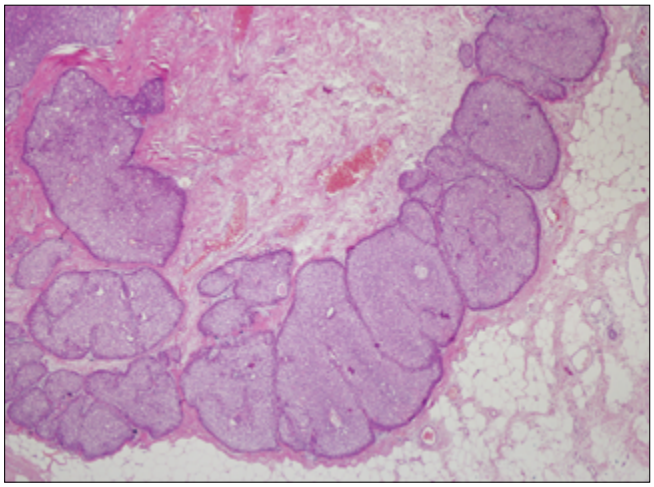

Figure 1. Tumor development is seen in solid isles. Note the similarity to DCIS (H&E, x40)

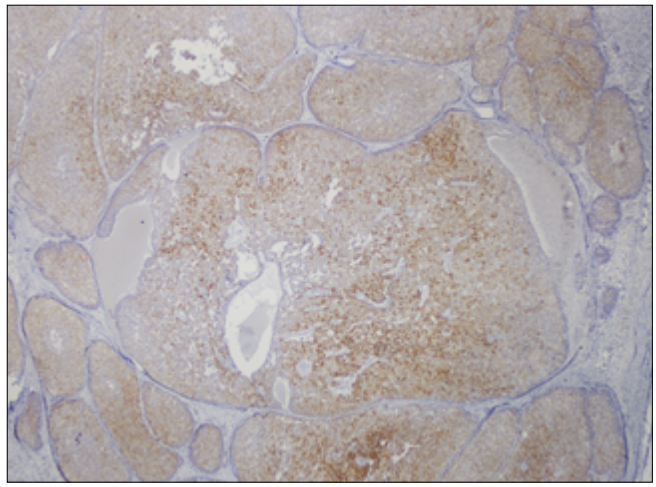

Figure 3. Common synaptophysin immunoreactivity in tumor cells is observed (DAB, x40)

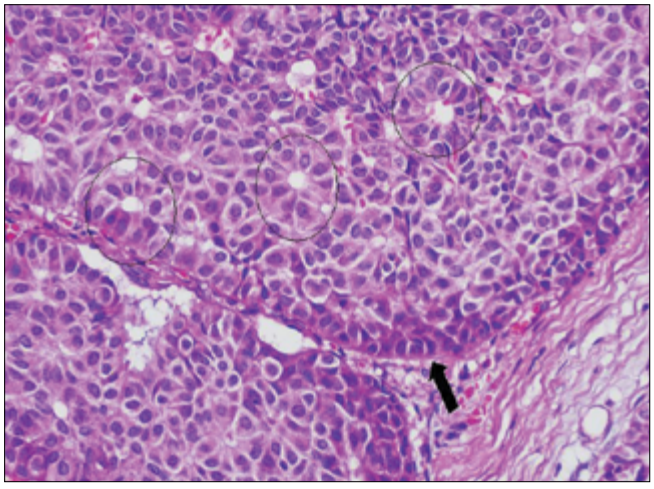

Figure 2. Tumor cells form rosette-like structures (ring) and they show palizatic string on the periphery (arrow) (H&E, x400)

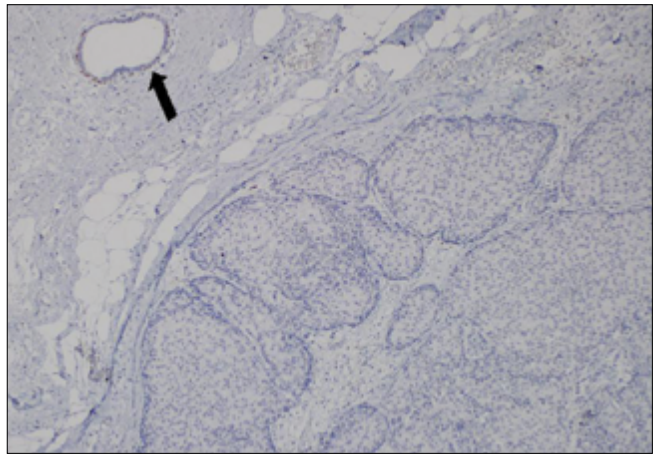

Figure 4. P63 immunoreactivity; while myoepithelial cells in the periphery normal ductus are stained (arrow), the isles of tumor cells in the periphery (right side) are not stained (DAB, x40)

Discussion and Conclusions

The concept of NE breast tumors was initially defined in 1977 (2). In 2000, Sapino et al. (4) defined breast tumors with NE differentiation in which NE indicators were identified in more than 50% of tumor cells as pure NE tumors. In 2003, the World Health Organization (3) categorized those tumors into a different group of breast tumors. These tumors are common in women in their 6th or 7th decades of life. NE differentiation is also defined for male breast tumors. NE tumors do not have specific clinical or radiological characteristics to distinguish them from other breast tumors (1-3).

Neuroendocrine (NE) breast carcinomas morphologically have three sub-types: solid, small cell/oat cell, and large cell NE carcinomas (3). Cellular uniformity, peripheral nuclear palisades, and pseudo-rosette formation are basic histological features that permit diagnosis. However, NE immune determinants must be expressed in more than half of tumor cells to make a diagnosis (3, 4).

The grade of histological differentiation in NE tumors is considered the most important factor for prognosis (5). Solid NE carcinomas are well-differentiated tumors. On the contrary, small cell/oat cell and large cell NE carcinomas are poorly differentiated (6). From this point, some researchers have suggested that solid NE carcinomas have a better prognosis than small cell/oat cell and large cell NE carcinomas (6). Receptor positivity of estrogen and progesterone and the presence of mucinosis differentiation are defined as good prognostic factors as well (5). It is important to differentiate these tumors from NE tumor metastases located on the other organs, as it will affect treatment and thus prognosis (7).

Making an accurate differential diagnosis is very important because NE breast tumors morphologically and immunohistochemically resemble NE carcinomas of other organs such as the gastrointestinal system and lungs (8). The presence of ductal carcinoma in situ within a tumor strongly su ggests that the breast is the primary focus (8). However, patients with primary NE breast carcinomas that do not include DCIS have been reported in the literature (9). Although receptor positivity of estrogen and progesterone initially suggests that the breast is the primary focus, it has been reported for some non-breast NE tumors as well, such as the lungs (8). Thus, this positivity supports the diagnosis of primary breast tumors, but it does not necessarily confirm it. In this context, it is important to scan patients through imaging methods on a regular basis to rule out other diagnoses. This can increase the likelihood of obtaining a more accurate diagnosis, accompanied by pathological and radiological findings (9).

Our case was morphologically and immunohistochemically parallel with data in the literature. As defined in many cases of primary NE breast carcinoma, there was a higher receptor positivity of estrogen and progesterone. Cerb B2 was negative, supporting previous findings. DCIS focus was not present, which is commonly defined in the literature and considered quite important for diagnosis. To exclude the possibility of metastatic NE carcinoma, positron emmission tomography / computed tomography (PET/CT) scanning was also performed. As no secondary focus was detected, the case was considered a primary solid NE breast carcinoma.

Another issue requiring attention is the need to differentiate solid NE carcinomas from DCIS due to their similar morphological characteristic, as in our case the solid NE carcinoma could easily be confused with DCIS. In addition, morphological characteristics such as the formation of pseudo-rosette viewed in NE carcinomas should draw the attention of the pathologist during diagnosis. Furthermore, immunohistochemical negativity of myoepithelial cell markers around the tumor islands could help eliminate a diagnosis of DCIS. However, r it is not enough to demonstrate the invasive nature of the tumor in some cases such as solid papillary carcinomas. In this case, immunohistochemical tests can be useful for basal membrane components such as laminin and collagen type IV. Positivity of basal membrane components is considered in favor of DCIS (10). Apart from that, the existence of cases of pure or focal invasive in situ NE carcinomas should be taken into consideration (11). In this sense, immunohistochemical methods evaluated with morphology will be a guide for the differential diagnosis.

Consequently, primary NE breast carcinomas can be identified by proving that a tumor is not metastatic as well as by a careful histopathological examination. Furthermore, one should bear in mind the possibility that solid neuroendocrine carcinomas may be confused with DCIS due to similar morphological features. We should bear in mind that the treatment will be delivered according to the type of tumor; therefore, accurate diagnosis is critical for patient survival.

Ethis Committee Approval: Ethics committee approval was obtained from Samsun Education and Research Hospital EPK.

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

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Case Report

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Virginal Breast Hypertrophy and Symptomatic Treatment: A Case Report

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ABSTRACT

Virginal breast hypertrophy is a rare benign disease. It is characterized by rapid and excessive growth of one or two breasts during peripubertal period. There is no specific treatment algorithm, subcutaneous mastectomy and prosthesis replacement, reduction mammoplasty, medical treatment with particularly tamoxifen are all recommended in the literature. Unfortunately, all treatment methods have some disadvantages in this patient group who have not completed their sexual and physical maturation. Although these treatments are usually required, it should be noted that spontaneous remission could rarely be seen in virginal hypertrophy. We aimed to present a case of virginal hypertrophy, in whom symptomatic treatment has been used and breast growth regressed spontaneously.

Key words: Breast, hypertrophy, adolescent gynecomastia, mammoplasty, mastectomy

Introduction

Durston (1) first reported virginal breast hypertrophy (VBH) in 1669. VBH is a rare benign breast disease, characterized by excessive and rapid growth of one or both breasts. It usually occurs within one or two years before menarche, in the peripubertal period. The cases with VBH reported in the literature are between the ages of 10-24 years (2-6). This disease is often sporadic, rare familial cases associated with congenital anonychia have been reported (7, 8).

The definitive treatment of VBH is not known. Recommended treatment methods are subcutaneous mastectomy with silicone prosthesis application, reduction mammoplasty, hormone therapy and combinations of these treatments (9). However, each of these treatments also brings additional problems in the patient group who has not completed their sexual and physical maturation.

In this case report, we aimed to present a rare condition of spontaneous cessation of breast growth in virginal breast hypertrophy and the successful outcome achieved by symptomatic treatment.

Case Presentation

A 12-year-old female patient was admitted with complaints of rapid growth in both breasts within 2 months, redness and pain and was hospitalized. On physical examination, there was increase in size in both breasts, edema, erythema, and the superficial veins were evident (Figure 1). The volumes of the right and left breasts were measured as 1300 cc and 1000 cc, respectively. Her bilateral breast and axilla examinations were otherwise normal. Her past medical and family history was uneventful. The age at menarche was 11 years. She described regular menstrual cycles in every 28 days, lasting for 6 days for the last 3 months. The breast ultrasound and magnetic resonance imaging showed thickening of the skin and subcutaneous tissue in both breasts, and glandular hyperplasia and both reports were interpreted as BIRADS 3. The abdominopelvic ultrasonography was normal. The biochemical investigations (complete blood count , biochemistry, C-reactive protein , hormone panels , thyroid hormones (FT3, FT4), thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH) , luteinizing hormone (LH) , estradiol , progesterone, total testosterone , prolactin, dehydroepiandrosterone sulfate (DHEAS) revealed that the patient had anemia (Hb: 10.9 and Htc: 32), and all the other values were within normal range. Breast elevation, warm dressings, and oral nonsteroidal anti-inflammatory (NSAID) therapy was initiated.

The inflammation regressed within 1 week. The surgical and medical treatment methods that can be applied to were discussed. The patient and her family were informed about the possibility of disease progression and that these treatments might still be necessary in the future.

This case was presented at the 18th National Surgical Congress, 23-27 May 2012, İzmir, Turkey.
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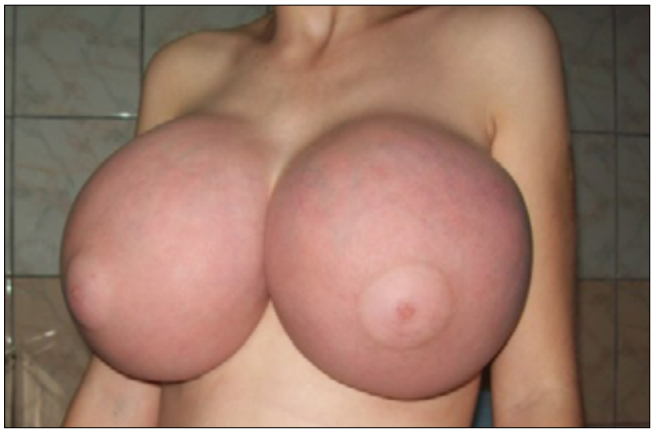

Figure 1. The case with virginal hypertrophy

However, due to reduced patient complaints and lack of a serious concern about cosmesis, they denied any further treatment and the patient was scheduled for close follow-up. At the 2nd and 6th month's evaluation, the breast volumes were measured and it was observed that the breast growth has stopped. The patient is planned to undergo evaluation every 6 months with physical examination, height and weight measurements, breast ultrasonography and cervical, thoracic, lumbar X-rays against the risk of kyphosis. Re-assesment for reconstruction was scheduled after the completion of pubertal and physical development, unless no recurrences or other pathologies occurred in the meanwhile.

Discussion and Conclusions

The normal physical development of the female breast is gradually completed in 3-5 years with the proliferation of all components of the organ. In contrast to this, in VBH there is a rapid and excessive amount of growth in one or both breasts despite normal levels of gonadal hormones (9).

The exact etiology is unknown, but several estrogen-related theories have been suggested. The most popular of these theories is end-organ hypersensitivity despite normal estrogen levels (3, 10).

The pathology in virginal breast hypertrophy (VBH) is limited to the breast without any other deformity in the body, with normal growth and sexual development. Due to the rapid growth of the breast mastalgia, back and neck pain, dilatation of breast's superficial veins, skin hyperemia, skin ulceration and skin necrosis may be observed clinically. Sometimes it can lead to serious psychological and cosmetic disorders (8, 11-13).

Virginal breast hypertrophy (VBH) is a rare disease and has been reported as case reports in the literature. There is no specific treatment algorithm that has been adopted. Treatment recommendations include medical, surgical treatments, and their combinations (8).

Virginal breast hypertrophy (VBH) is usually treated with surgical procedures. Surgery may be sufficient in some patients by itself, however the role of reduction mammoplasty is controversial especially due to the high rate of recurrence. Subcutaneous mastectomy and implant application is the surgical technique with the lowest rate of recurrence since all the breast tissue is removed. Nevertheless, the cosmetic results of subcutaneous mastectomy is less satisfactory than reduction mammoplasty, leaving no reserve for lactation and creating a lifetime risk of implant complications (3-5, 7, 14).

Agents used alone following or reduction mammoplasty as part of medical therapy are tamoxifen, bromocriptine, medroxyprogesterone, danazol , dydrogesterone, chorionic gonadotropin hormone and thyroid extracts. There is no proven superiority over another agent within this group. Tamoxifen is the most popular of these agents. It has been reported to stop breast growth preoperatively and to inhibit breast growth postoperatively. Unfortunately, its well-known side effects such as endometrial hyperplasia, increased endometrial cancer risk, hot flashes, increased risk of venous thrombosis, bone density changes, negative effects on cognitive function and depression limit its use (3, 5, 7, 8, 10).

When reviewing these proposed treatments, none of which is perfect, for VBH, it should be noted that spontaneous remission could rarely occur (12). In the literature, this probability and symptomatic treatment is not addressed. In our clinic, we primarily began symptomatic treatment for inflammation in a patient with VBH who lacked skin ulcers and skin necrosis. The treatment response was good and within approximately one month the growth ceased spontaneously. During follow-up spontaneous remission was not observed, but she did not have any significant physical and psychological complaints except mild back pain. Re-evaluation of the patient for reconstruction was scheduled after the completion of pubertal and physical development, unless no recurrences occurred in the meanwhile. It is thought that by performing the reconstruction in the postpubertal period, the aesthetic results will be more satisfactory and a surgical procedure capable of maintaining lactation may be applied.

The recommended medical and surgical treatments are usually required in virginal breast hypertrophy (VBH). However, considering the adverse effects of these treatments in peripubertal period, the probability of spontaneous cessation or regression of breast growth should not be ignored. In virginal hypertrophy patients with appropriate clinical status, as in this case, symptomatic treatment may be applied as a first step and the reconstruction process may be delayed until the postpubertal period.

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Case Report

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Primary Neuroendocrine Carcinoma of the Breast: A Report of Three Cases

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ABSTRACT

Primary neuroendocrine carcinoma of the breast is extremely rare. More than 97% of neuroendocrine tumors occur in the gastrointestinal and respiratory tracts. Three cases that have been operated in our clinic and had a diagnosis of primary neuroendocrine carcinoma of the breast were assessed, along with literature data. Histopathological diagnoses were obtained by preoperative core needle biopsy. Breast-conserving surgery was performed in two cases, and modified radical mastectomy in one. In all cases, immunohistochemical studies were positive for neuron-specific enolase and synaptophysin. All patients received adjuvant chemotherapy (CT) and one patient received additional radiotherapy (RT). Recurrence or distant metastasis was not detected during long-term follow-up after surgery.

Key words: Mastectomy, breast cancer, carcinoma, neuroendocrine

Introduction

The rare primary neuroendocrine tumor of the breast can be identified by histopathological examination as well as detection of whether the tumor is metastatic. Primary neuroendocrine carcinoma of the breast is a relatively rare neoplasm, known to behave aggressively (1, 2). Cubilla and Woodruff have described this entity first in 1977 (1, 3) and since then only a few case reports have been published. Adequate excision and adjuvant chemotherapy provide a favorable prognosis (2). There are no disease-specific clinical and radiological findings (4). The definitive diagnosis is made by histopathological evaluation. We aimed to present three cases that were operated for breast cancer in our clinic, and had a pathological diagnosis of primary neuroendocrine carcinoma of the breast.

Case Presentations

Case 1

A 37 year-old female patient complained of a mass in her right breast for the last year. Her past medical history was uneventful. On physical examination, a mobile, firm lesion about 4x4 cm in size was palpated in the upper outer quadrant of the right breast. Both the left breast and axilla were normal. The mammography and ultrasonography revealed a 4x3 cm in size, lobulated lesion that was sharply separated from the surrounding glandular tissue and was located peripherally in the upper outer quadrant of the right breast. It was interpreted as BIRADS 3 and a biopsy was recommended. The chest X-ray, abdominal ultrasonography and bone scans were normal. The core needle biopsy showed neuroendocrine carcinoma, and breast conserving surgery and sentinel lymph node biopsy was performed. Due to sentinel lymph node positivity, axillary dissection was performed. The postoperative course was uneventful and the patient was discharged on the fifth day after withdrawal of her surgical drains.

The histopathological tumor size was 4x4x3.5 cm. On microscopic tumor sections, round or oval atypical cells with hyperchromatic pleomorphic core and narrow pink cytoplasm were observed to form nests or solid islands. In addition, tumor cells formed scarce rosette-like sequences and contained areas of atypical mitosis or necrosis. Immunohistochemically, the tumor cells stained positive for neuron specific enolase (NSE) and synaptophysin, and negative for estrogen, progesterone, CerbB2 and chromogranin. Following axillary dissection, metastases were detected in 3 out of 16 lymph nodes. The patient received adjuvant chemotherapy and radiotherapy after surgery. Neither recurrence nor distant metastasis was detected during the postoperative follow-up of 56 months .

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Case 2

A 30-year-old woman who noticed a swelling on her right breast about 6 months ago admitted to our clinic. On physical examination, a painless, mobile, hard mass of about 5x4 cm in size was palpated in the lower outer quadrant of the right breast. There was right axillary lymphadenopathy. The left breast and axilla were normal. On ultrasonography a hypoechoic heterogeneous lobulated mass lesion, 44x40 mm in size was observed in the upper outer quadrant of the right breast. In breast magnetic resonance imaging, a mass that was heterogeneously hypointense on T2-weighted sequences and slightly hypointense as compared to glandular tissue on T1-weighted sequences was visualized in the axial plane of the lower outer quadrant of the right breast (Figure 1). It was interpreted as BIRADS-4 and a biopsy was recommended. The chest X-ray, abdominal ultrasonography and bone scans were normal.

The core biopsy result showed a carcinoma and the patient underwent modified radical mastectomy (Figure 2a, b). On pathological examination two separate tumors, 4.5 x3 and 2x2 in size were detected. The tumor was composed of round or oval cells with hyperchromatic or vesiculated cores and marked pink granular cytoplasm that form rosette-like structures and solid islands separated by fibrovascular septa (Figure 3). On immunohistochemical studies, the tumor stained positive for NSE, synaptophysin, CerbB2 and estrogen and negative for progesterone and chromogranin. All 18 lymph nodes removed by axillary dissection were reactive. She received chemotherapy as adjuvant treatment. During the postoperative follow-up of 25 months, there was no recurrence or distant metastasis.

Case 3

A 61-year-old female patient was referred to our clinic due to a mass in her left breast that was detected during routine breast examination. Her past medical history was unremarkable. Her family history revealed that her mother had breast cancer. On physical examination, an approximately 1x1 cm sized, mobile, hard mass was palpated in the upper inner quadrant of the left breast. The mammography and ultrasonography showed a hypoechoic solid lesion with faint contours, 1x1 cm in size that was located in the upper inner quadrant of the left breast (Figure 4). The lesion was evaluated as BIRADS 4.

The core needle biopsy revealed neuroendocrine carcinoma. Breast conserving surgery and sentinel lymph node biopsy was performed. The sentinel node biopsy was negative and axillary dissection was not applied. The tumor was 1,5 x1x1 cm in size. On microscopic evaluation, the tumor was composed of round or oval atypical cells with hyperchromatic pleomorphic cores and narrow pink cytoplasm that form nests and solid islands. Immunohistochemically, the tumor stained positive for NSE, synaptophysin, estrogen, progesterone, and chromogranin, and negative for CerbB2. She received adjuvant che-

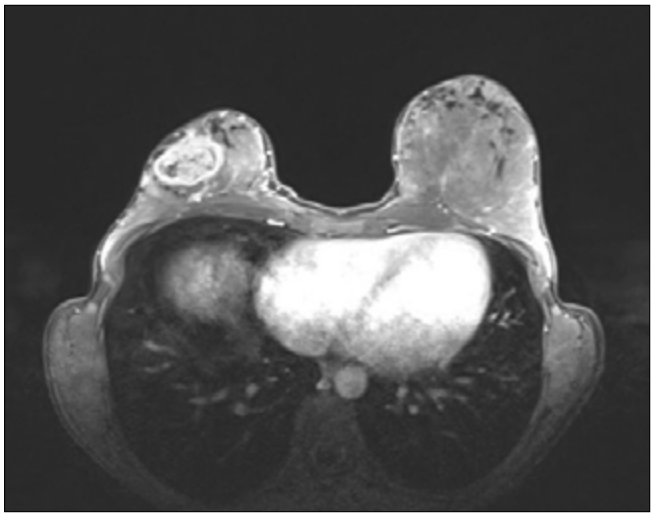

Figure 1. Magnetic resonance imaging view of breast mass in case 2.

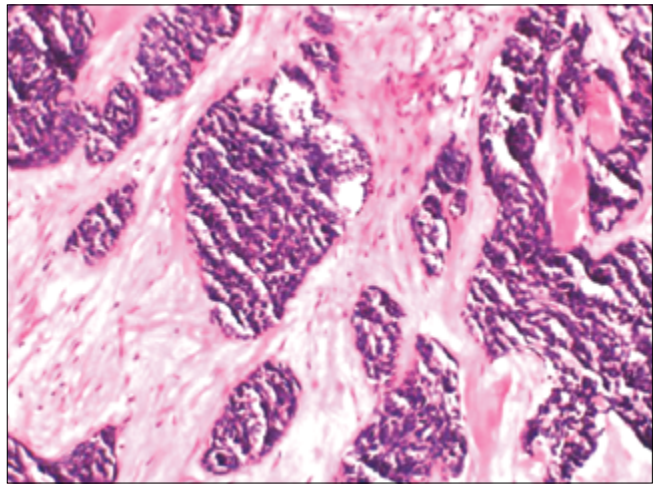

Figure 3. Neuroendocrine carcinoma composed of trabecular and solid islands with peripheral palisading pattern separated by fibrovascular stroma (HEx10)

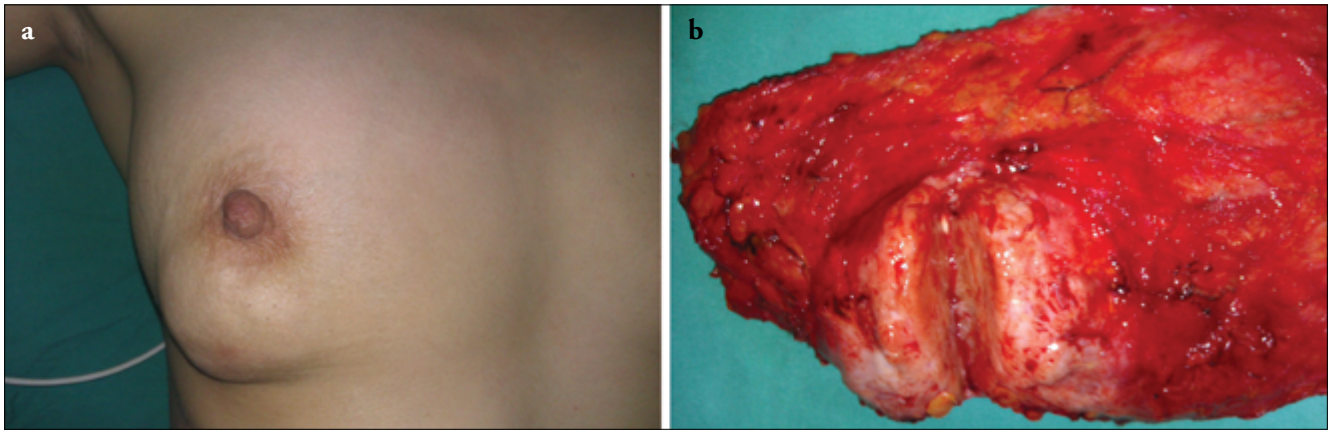

Figure 2. Preoperative view of the breast in case 2 (a). Cross-section of the specimen (b)

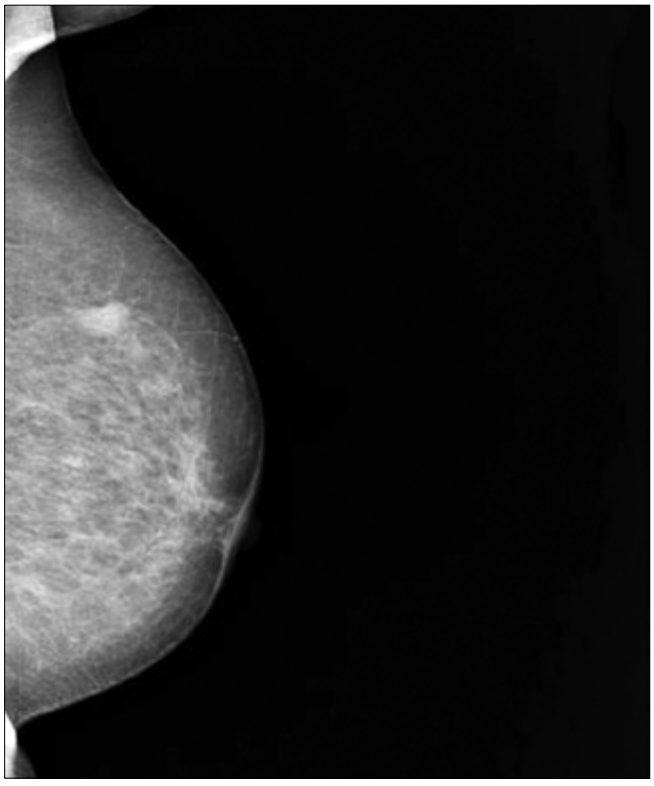

Figure 4. Mammographic view of a hypoechoic 1x1 cm solid lesion in the left breast upper inner quadrant in Case 3

motherapy. During the postoperative follow-up of 12 months, there was no recurrence or distant metastasis.

Discussion and Conclusions

Primary neuroendocrine carcinomas of the breast are relatively rare (1). Cubilla and Woodruff first defined it in 1977 (3). More than 97% of neuroendocrine tumors occur in the gastrointestinal and respiratory systems (1, 2). Neuroendocrine tumors are rarely described in cervix, prostate, pancreas, stomach, intestine, trachea, larynx and skin (5, 6). Although several authors have defined neuroendocrine neoplasms of the breast, the histogenesis is still uncertain, since the presence of neuroendocrine cells in the normal breast has not been proven yet (1-5). Endocrine differentiation is seen in 5-8% of breast carcinomas (6).

Diagnosis of primary neuroendocrine carcinoma can be made by proving that it does not originate from tissues other than the breast or identification of the in situ component (2-4). The World Health Organization (WHO) defined these tumors as 3 histological types in 2003; solid, small cell, large cell neuroendocrine carcinoma (2).

Neuron specific enolase, chromogranin A, and synaptophysin are considered as neuroendocrine markers and indicate the presence of neuroendocrine differentiation (2, 6). If neuroendocrine markers are observed in more than 50% of malignant cells, it is considered as a pure neuroendocrine tumor (1, 7). In addition, estrogen and progesterone receptor positivity provide additional evidence that the tumor is of primary breast origin (1). However, estrogen and progesterone positivity have been reported in some non-breast neuroendocrine tumors, especially in the lung (5, 8). In all three of our cases, NSE and synaptophysin were positive and the breast was found to be the primary focus.

Table 1. Patient demographics

	Case 1	Case 2	Case3
Age	37	30	61
Location	Right breast	Right breast	Left breast
Size (cm)	4	4.5	1.5
Treatment	BCS + CT + RT	MRM + CT	BCS + CT
Lymph node status	Positive	Negative	Negative
Disease-free follow up (month)	56	25	12
Recurrence or metastasis	No	No	No

BCS: Breast Conserving Surgery; CT: chemotherapy; RT: radiotherapy; MRM: modified radical mastectomy

Table 2. Immunohistochemical properties of the tumors

	Case 1	Case 2	Case3
NSE	+	+	+
Synaptophysin	+	+	+
Chromogranin A	-	-	+
ER	-	+	+
PR	-	-	+
Cerb B2	-	+	-

NSE: Neuron specific enolase; ER: estrogen receptor; PR: progesterone receptor

These tumors are usually seen in the 6th and 7th decades (1, 2, 5). There is only one report of a 52-year-old male patient in the literature (9). There are no specific clinical and imaging findings (1). The mean age of our patients was 42 (37-61) years. Clinical and radiographic findings were suggesting malignancy, but they were not specific for neuroendocrine carcinoma. The definitive preoperative diagnosis was made by core needle biopsy. The estrogen and progesterone receptors were both positive in one patient, both negative in another and one patient was positive for progesterone only. Patient demographic characteristics and immunohistochemical features of the tumor are summarized in Table 1 and Table 2.

With the determination of absence of any other primary focus, it was concluded that this tumor located in the breast is a pure primary neuroendocrine tumor of the breast. A sufficient idea regarding the presence of another tumor or metastasis can be obtained by thoracoabdominal CT and whole body bone scintigraphy (4, 5, 8). In all three cases, whole body scan was performed and there no other focus was detected.

Neuroendocrine carcinoma prognosis is still debatable due to the insufficient number of cases. Histologic grade is the most important prognostic factor (1). It is thought to have a good prognosis with adequate excision and adjuvant chemotherapy (2). The relationship of neuroendocrine differentiation with breast carcinoma prognosis has not been shown (5). According to latest reports, detection of the tumor at an early stage without lymph node metastasis is thought to provide a better prognosis (5, 6, 10, 11). Mucinous differentiation, estrogen and progesterone receptor positivity are favorable prognostic factors (1). The surgical treatment options were discussed with our patients; two cases underwent breast-conserving surgery, and modified radical mas-

tectomy was performed in one patient. Only one patient had axillary lymph node metastases. All patients received chemotherapy as adjuvant therapy and in the patient with axillary lymph node metastases RT was given in addition. No recurrence or metastasis was detected during the mean follow-up period of 33 (12-56) months.

Standard treatment method is controversial due to the rarity of these tumors. The detection of neuroendocrine tumors localized to the breast, either as classic breast cancer or as a separate clinical diagnosis, alters the treatment. Small cell neuroendocrine carcinoma of the breast is similar to small cell carcinoma of the lung in terms of morphological, clinical and histological features, thus their treatments are similar (6, 10-12).

Histopathological examination and excluding the presence of metastasis is important in primary neuroendocrine tumors of the breast. The impact of neuroendocrine differentiation on the clinical outcome is controversial. In all three cases, treatment approach for invasive breast tumors has been adopted. We believe that the prognosis of these tumors is favorable with early diagnosis, appropriate surgical and adjuvant treatments according to oncological principles. Data on larger series are required for clarification of treatment approaches.

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

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